



Meniscal allograft transplants and new scaffolding techniques

Hélder Pereira^{1,2,3,4,5}

Ibrahim Fatih Cengiz^{4,5}

Sérgio Gomes³

João Espregueira-Mendes^{4,5,6,7}

Pedro L. Ripoll²

Joan C. Monllau⁸

Rui L. Reis^{4,5,9}

J. Miguel Oliveira^{4,5,8,9}

- Clinical management of meniscal injuries has changed radically in recent years. We have moved from the model of systematic tissue removal (meniscectomy) to understanding the need to preserve the tissue.
- Based on the increased knowledge of the basic science of meniscal functions and their role in joint homeostasis, meniscus preservation and/or repair, whenever indicated and possible, are currently the guidelines for management.
- However, when repair is no longer possible or when facing the fact of the previous partial, subtotal or total loss of the meniscus, meniscus replacement has proved its clinical value. Nevertheless, meniscectomy remains amongst the most frequent orthopaedic procedures.
- Meniscus replacement is currently possible by means of meniscal allograft transplantation (MAT) which provides replacement of the whole meniscus with or without bone plugs/slots. Partial replacement has been achieved by means of meniscal scaffolds (mainly collagen or polyurethane-based). Despite the favourable clinical outcomes, it is still debatable whether MAT is capable of preventing progression to osteoarthritis. Moreover, current scaffolds have shown some fundamental limitations, such as the fact that the newly formed tissue may be different from the native fibrocartilage of the meniscus.
- Regenerative tissue engineering strategies have been used in an attempt to provide a new generation of meniscal implants, either for partial or total replacement. The goal is to provide biomaterials (acellular or cell-seeded constructs) which provide the biomechanical properties but also the biological features to replace the loss of native tissue. Moreover, these approaches include possibilities for

patient-specific implants of correct size and shape, as well as advanced strategies combining cells, bioactive agents, hydrogels or gene therapy.

- Herein, the clinical evidence and tips concerning MAT, currently available meniscus scaffolds and future perspectives are discussed.

Keywords: meniscal repair; meniscectomy; meniscus allograft transplantation (MAT); partial meniscus replacement; scaffold; tissue engineering and regenerative medicine

Cite this article: *EFORT Open Rev* 2019;4

DOI: 10.1302/2058-5241.4.180103

Introduction

Injuries of the meniscus are probably the most frequent injuries occurring in the knee.¹ According to the statement from Prof. René Verdonk, 'Nothing has changed so much in recent years of orthopedics as the treatment algorithm of meniscus lesions'.² A radical change occurred since the 'recommendation' during the 1970s to remove as much as possible of what was formerly considered as a useless structure,³ to the present-day movement supporting the preservation, repair or replacement of the meniscus.² Recent basic science research reinforced the claim that the menisci are fundamental components of a healthy knee joint.⁴⁻⁶ Menisci are C-shaped fibro-cartilage structures with a wedge-like cross-section (Fig. 1), present between each tibial plateau and the corresponding femoral condyle.^{5,7} They have a specific extracellular matrix,^{8,9} multiple cell types^{10,11} and particular cell distribution.^{5,12} They

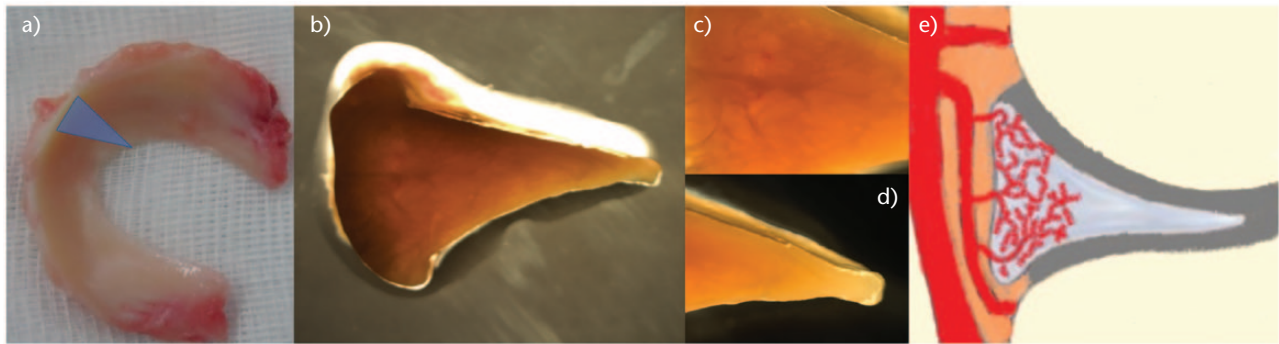


Fig. 1 (a) Lateral meniscus of a right knee; in blue is demonstrated a radial cut; (b) light optical amplification of a radial cut for ultra-structure evaluation; (c) and (d) the density of collagen network is visible; (e) schematic drawing of meniscus vascularization on the sagittal view.

have unique biomechanical features¹³ and are known to have segmental and regional variations concerning ultra-structure, vascularity, biology, and function.^{7,12,13} There are differences between the medial and the lateral menisci in knee kinematics. The lateral meniscus is accountable for most of the load transfer within the lateral compartment (around 70%),¹⁴ while the transmission of loading is more equally dispersed through the cartilage surfaces and the medial meniscus (50%) in the medial compartment.^{15,16} Concerning kinematics, the lateral meniscus is more mobile, while the medial one is more static to resist anterior tibial translation, acting as a secondary agonist of the anterior cruciate ligament (ACL).^{6,14}

It has been recently shown by 2-dimensional (2-D) and 3-dimensional (3-D) analysis of the menisci segments that cellular density is relatively higher on the anterior segment when compared to other parts, and that the posterior segments tend to be stiffer.^{12,13} It was hypothesized that the higher damping properties of the anterior segments could be related to the higher cellular density, meaning that biology and biomechanical features are combined.^{12,13}

One should bear in mind the basic science knowledge related to each meniscus since it surely has implications for tissue loss, repair, healing and outcomes of replacement.^{12,17} Moreover, vascularization of the menisci is critical for treatment decisions. The peripheral vessels infiltrate around 10% to 25% of the width of the lateral meniscus and 10% to 30% of the width of the medial meniscus in adults (Fig. 1).¹⁸ Children and adolescents are known to have increased vascular supply. Thus, they have more possibilities for repair when a meniscal injury occurs, despite sometimes suffering from more complex meniscus lesions.¹⁹

Meniscectomy has significant consequences for the joint and causes a higher risk of early joint degeneration, despite remaining one of the most frequent orthopaedic

procedures worldwide.^{20–24} Meniscus repair commonly provides superior clinical outcomes when compared with meniscectomy.^{25,26} As a general rule, the meniscus tissue should be preserved whenever possible. However, meniscus repair has specific indications and limitations.^{26–28}

It is widely recognized that there is an urgent need for an improved description of meniscal tear patterns,²⁹ standardized reporting of outcome measures, and better-quality study methodologies in order to help in making the best decision for the treatment option and/or technique, as well as establishing prognosis.²⁶ A very important distinction, which often is not easy to make, is between traumatic and degenerative lesions.^{30–33} The physiopathology of meniscal lesions is not always easy to understand and frequently is part of the whole of the knee joint loss of balance.⁶ A traumatic meniscus tear is typically related to an acute trauma which produces sufficient energy to split the tissue. The tear patterns more commonly linked to traumatic tears are: longitudinal, bucket-handle and radial tears.³⁴ Nevertheless, most flap tears are also classified as traumatic. High-energy traumatic events which might cause fractures around the knee can also be involved in meniscus tears.³⁵ Some of these lesions require combined osteochondral and meniscal transplantation.^{36,37} Contrarywise, degenerative meniscus lesions are characteristically caused by chronic degenerative changes including cavitation, fibrillation, softened/brittle tissue, or more complex tear patterns, among others.²⁹ Horizontal lesions represent the typical type of such lesions.^{38–40} Such cases often have a degenerative nature even in younger patients.^{37–39}

Considering posterior root tears, lateral tears are more frequently traumatic (often combined with anterior cruciate ligament rupture), while medial meniscus root tears have more often a degenerative nature.^{41,42} There has been a recent technical development linked to meniscal repair, and some lesions classically classified as irreparable

(e.g. radial or horizontal tears) are having encouraging results with repair.²⁶ Globally, a failure rate for meniscus repair of approximately 15% is widely accepted, despite the fact that in the literature it ranges from 5% to 43.5%.⁴³ Furthermore, it has been demonstrated that the failure of a meniscal repair does not worsen the outcome, nor dictate a need for a bigger loss of tissue volume, if a reoperation and meniscectomy is needed.⁴³ This fact reinforces the point that it is fair and advisable to 'save the meniscus and preserve the future of the joint' whenever possible.

However, if repair is not possible, partial or total meniscal replacement seems to be the most adequate method, whenever possible.⁴⁴ This choice is not purely based on the meniscus injury but also on the global condition and function of the joint, considering the cartilage condition and ligament status and function.⁴⁵ The first description of meniscus allograft transplantation (MAT) was in the 1970s, in patients with post-traumatic osteoarthritis secondary to fractures of the tibial plateau treated by an osteochondral allograft resurfacing procedure combining bone, cartilage, and meniscus in a single step.^{46,47} The first free MAT was performed in 1984.⁴⁸ Since then the technique has been intensely developed and proposed for the treatment of patients with a symptomatic painful knee as consequence of meniscectomy, under specific indications and contraindications.⁴⁹ MAT has been demonstrated to be a reliable therapeutic option.^{50,51} It has received and keeps receiving relevant improvements and increasing interest from surgeons and researchers based on favourable outcomes, already with long-term follow-up.^{37,50-55}

The concept of meniscal replacement by means of using a scaffold was introduced in the 1990s.⁵⁶ Total meniscus allograft transplantation and partial meniscal replacement by means of scaffolds (with or without biological enhancement) have, by definition, different indications and possibilities. The implantation of a scaffold for partial meniscus replacement necessitates that the meniscal roots and peripheral rim remain conserved. These requirements are not needed for MAT, which enables complete replacement of the meniscus by means of creating new 'root-like' attachments.⁴⁹

Access to and acceptance of allografts are not equal in all countries, because of some legal, economical, disease transmission concerns, as well as ethical, or even religious objections.⁵⁷ For all these reasons, considerable restrictions of access to proper meniscal allografts remain in several countries.^{44,57,58}

There are high expectations of tissue engineering and regenerative medicine. Future perspectives include new, more effective, biomaterials, combined with augmentation by means of effective use of cells, bioactive agents (e.g. growth factors or medication molecules), nanotechnology or gene therapy in advanced strategies.^{27,59} Moreover, it is also possible to produce patient-specific implants

by using 3-D printing based on patient imaging.^{60,61} Tissue engineering technologies raise the possibilities, in future, of providing a limitless source of effective tissue for meniscus replacement (partial or total), avoiding the previously described limitations and concerns of allografts related to donors, with the associated complicated processing and size-matching issues.^{27,62}

Meniscus allograft transplantation (MAT)

Fundamentals, indications and techniques of MAT

The 'ideal candidate' for MAT is a young patient with a history of symptomatic femorotibial compartment symptoms having undergone a previous meniscectomy, with a stable knee, neutral alignment and no severe chondral damage or arthritis. Presence of cartilage degeneration, obesity and smoking habit are considered risk factors.^{49,63} A summary of indications and contraindications for MAT are summarized in Table 1.

Preservation and sterilization methods

Preservation and sterilization methods of the meniscal allografts appear to play a role in outcome.^{49,50} Currently, there are four types of meniscal allograft: fresh, cryopreserved, deep-frozen⁴⁹ and lyophilized, although lyophilization is not currently used anymore (Table 2).^{37,63-65} Deep-frozen (fresh-frozen) and cryopreserved meniscal allografts are the most frequently used.⁶⁵ There is a growing trend for the use of fresh allografts.^{37,57,65}

Cryopreservation proved to be a significantly better method of preservation, when compared with fresh-frozen. Fresh meniscal transplantation is logistically demanding and expensive given the short period of time between the donor's death and transplantation. The use of fresh tissue transplantation has inherently a higher risk for disease transmission.⁶⁵ This risk has been estimated to be 1:8,000,000 for HIV⁶⁷ and 1:2600 for Clostridium⁶⁷ (as examples). However, most likely this method shall be the one which preserves the most native biological and biomechanical features of the meniscus for MAT.^{37,57,65} In the case of fresh meniscal allografts transplantation, there is also a risk of transmission of pathogens, so specific care and procedures are required to minimize risks, including special tests aiming to exclude infection.⁶⁵ Moreover, concerning cells, the advantage of preserving donor cells is debatable once host cells are capable of repopulating the graft within a few weeks following MAT.⁶⁵

Technical choices for MAT fixation

As technical choices for MAT fixation, several techniques have been proposed including bone blocks, or soft tissue only (Fig. 2).^{49,68} There is still no clinical evidence favouring any technique over another.^{49,68} Concerning fixation,

Table 1. Meniscus replacement options: indications and contraindications

<p>Meniscus allograft transplantation</p> <p>INDICATIONS</p> <ul style="list-style-type: none"> • Prior total or subtotal meniscectomy, with pain in the involved tibiofemoral compartment. • Age of 50 years or younger (relative). • Cartilage degenerative changes in young patients after meniscectomy. • Absence of radiographic evidence of advanced joint arthritis. • 2 mm or more of tibiofemoral joint space on 45° weight-bearing posteroanterior radiographs. <p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> • Advanced joint arthritis with flattening of the femoral condyle, concavity of the tibial plateau, and osteophytes that impairs anatomic placement of the meniscus allograft. • Less than 2 mm of tibiofemoral joint space remaining on 45° weight-bearing posteroanterior radiographs. • Axial malalignment. • Uncorrected ligamentous instability. • Arthrofibrosis. • Muscular atrophy. • Systemic or local infection. • Autoimmune diseases or inflammatory arthritis. • Presence of cartilage degeneration, smokers and obese (Body Mass Index > 35) patients have higher risk of failure. 	<p>Meniscus partial replacement by acellular scaffold</p> <p>INDICATIONS</p> <ul style="list-style-type: none"> • Age between 16 and 50 years old. • Skeletally mature patient. • Irreparable medial or lateral meniscal tear or partial meniscal loss (> 25%). • Partial meniscus defect with preservation of meniscal roots and peripheral rim. • Aligned knee joint (favourable axis of less than 5°). <p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> • Full-thickness loss of articular cartilage with exposed bone –International Cartilage Repair Society classification > 3. • Meniscal root lesions. • Uncorrected ligamentous instability. • Axial malalignment (deformity greater than 5°). • Osteonecrosis of the involved knee. • Uncorrected ligamentous instability. • Systemic or local infection. • Autoimmune diseases or inflammatory arthritis. • Presence of cartilage degeneration, smokers and obese (Body Mass Index > 35) patients have higher risk of failure.
---	---

Table 2. Preservation and sterilization methods of the meniscal allografts

- **Freeze drying or lyophilization** – this preservation technique includes dehydration. It has been shown that it increases the risk of meniscal shrinkage, so it is no longer used.^{49,65}
- **Deep or fresh frozen** – the tissues are frozen without further processing, at –80 °C, which makes it simple and relatively cheap. It annihilates the cells from the graft; however, it reasonably preserves the collagen architecture, despite some changes in collagen structure having been reported.⁶⁴
- **Cryopreservation** – Cryopreservation freezes the graft at –180 °C with the addition of glycerol or dimethyl sulfoxide as antifreezing agents. This method is believed to preserve some donor cells’ integrity and viability. It has been demonstrated to preserve the most relevant meniscal ultrastructure despite the preservation of cellular viability being less reliable.¹⁶⁶
- **Fresh and viable** – Fresh menisci can be obtained from multiorgan donors. This maintains cellular viability but concerns exist in relation to risk of infectious disease transmission. Incubation of the fresh meniscus in serum for 15 days is required, to preserve viability as well as diminishing risks by performing specific tests. Although expensive and logistically complex, this is an attractive option.^{37,57}

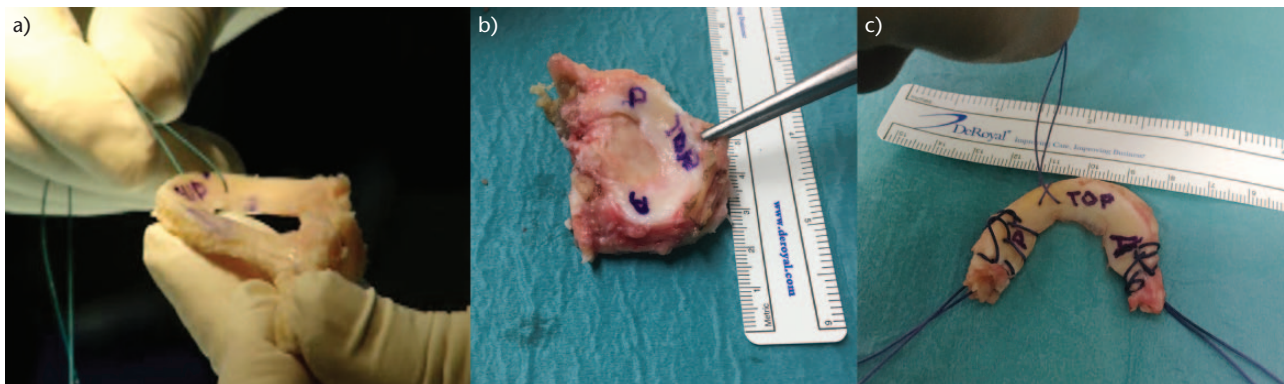


Fig. 2 (a) Cryopreserved lateral meniscus graft prepared with bone slot and a suture in the junction of the posterior segment to the mid-body to assist in introducing the graft in the joint; (b) Preparation of a fresh meniscus graft (anterior and posterior horns as well as top side are marked); (c) soft tissue only allograft with all the marks and the suture to assist introduction within the joint.

multiple studies have shown comparable graft survival and outcomes between different fixation options.^{49,50} Some authors have reported that a meniscus allograft fixed with the suture-only technique had a higher degree of extrusion of the meniscal body and a trend for higher rate of MAT tears (Fig. 3) when compared to the bony fixation method.⁶⁹ However, no influence on the functional

outcome was noticed for either, and more studies are still required on the topic.⁶⁹

Two relevant topics for research on MAT are the fixation and integration of the meniscus tissue itself and its anchorage to the bone. There are different anatomic characteristics for the lateral and medial meniscus which influence the technical approach considering the previous

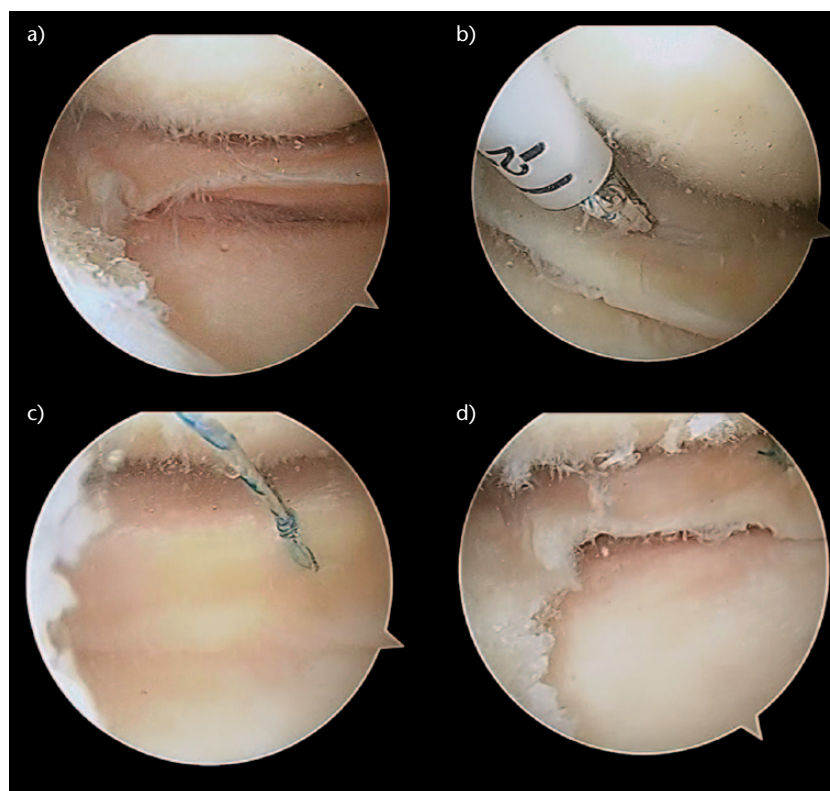


Fig. 3 (a) Arthroscopic view of a posterior longitudinal peripheral tear of a lateral meniscus transplant 3 years after implantations; (b) all-inside suture; (c) knot tying; (d) stable suture.

topics. The anterior and posterior root attachments of the lateral meniscus are closer when compared to the medial meniscus in which they are more separated.^{5,26,70} Considering the previous, when performing a medial MAT, two bone tunnels in the tibia will often be required. For lateral MAT, the vicinity of root attachments makes it more difficult to create such tunnels (risk of coalescence) and a bone slot/block technique can be considered as it preserves the native tibial root attachments of the graft.⁴⁹

Measurement techniques for sizing

One determinant pre-operative requirement is evaluation of the size of the knee receptor compartment and finding a matching meniscus allograft. Several measurement techniques for sizing the recipient compartment have been studied based on plain X-ray, CT, MRI and anthropometric data.⁶³ A graft which is too small will be exposed to an increased biomechanical load, which will most likely lead to an early failure. Conversely, a graft that is too big will have an extruded position within the joint, lowering its biomechanical function and resulting in a continuous overload of the articular cartilage.⁶³

Three types of medial anterior horn anatomy have been described: the most common is type 1, with an insertion posterior to the anterior tibial edge and lateral to the

spine; type 2 has an insertion medial to the spine; and type 3 (less frequent) has an insertion anterior to the anterior edge of the tibial plateau.⁷¹ Gelber et al hypothesized that placing a MAT posterior to the tibial edge in a knee with previous type 3 meniscus might result in overstuffing of the anterior compartment.⁶³ These details are examples of technical tips based on anatomic and biomechanical knowledge which play a major role in outcome.

The most frequently used sizing method was described by Pollard et al, and is based on calibrated anteroposterior (AP) and lateral radiographs.⁷² However, its major limitation mainly affects lateral allograft sizing given the significant interindividual variability between the medial and the lateral compartment dimensions measured on plain X-rays (mainly in the AP view).⁷² Some attempts have been made to increase its effectiveness by means of mathematical models.⁶³ CT and MRI-based imaging are considered to be more precise but increase the cost, and CT has inherent radiation. However, to assess the anterior horn of the medial meniscus, an MRI of the opposite knee is required.

The choice of surgical technique (with or without bony fixation) is also linked with the reliability of sizing and matching the graft. Bone block fixation requires anatomical reconstruction of the anterior and posterior horns.

Table 3. Technical tips for meniscus allograft transplantation

- Have a good communication with your tissue bank.
- In tight knees (varus), if required for visualization and access, do not hesitate to release the medial collateral ligament (pie-crust technique).
- The suture-only fixation technique is usually less demanding than bony fixation.
- A larger graft can be implanted anatomically by pulling it more to the inside of the osseous tunnel.
- A smaller graft can be positioned short of the anterior horn in the tibial plateau to avoid overtension and achieve fair coverage of the joint surface.
- A suture passed at the junction between the posterior one third and mid-body of the allograft, is very useful to bring the graft in place. This suture shall be retrieved out of the joint from an outside-in pulling loop, and tension is applied while bringing the graft in place.
- Enlarge the arthroscopic portal of the involved compartment generously to facilitate introducing the graft in the joint.

Source: Based on Gelber PE, et al. *JISAKOS* 2017;2:339–349.⁶³

Thus, this technique is more demanding in terms of matching the receptor and the graft, and requires an experienced allograft bank. Bone-free MAT technique is less demanding concerning size mismatching.

To date, no method of sizing has proven to be more reliable or user-friendly than any other.

MAT's extrusion

MAT's extrusion (radial displacement of the allograft) has been a matter of debate for several years. Its relation with clinical outcome is not completely clear and an extrusion up to 3 mm has been considered as 'normal'.^{63,73,74} However, one can understand that, if significant displacement of a graft occurs, its biomechanical role in resisting compressive, radial, cutting or hoop stresses could be compromised.⁶ Extrusion following MAT seems to be a frequent finding, which usually appears shortly after surgery, and does not always progress through time. It seems that bony fixation is less prone to extrusion than soft tissue technique.⁶⁹ Lateral MAT seems to be more prone to extrusion than the medial.⁷⁵ Some attempts have been made to diminish extrusion such as aiming for the most anatomical graft placement, reducing the size of the graft by 5%,⁷⁶ the excision of peripheral osteophytes of the tibial plateau, the fixation of the meniscus allograft on the tibial surface or the reduction and fixation of the lateral capsule to the tibia.⁶³ However, as previously stated, based on the literature, no major adverse consequences have been linked to extrusion, so one cannot favour any technique over another.^{63,73}

Currently, most MAT procedures are performed by arthroscopy. Fixation of the meniscal horns may be achieved either by sutures passed through bone tunnels or bony fixation (press-fit, anchors, interference screws). Peripheral fixation is usually performed by combining all-inside with outside-in meniscus sutures.²⁶ Some technical tips are described in Table 3.

MAT in the pediatric population

There is a paucity of data concerning the application of MAT in the pediatric population.⁷⁷ The increasing participation of children in sports, including elite sports, has led to a rising number of sports-related injuries in children and adolescents. This results in a higher number of children

with premature loss of meniscus leading to early progressive degenerative joint disease. Discoid meniscus tears represent another possible cause of meniscus-deficient knees in youngsters, with further candidates for MAT.⁷⁷

Gelber et al advise that patients with open physis, might require an expectative attitude with clinical and MRI assessment every year, in order to follow the evolution of the articular cartilage's status.⁶³ If progressive cartilage deterioration is identified, a MAT may be suggested, even in the absence of clinical signs, beside considering that the clinical evidence in this population is low.⁶³

Rehabilitation

Concerning rehabilitation, once more there is no consensus. Some surgeons permit immediate weight-bearing while others recommend a variable period of non-weight-bearing (3 to 6 weeks). Similarly, some promote a period of immobilization, however, most surgeons permit early motion (in the first 2–3 weeks) from 0° to 60°. The rationale is that the movement of the menisci is minimal within this range. Therapy focuses on gradually restoring full knee extension, decreasing swelling and pain control. Another goal is recovery of quadriceps strength with isometric exercises, passive and active motion. After the first 3–4 weeks, gradual increase in knee flexion up to 90°, combined with progressive weight-bearing, and closed-chain kinetic exercises are advised. At 6–8 weeks after surgery, the patient should be capable to fully weight-bear, and at 4–6 months running on flat ground is usually encouraged.^{63,73} Forced flexion and pivoting maneuvers are avoided for the first 6–12 months.

Clinical outcome of MAT

The main goal of MAT is to prevent or delay the arthritic degeneration of the joint. However, it has not yet been confirmed whether this target is systematically accomplished.^{63,74,74} For many years, and to this day in some places, MAT was seen as an experimental procedure.⁵⁰ However, over time, MAT has provided reliable and reproducible favourable results if proper indications are followed.^{50,63,73} MAT has proven its effectiveness in reducing pain and improving function and quality of life.^{63,73} However, there are still some questions to address regarding the integration and longevity of the graft, the efficacy

of MAT in prevention of osteoarthritis and the possibility of returning to high-demand activities.⁴⁹

A recent meta-analysis reported the published outcome of 2977 patients (3157 allografts).⁷³ Thirty-eight per cent of cases received an isolated MAT while the remaining underwent at least one concomitant procedure. In different studies, clinical assessment included Lysholm, Knee Injury and Osteoarthritis Outcome (KOOS), International Knee Documentation Committee (IKDC) and Visual Analogue Scale (VAS) scores. A significant improvement in all scores and a good patient satisfaction at long-term follow-up was demonstrated. The mean overall survival rate reported was 80.9%. There was a negative evolution in radiological osteoarthritis with at least one grade lowering in 1760 of the studied patients. Concomitant procedures had no significant effect on outcome, although age at transplantation was determined as a negative prognostic factor and body mass index had a slight negative correlation with the outcome of MAT. The identified rate of complications was equivalent to standard meniscal repair surgery.⁷³

It has been recently stated, on a short-term follow-up, that it is possible to return to high-demand sports (e.g. soccer, basketball, rugby and volleyball) after MAT. Zaffagnini et al reported 74% of patients returning to sports, 50% of these at the previous level of participation, after 8 months of rehabilitation.^{51,78–80} Similar results have been reported from other small series at short term follow-up^{51,79,80}. Given these facts, such data must be considered with care before more definitive and broad conclusions can be drawn.

Concerning the pediatric population, there are few reports in the literature on the outcome of MAT.⁷⁷ MAT is an effective method for treating meniscal deficiency following irreparable tears in discoid meniscus based on a series that compared MAT in discoid versus nondiscoid knees at a minimum 2-year follow-up.⁸¹ Despite the fact that the discoid group had a significantly lower range of motion, functional scores improved similarly in both groups. A recent paper reported on 37 MAT procedures performed in 36 children, with mean age of 15 years, 84% lateral and 16% medial at 2-years follow-up, with at least similar improvements in functional outcomes as reported for adults.⁸² Moreover, another study reported 3 cases of MAT at 2-year follow-up (two after discoid meniscus and one after medial bucket-handle tear combined with anterior cruciate ligament rupture), with the authors concluding that MAT in skeletally immature patients leads to acceptable clinical outcomes without growth deviation.⁸³

There is limited analysis of the cost-effectiveness of MAT; however, a recent analysis concluded that MAT needs to be approximately one-third more effective in delaying osteoarthritis in post-meniscectomized knees to be considered as cost-effective.⁸⁴ According to the same

study, MAT is more cost-effective for young patients (20–29 years old) and less cost-effective in obese patients (Body Mass Index of 30–35).⁸⁴ However, further research is required.

Meniscus scaffold replacement (MSR)

Fundamentals, current options and clinical outcome of MSR

The concept of meniscal scaffolds was initiated in the 1990s.⁵⁶ Currently, two acellular meniscal scaffolds have been used in Europe for clinical application:⁸⁵ the collagen meniscus implant or ‘CMI’ (Ivy Sports Medicine, Lochhamer, Germany) which is based on type I bovine collagen matrix;^{56,85} and the polyurethane-based also known as ‘ACTIFIT’ (Orteq Bioengineering, London, UK).^{86,87} Partial meniscus substitution with scaffolds and MAT have different indications as scaffold implantation requires that the meniscal roots and peripheral rim remains preserved.⁷⁴ However, they were developed to overcome the consequences of symptomatic knees after partial meniscectomies.

A summary of indications and contraindications on the use of acellular meniscal scaffolds for partial meniscal replacement is presented in Table 1.

Partial meniscus replacement by using scaffolds has been used with promising short-term clinical results for chronic partial meniscus defects.^{85,88–90} Clinical studies are based on acellular scaffolds while basic science researchers promote some biological enhancement.⁸⁵ Its application in acute cases remains somewhat limited and controversial.⁹¹ Technically, these procedures are also performed arthroscopically (Fig. 4). A measurement of the defect is performed during surgery and the scaffold is cut in order to match the defect. A slight oversizing of the scaffold is recommended. A suture can be used in the middle of the scaffold to assist in bringing the scaffold into place (similarly to the technique described for MAT), and fixation is performed to the meniscus remnant by means of vertical and horizontal sutures by all-inside and/or outside-in/inside-out techniques.

Both scaffolds achieved positive clinical results in the treatment of partial medial and lateral meniscal loss with self-reported pain reduction, improved knee function and quality of life. These results have been described for both the polyurethane-based and the collagen-based implants. (745,88–90,92–103) Moreover, meniscal replacement by both implants has proven to be safe for medial and lateral menisci.^{85,97} However, the final tissue obtained has been documented as different from the native meniscus (Fig. 5).⁸⁵ Resorption of the implants⁹⁸ and extrusion (Fig. 6) of the scaffold has been a matter of growing debate and concern.¹⁰¹ Nevertheless, the clinical outcome does not completely correlate with the imaging findings,

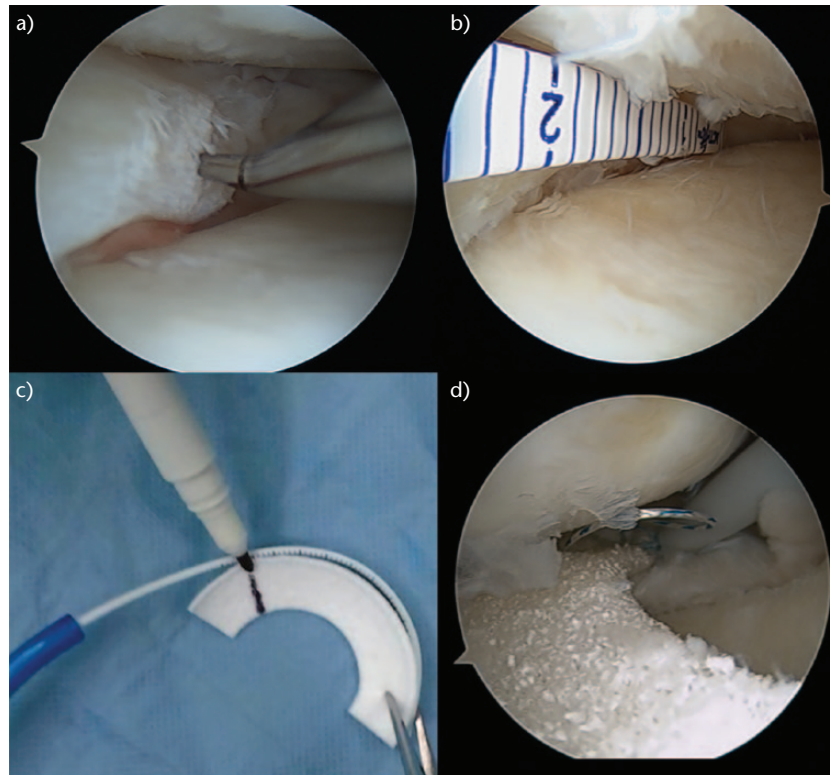


Fig. 4 (a) Debridement and trephination of the peripheral meniscus rim to enhance healing prior to scaffold implantation; (b) measurement of the defect; (c) cutting of the scaffold with slight oversizing; (d) suturing the scaffold with all-inside technique.

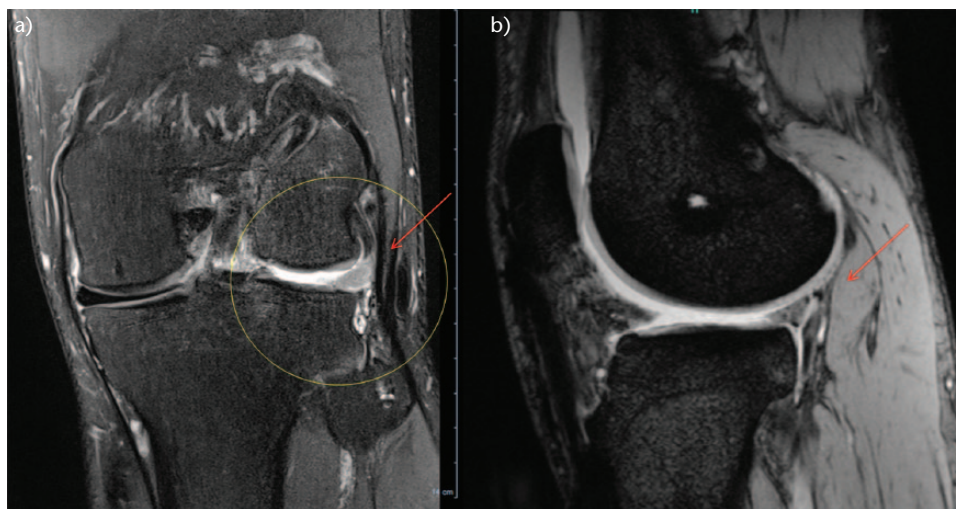


Fig. 5 (a) Frontal and (b) lateral MRI view of lateral ACTIFIT (yellow circle; red arrows) with morphologic Genovese Grade 3 and signal intensity grade 2 after 5 years' implantation.

with patients' satisfaction and clinical scores being reported has higher than for imaging assessment and outcome.⁹⁸

The ACTIFIT scaffold consists of porous polycaprolactone and urethane segments which degrade slowly over a

5-year period and it aimed to provide a template for tissue ingrowth (Fig. 7).¹⁰⁴ However, MRI assessment, including Genovese score (assessment of size/morphology and signal intensity; each in 3 degrees),¹⁰⁵ often shows extrusion, reduced volume with time or even complete resorption

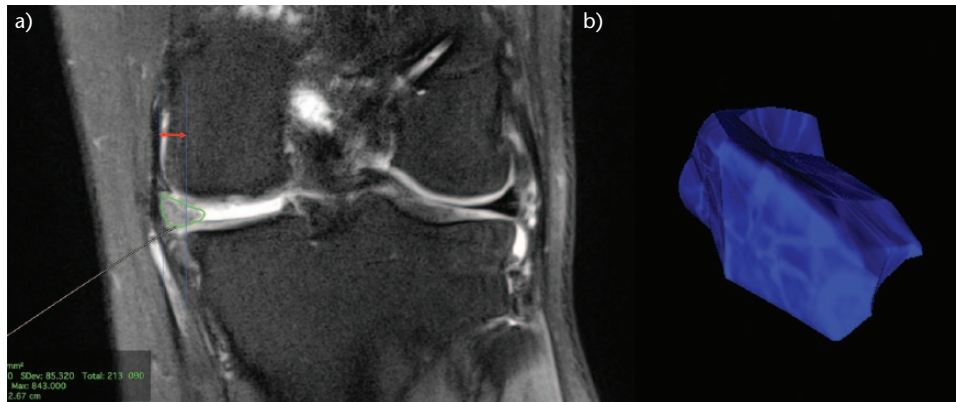


Fig. 6 (a) MRI of a medial ACTIFIT extrusion (red arrows between thin blue lines) with morphologic Genovese Grade 3 and signal intensity grade 2 after 5 years' implantation. (b) 3-D reconstruction of the morphology of the implanted ACTIFIT.

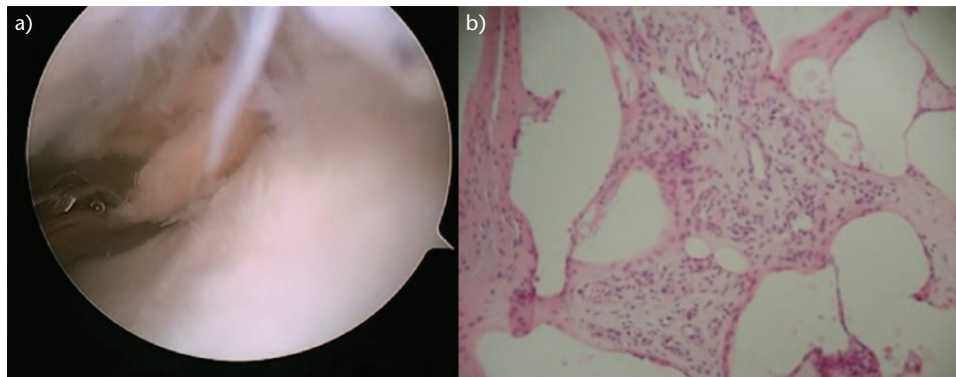


Fig. 7 (a) Arthroscopic view of an ACTIFIT 2 years after implantation (the colour and texture are very different than the native meniscus); (b) haematoxylin and eosin stain (H&E) histology of ACTIFIT biopsy showing increased neovascularization and paucity of fibrochondrocytes when compared to native meniscus.

Source: Courtesy of Dr. Pedro Pessoa and Dr. Manuel Virgolino.

without reaching normal signal.⁹⁸ The CMI theoretically has a more biocompatible profile (collagen type I from bovine Achilles tendons) and was 'designed as a regeneration template into which the body's own tissue may grow'.⁵⁶ According to a recent systematic review, higher rates of scaffolds with reduced size were found at longer follow-up when compared with initial evaluations.⁸⁹ However, MRI signal intensity was reported as more similar to normal meniscus.⁸⁹

A recent systematic review comparing both scaffolds has reported on 658 patients (347 ACTIFIT, 311 CMI) at mean 45 months' follow-up.⁹⁷ Treatment failure occurred in 9.9% of patients receiving the ACTIFIT scaffold and 6.7% of patients receiving CMI. However, failure rate ranged from 0% to 31.8% amongst the evaluated studies.⁹⁷ Such discrepancy might be due to a variable definition of 'failure' or publication bias (authors are less prone to publish failures).¹⁰⁶ Moreover, the presence of

concomitant surgeries such as anterior cruciate ligament reconstruction (ACLR) and high tibial osteotomy (HTO) could have an influence on these results. Clinical outcome evaluation using VAS for pain, Lysholm Knee Scores, and Tegner Activity Scores improved from pre-operatively to latest follow-up for both scaffolds. The KOOS and IKDC scores improved from pre-operatively to latest follow-up only for ACTIFIT patients. Overall, patients receiving CMI scaffolds had higher grades for Genovese morphology and signal intensity (Fig. 4) when compared to ACTIFIT scaffold patients. In conclusion, the authors stated that patients might expect improved clinical outcome with either or both scaffolds, particularly when combined with ACLR or HTO.⁹⁷

There is one single case report describing return to sports activity at pre-injury level on a professional footballer after partial lateral meniscus replacement, 10 months after the operation, with lasting results.¹⁰⁷

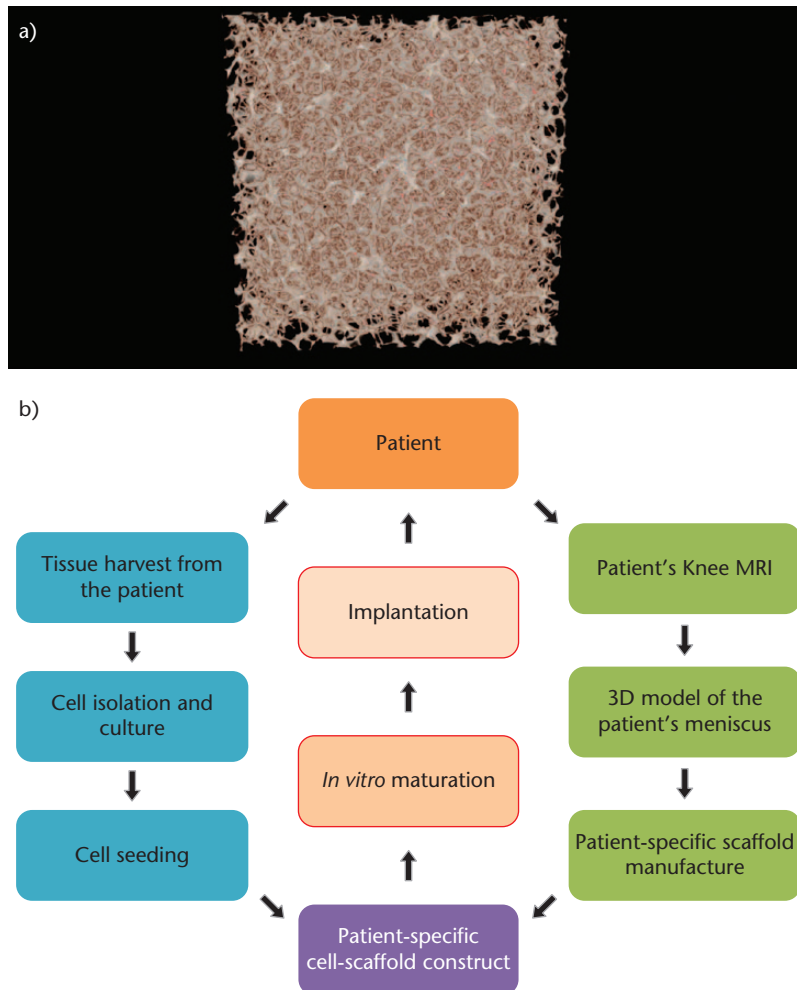


Fig. 8 A silk fibroin scaffold for meniscus tissue engineering applications.

Therefore there is insufficient evidence in the literature supporting the use of these strategies when aiming for return to high-level sports.

Concerning rehabilitation protocol as described for MAT, there is a lack of consensus. However, despite the fact that this surgery of scaffold implantation is usually less invasive as it does not require bone tunnels for root fixation, the basics of rehabilitation are quite similar to those for MAT. However, a lower inflammatory post-operative response is expected.

Road for future in meniscus replacement

Since the implications of meniscectomy have been recognized (loss or diminished meniscus function), the future developments of meniscus replacement are strongly motivated by a clinical need.

Synthetic, non-anatomical approaches are being tested. NUsurface Meniscus Implant[®], intends to function

as a spacer, trying to redistribute loads transmitted across the knee joint, even if it does not replace normal anatomy. It is made of polycarbonate-urethane, and is under clinical trial and development.^{74,108} Despite early favorable clinical outcome reported from developers, some complications have been described (e.g. dislocation).¹⁰⁹

Tissue Engineering and Regenerative Medicine (TERM) approaches aim to develop new implants, biomaterials (Fig. 8), biological enhancement of surgical approaches (cells, growth factors, proteins, nanotechnology, hydrogels), amongst many other advanced approaches aiming to fix, replace or improve any biological system.^{44,45,62,110,111}

Gene therapy is another promising research field dedicated to improving meniscal repair or replacement.^{112,113} Growth factor technology is under intense development aiming to permit the selective control of cell activity to accelerate tissue healing, in future.^{44,114} Nevertheless, the understanding of the complex mechanisms of cell

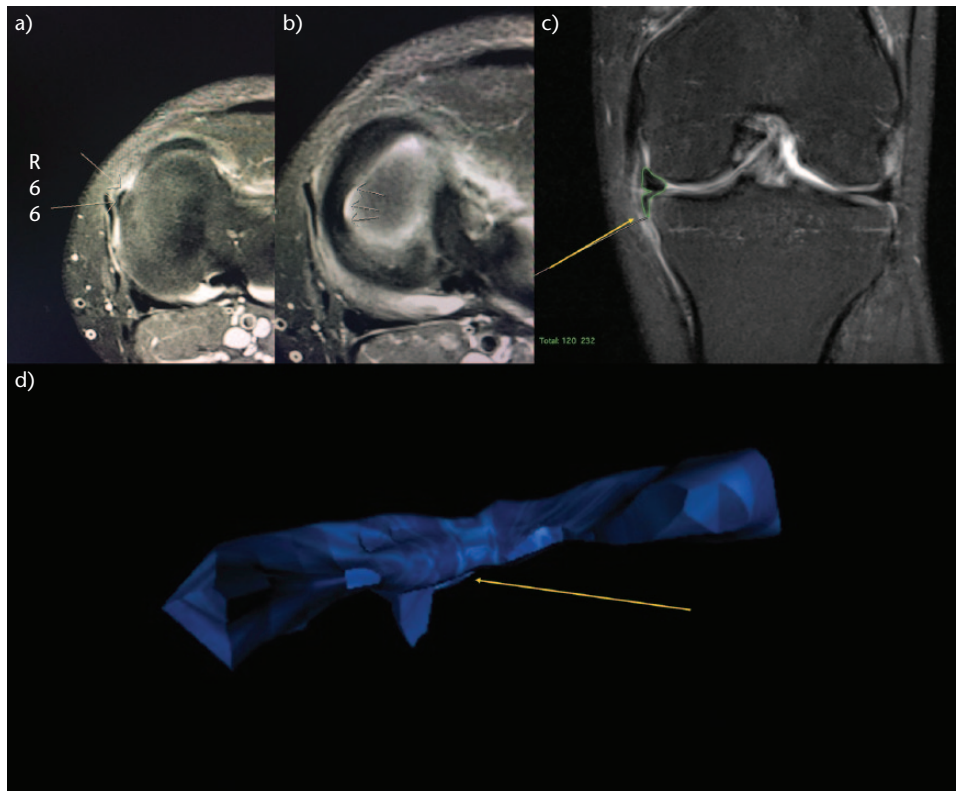


Fig. 9 (a) and (b) MRI axial views showing meniscus tear dislocated to the meniscotibial recess (white arrows); (c) frontal MRI view of the same lesion with the meniscus fragment contoured in green (yellow arrow); (d) 3-D MRI-based image showing the tear and enabling use for rapid prototype scaffold printing.

function, activation and differentiation, together with comprehension of their interaction, is far from being achieved. Mesenchymal stem cell (MSC) research is another field under powerful expansion.^{44,111,113,115–117} A clinical study using human adult MSCs injected into the knee for treatment of symptomatic consequences from partial medial meniscectomy has shown a significant increase in the volume of the menisci as assessed by MRI at 2-years follow-up.¹¹⁸ The more advanced strategy of using cell-laden scaffolds (constructs) for meniscus repair has been described in several pre-clinical studies.^{44,85} However, a fibrocartilage with similar biological and biomechanical characteristics to the native meniscus has not been consistently obtained so far. Maturation of such constructs in dedicated bioreactors might be required in the process (simulating the biomechanical environment of the meniscus, thus assisting cells in their activity to produce a similar tissue).^{95,119}

When considering acellular strategies, the most critical component of meniscus TERM is the scaffold. The scaffold is used as a replacement for the missing tissue, and receives and interrelates with the cells that are either previously seeded in vitro, and/or migrate after surgical placement. The size and shape of the scaffold are critical

to its function.^{27,59,60,120,121} With the developments in medical imaging (Fig. 9), the scaffold is manufactured in a patient-specific way. Additional developments could be obtainable through new technologies such as rapid prototyping (RP).^{60,61,121} Besides permitting patient-specific scaffolds with the accurate architecture, it could ease the correct distribution of different cells within the meniscus implant.^{60,61} Cengiz et al⁶⁰ have described how to produce patient-specific meniscal implants from medical images.

Once the cells and the bioactive molecules are introduced into the scaffold, and the implant is cultured and matured within a bioreactor, the extracellular matrix will start to be synthesized inside the scaffold leading to final formation of the tissue, hopefully similar to the native. Once this is achieved we could have an implant for adequate and effective replacement. This is the future road we hope for, creating an endless source of meniscal implants without further clinical complications or limitations.^{44,85,111}

Many materials are under study as possibilities for meniscal scaffolds: collagen,^{122–125} poly(lactic acid) based,^{126–128} poly(glycolic acid),^{128,129} poly(lactic-co-glycolic acid),^{130,131} polycaprolactone,^{116,132} hyaluronic acid/polycaprolactone,^{133–135} hyaluronic acid/gelatin,^{115,136,137} poly(glycolic

acid)/hyaluronic acid,¹³⁸ silk-based,^{139–141} gelatin/chitosan,¹⁴² bacterial cellulose,^{143,144} and vicryl.¹⁴⁵

Nanobiomaterials have been considered for TERM applications.^{146,147} These can be produced with different methods into various structures including nanofibres,^{148,149} nanoparticles,¹⁵⁰ nanotubes¹⁵¹ and nanofilms.¹⁵² Nanotechnology also permits modification of the surfaces of biomaterials.¹⁵³ Biologics are biologically active natural components that can activate cells and enhance tissue healing, including specific growth factors^{154,155} and platelet rich plasma (PRP).¹¹⁴ PRP is an autologous source of a ‘cocktail’ of several autologous growth factors (including platelet-derived growth factor, endothelial growth factor, and transforming growth factor) as well as anti- and pro-inflammatory cytokines (including interleukin-4, -8, -13, -17, tumor necrosis factor- α , and interferon- α) which might influence the process of tissue healing.^{156–160} There are methodological limitations in current studies including the preparation of PRP, and inclusion/type of cells and scaffolds as well as the lack of standardization on evaluating the outcomes PRP clinical studies, which limits further conclusions regarding this therapy.⁵⁹ Hydrogels can serve as scaffolds, carriers of cells, or biologics, or can even control the neovascularization process.^{161–163}

TERM research is engaged in the search for effective partial but also total meniscal replacement, which has proven to be an even more demanding task. However, the first steps have been made. Lee et al, using a sheep model,¹⁶⁴ produced polycaprolactone scaffolds which were 3-D printed into anatomically correct scaffolds. These were loaded with microspheres for the controlled release (in time and space) of connective tissue growth factor and transforming growth factor- β . The release of growth factors induced autologous cells to differentiate and generate zone-specific collagen type I and II in order to obtain a neotissue biologically and biomechanically closer to the native tissue.¹⁶⁴ This study summarizes the application of advanced TERM strategies for meniscus replacement.

Considering scaffolds for complete meniscal replacement, a recent study on a sheep model suggests total medial meniscal replacement could successfully be performed (one year follow-up) by using a cross-linked collagen-hyaluronan sponge reinforced with synthetic, resorbable poly(DTD DD) fibres.¹⁶⁵ The anchorage of the scaffold to the tibial plateau was carried out using titanium interference screws at the anterior and posterior roots and was peripherally sutured to the medial capsule achieving promising results.¹⁶⁵

Conclusions and take-home messages

Arthroscopic meniscectomy is still one of the most frequent orthopedic procedures given the high incidence

of meniscus lesions. This option has provided satisfactory outcome for the treatment of irreparable meniscal lesions in some patients, but it might also lead to subsequent joint degeneration due to the loss of meniscal function.

With the growing knowledge of the menisci functions in the knee joint homeostasis, there is a growing trend towards meniscal preservation. There has been a gradual increase in indications for meniscal repair rather than meniscectomy.

When preservation is no longer possible, replacement is the next step for symptomatic patients or those with evidence of systematic progression towards arthritis at a young age.

Meniscal allograft transplantation (MAT) is no longer an experimental treatment and enables favourable outcome in the long term. Concerning preservation and sterilization methods, cryopreservation is the most frequently used, with a growing trend towards fresh allograft. As for technical choices for MAT fixation, bone block seems to be technically more demanding but has lower incidence of extrusion and re-rupture. Sizing methods are required in order to obtain matching between graft and patient which influences outcome.

There is no straight correlation between extrusion and clinical outcome.

Application of MAT in skeletally immature patients and high-demand athletes is in its early stages and under research.

There are two clinically available meniscus scaffolds for partial meniscus replacement when indicated (collagen-based and polyurethane-based). Despite promising clinical results, imaging assessment has shown that the achieved tissue is different than the native meniscus. Both enable similar clinical outcome but diminished volume with time has been described for both.

Despite the favourable clinical outcome, it is still debatable whether meniscus replacement enables prevention of osteoarthritis.

While most basic-science researchers are enhancing scaffolds for this propose, most clinical studies report only to acellular scaffold replacement.

Current TERM strategies have not yet met the clinical needs. The problems are related to the lack of simultaneous success in biology (tissue infiltration, neovascularization, matrix maturation) and biomechanics (capable to withstand suture and early mechanical function) of the scaffolds. The achieved tissue, so far, does not completely achieves the biologic and mechanical requirements of the native meniscus. However, we have found a road: a combination of agents, methods and technologies. The pathway is promising but the walk will certainly be long.

AUTHOR INFORMATION

¹Orthopedic Department of Póvoa de Varzim - Vila do Conde Hospital Centre, Vila do Conde, Portugal.

²Ripoll y De Prado Sports Clinic, Murcia-Madrid, FIFA Medical Centre of Excellence, Madrid, Spain.

³International Centre of Sports Traumatology of the Ave, Vila do Conde, Portugal.

⁴3Bs Research Group, I3Bs, Research Institute on Biomaterials, Biodegradables and Biomimetics, University of Minho, Headquarters of the European Institute of Excellence on Tissue Engineering and Regenerative Medicine, AvePark, Parque de Ciência e Tecnologia, Barco, Guimarães, Portugal.

⁵ICVS/3Bs, PT Government Associate Laboratory, Braga/Guimarães, Portugal.

⁶Clínica do Dragão, Espregueira-Mendes Sports Centre, FIFA Medical Centre of Excellence, Porto, Portugal.

⁷Orthopedic Department, University of Minho, Braga, Portugal.

⁸Orthopaedic Department, Hospital del Mar, Universitat Autònoma de Barcelona, Barcelona, Spain.

⁹The Discoveries Centre for Regenerative and Precision Medicine, Headquarters at University of Minho, Avepark, Barco, Guimarães, Portugal.

Correspondence should be sent to: Hélder Pereira, Orthopedic Department of Póvoa de Varzim-Vila do Conde, Porto, Portugal.

Email: helderduartepereira@gmail.com

ACKNOWLEDGEMENTS

I. F. Cengiz thanks the Portuguese Foundation for Science and Technology (FCT) for the Ph.D. scholarship (SFRH/BD/99555/2014).

J. M. Oliveira also thanks the FCT for the funds provided under the program Investigador FCT 2012 and 2015 (IF/00423/2012 and IF/01285/2015).

The authors thank Dr. Pedro Pessoa and Dr. Manuel Virgolino for the courtesy of providing Figure 7.

ICMJE CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest in relation to this work.

FUNDING STATEMENT

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

LICENCE

© 2019 The author(s)

This article is distributed under the terms of the Creative Commons Attribution-Non Commercial 4.0 International (CC BY-NC 4.0) licence (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed.

REFERENCES

1. Clayton RAE, Court-Brown CM. The epidemiology of musculoskeletal tendinous and ligamentous injuries. *Injury* 2008;39:1338–1344.
2. Verdonk R. The meniscus: past, present and future. *Knee Surg Sports Traumatol Arthrosc* 2011;19:145–146.
3. Smillie IS. Injuries of the knee joint. *Fourth ed.* Edinburgh: Churchill Livingstone, 1972.
4. Greis PE, Bardana DD, Holmstrom MC, Burks RT. Meniscal injury: I. Basic science and evaluation. *J Am Acad Orthop Surg* 2002;10:168–176.
5. Pereira H, Cengiz IF, Silva-Correia J, et al. *Histology-ultrastructure-biology: surgery of the Meniscus.* Berlin, Heidelberg: Springer, 2016:23–33.
6. Pereira H, Varatojo R, Sevivas N, et al. Physiopathology of the meniscal lesions. In: Hulet C, Pereira H, Peretti G, Denti M, eds. *Surgery of the meniscus.* Berlin, Heidelberg: Springer, 2016:47–61.
7. Cengiz IF, Silva-Correia J, Pereira H, Espregueira-Mendes J, Oliveira JM, Reis RL. *Basics of the meniscus: regenerative strategies for the treatment of knee joint disabilities.* Berlin, Heidelberg: Springer, 2017:237–247.
8. McDevitt CA, Webber RJ. The ultrastructure and biochemistry of meniscal cartilage. *Clin Orthop Relat Res* 1990;252:8–18.
9. Tudor F, McDermott ID, Myers P. Meniscal repair: a review of current practice. *Orthop Trauma* 2014;28:88–96.
10. Sanchez-Adams J, Athanasiou KA. The knee meniscus: a complex tissue of diverse cells. *Cell Mol Bioeng* 2009;2:332–340.
11. Verdonk PC, Forsyth RG, Wang J, et al. Characterisation of human knee meniscus cell phenotype. *Osteoarthritis Cartilage* 2005;13:548–560.
12. Cengiz IF, Pereira H, Pêgo JM, et al. Segmental and regional quantification of 3D cellular density of human meniscus from osteoarthritic knee. *J Tissue Eng Regen Med* 2017;11:1844–1852.
13. Pereira H, Caridade SG, Frias AM, Silva-Correia J, Pereira DR, Cengiz IF, et al. Biomechanical and cellular segmental characterization of human meniscus: building the basis for tissue engineering therapies. *Osteoarthritis Cartilage* 2014;22:1271–1281.
14. McDermott ID, Masouros SD, Amis AA. Biomechanics of the menisci of the knee. *Curr Orthop* 2008;22:193–201.
15. Walker PS, Hajek JV. The load-bearing area in the knee joint. *J Biomech* 1972;5:581–589.
16. Bourne RB, Finlay JB, Papadopoulos P, Andrae P. The effect of medial meniscectomy on strain distribution in the proximal part of the tibia. *J Bone Joint Surg Am* 1984;66:1431–1437.
17. Śmigielski R, Becker R, Zdanowicz U, Cizek B. Medial meniscus anatomy: from basic science to treatment. *Knee Surg Sports Traumatol Arthrosc* 2015;23:8–14.
18. Arnoczky SP, Warren RF. Microvasculature of the human meniscus. *Am J Sports Med* 1982;10:90–95.
19. Mosich GM, Lieu V, Ebramzadeh E, Beck JJ. Operative treatment of isolated meniscus injuries in adolescent patients: a meta-analysis and review. *Sports Health* 2018;10:311–316.
20. Allen PR, Denham RA, Swan AV. Late degenerative changes after meniscectomy: factors affecting the knee after operation. *J Bone Joint Surg Br* 1984;66:666–671.
21. Fairbank TJ. Knee joint changes after meniscectomy. *J Bone Joint Surg Br* 1948;30B:664–670.
22. Jackson JP. Degenerative changes in the knee after meniscectomy. *BMJ* 1968;2:525–527.
23. McDermott ID, Amis AA. The consequences of meniscectomy. *J Bone Joint Surg Br* 2006;88:1549–1556.
24. Salata MJ, Gibbs AE, Sekiya JK. A systematic review of clinical outcomes in patients undergoing meniscectomy. *Am J Sports Med* 2010;38:1907–1916.
25. Paxton ES, Stock MV, Brophy RH. Meniscal repair versus partial meniscectomy: a systematic review comparing reoperation rates and clinical outcomes. *Arthroscopy* 2011;27:1275–1288.

26. **Pereira H, Cengiz IF, Silva-Correia J, et al.** *Meniscal repair: indications, techniques, and outcome.* *Arthroscopy.* Berlin, Heidelberg: Springer, 2016:125–142.
27. **Cengiz IF, Pereira H, Espregueira-Mendes J, et al.** Treatments of meniscus lesions of the knee: current concepts and future perspectives. *Regen Eng Transl Med* 2017;3:32–50.
28. **Cengiz IF, et al.** Meniscal lesions: from basic science to clinical management in footballers. In: Espregueira-Mendes, J, van Dijk, CN, Neyret, P, Cohen, M, Della Villa, S, Pereira, H, Oliveira, M, eds. *Injuries and Health Problems in Football.* Berlin, Heidelberg: Springer 2017:145–163.
29. **Anderson AF, Irrgang JJ, Dunn W, et al.** Interobserver reliability of the International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (ISAKOS) classification of meniscal tears. *Am J Sports Med* 2011;39:926–932.
30. **Beaufils P, Englund M, Järvinen TLN, Pereira H, Pujol N.** How to share guidelines in daily practice on meniscus repair, degenerate meniscal lesion, and meniscectomy. In: Zaffagnini S, Becker R, Kerkhoffs GMMJ, Espregueira-Mendes J, van Dijk CN, eds. *ESSKA Instructional Course Lecture Book Amsterdam 2014.* Berlin, Heidelberg: Springer, 2014:97–112.
31. **ESSKA Meniscus Consensus Project.** http://c.ymcdn.com/sites/www.esska.org/resource/resmgr/Docs/2016_DML_full_text.pdf (date last accessed 17 November 2016).
32. **Denti M, Espregueira-Mendes J, Pereira H, Raoulis V, Hantes M.** *Traumatic meniscal lesions: surgery of the meniscus.* Berlin, Heidelberg: Springer, 2016: 67–78.
33. **Pereira H, Cengiz IF, Silva-Correia J, Oliveira JM, Reis RL, Espregueira-Mendes J.** *The role of arthroscopy in the treatment of degenerative meniscus tear.* *Arthroscopy.* Berlin, Heidelberg: Springer, 2016:107–117.
34. **Poehling GG, Ruch DS, Chabon SJ.** The landscape of meniscal injuries. *Clin Sports Med* 1990;9:539–549.
35. **Ruiz-Ibán MA, Diaz-Heredia J, Elías-Martín E, Moros-Marco S, Cebreiro Martínez Del Val I.** Repair of meniscal tears associated with tibial plateau fractures: a review of 15 cases. *Am J Sports Med* 2012;40:2289–2295.
36. **Frank RM, Lee S, Cotter EJ, Hannon CP, Leroux T, Cole BJ.** Outcomes of osteochondral allograft transplantation with and without concomitant meniscus allograft transplantation: a comparative matched group analysis. *Am J Sports Med* 2018;46:573–580.
37. **Gelber PE, Erquicia JI, Ramirez-Bermejo E, Fariñas O, Monllau JC.** Fresh osteochondral and meniscus allografting for post-traumatic tibial plateau defects. *Arthrosc Tech* 2018;7:e661–e667.
38. **Smillie IS.** The current pattern of the pathology of meniscus tears. *Proc R Soc Med* 1968;61:44–45.
39. **Christoforakis J, Pradhan R, Sanchez-Ballester J, Hunt N, Strachan RK.** Is there an association between articular cartilage changes and degenerative meniscus tears? *Arthroscopy* 2005;21:1366–1369.
40. **Yim JH, Seon JK, Song EK, et al.** A comparative study of meniscectomy and nonoperative treatment for degenerative horizontal tears of the medial meniscus. *Am J Sports Med* 2013;41:1565–1570.
41. **LaPrade CM, Foad A, Smith SD, et al.** Biomechanical consequences of a nonanatomic posterior medial meniscal root repair. *Am J Sports Med* 2015;43:912–920.
42. **Koenig JH, Ranawat AS, Umans HR, Difelice GS.** Meniscal root tears: diagnosis and treatment. *Arthroscopy* 2009;25:1025–1032.
43. **Pujol N, Barbier O, Boisrenoult P, Beaufils P.** Amount of meniscal resection after failed meniscal repair. *Am J Sports Med* 2011;39:1648–1652.
44. **Pereira H, Silva-Correia J, Oliveira JM, Reis RL, Espregueira-Mendes J.** Future trends in the treatment of meniscus lesions: from repair to regeneration. In: Verdonk R, Espregueira-Mendes J, Monllau JC, eds. *Meniscal transplantation.* Heidelberg, New York, Dordrecht, London: Springer, 2013:103–112.
45. **Pereira H, Cengiz IF, Vilela C, et al.** *Emerging concepts in treating cartilage, osteochondral defects, and osteoarthritis of the knee and ankle. Osteochondral tissue engineering.* Berlin, Heidelberg: Springer, 2018:25–62.
46. **Zukor D, Brooks P, Gross A, Cameron J.** Meniscal allograft experimental and clinical study. *Orthop Rev* 1988;17:522–550.
47. **Locht RC, Gross AE, Langer F.** Late osteochondral allograft resurfacing for tibial plateau fractures. *J Bone Joint Surg Am* 1984;66:328–335.
48. **Milachowski KA, Weismeier K, Wirth CJ.** Homologous meniscus transplantation: experimental and clinical results. *Int Orthop* 1989;13:1–11.
49. **Monllau JC, González-Lucena G, Gelber PE, Pelfort X.** Allograft meniscus transplantation: a current review. *Tech Knee Surg* 2010;9:107–113.
50. **Elattar M, Dhollander A, Verdonk R, Almqvist KF, Verdonk P.** Twenty-six years of meniscal allograft transplantation: is it still experimental? A meta-analysis of 44 trials. *Knee Surg Sports Traumatol Arthrosc* 2011;19:147–157.
51. **Chalmers PN, Karas V, Sherman SL, Cole BJ.** Return to high-level sport after meniscal allograft transplantation. *Arthroscopy* 2013;29:539–544.
52. **Nyland J, Campbell K, Kalloub A, Strauss EJ, Kuban K, Caborn DNM.** Medial meniscus grafting restores normal tibiofemoral contact pressures. *Arch Orthop Trauma Surg* 2018;138:361–367.
53. **Mahmoud A, Young J, Bullock-Saxton J, Myers P.** Meniscal allograft transplantation: the effect of cartilage status on survivorship and clinical outcome. *Arthroscopy* 2018;34:1871–1876.
54. **Gitelis ME, Frank RM, Meyer MA, Cvetanovich G, Cole BJ.** 5 points on meniscal allograft transplantation. *Am J Orthop (Belle Mead NJ)* 2018;47:1–11.
55. **Lee BS, Bin SI, Kim JM, Kim WK, Choi JW.** Survivorship after meniscal allograft transplantation according to articular cartilage status. *Am J Sports Med* 2017;45:1095–1101.
56. **Rodkey WG, Steadman JR, Li ST.** A clinical study of collagen meniscus implants to restore the injured meniscus. *Clin Orthop Relat Res* 1999;367 Suppl:S281–S292.
57. **Tírico LE, Demange MK, Santos LA, et al.** Development of a fresh osteochondral allograft program outside North America. *Cartilage* 2016;7:222–228.
58. **Pereira H, Cengiz IF, Silva-Correia J, Oliveira JM, Reis RL, Espregueira-Mendes J.** Human meniscus: from biology to tissue engineering strategies. In: Doral M, Karlsson J, eds. *Sports injuries.* Berlin, Heidelberg: Springer, 2013:1–16.
59. **Cengiz IF, Silva-Correia J, Pereira H, Espregueira-Mendes J, Oliveira JM, Reis RL.** *Advanced regenerative strategies for human knee meniscus: regenerative strategies for the treatment of knee joint disabilities.* Berlin, Heidelberg: Springer, 2017:271–285.
60. **Cengiz I, Pitikakis M, Cesario L, et al.** Building the basis for patient-specific meniscal scaffolds: from human knee MRI to fabrication of 3D printed scaffolds. *Bioprinting* 2016;1:2:1–10.
61. **Cengiz IF, Pereira H, Pitikakis M, Espregueira-Mendes J, Oliveira JM, Reis RL.** *Building the basis for patient-specific meniscal scaffolds: bio-orthopaedics.* Berlin, Heidelberg: Springer, 2017:411–418.

- 62. Cengiz IF, Pereira H, de Girolamo L, et al.** Orthopaedic regenerative tissue engineering en route to the holy grail: disequilibrium between the demand and the supply in the operating room. *J Exp Orthop* 2018;5:14.
- 63. Gelber PE, Verdonk P, Getgood AM, Monllau JC.** Meniscal transplantation: state of the art. *J ISAKOS* 2017;2:339–349.
- 64. Gelber PE, Gonzalez G, Lloreta JL, Reina F, Caceres E, Monllau JC.** Freezing causes changes in the meniscus collagen net: a new ultrastructural meniscus disarray scale. *Knee Surg Sports Traumatol Arthrosc* 2008;16:353–359.
- 65. Mickiewicz P, Binkowski M, Bursig H, Wróbel Z.** Preservation and sterilization methods of the meniscal allografts: literature review. *Cell Tissue Bank* 2014;15:307–317.
- 66. Buck BE, Resnick L, Shah SM, Malinin TI.** Human immunodeficiency virus cultured from bone: implications for transplantation. *Clin Orthop Relat Res* 1990;251:249–253.
- 67. Kainer MA, Linden JV, Whaley DN, et al.** Clostridium infections associated with musculoskeletal-tissue allografts. *N Engl J Med* 2004;350:2564–2571.
- 68. Frank RM, Cole BJ.** Meniscus transplantation. *Curr Rev Musculoskelet Med* 2015;8:443–450.
- 69. Abat F, Gelber PE, Erquicia JI, Pelfort X, Gonzalez-Lucena G, Monllau JC.** Suture-only fixation technique leads to a higher degree of extrusion than bony fixation in meniscal allograft transplantation. *Am J Sports Med* 2012;40:1591–1596.
- 70. Pereira H, Caridade SG, Frias AM, et al.** Biomechanical and cellular segmental characterization of human meniscus: building the basis for tissue engineering therapies. *Osteoarthritis Cartilage* 2014;22:1271–1281.
- 71. De Coninck T, Vanrietvelde F, Seynaeve P, Verdonk P, Verstraete K.** MR imaging of the anatomy of the anterior horn of the medial meniscus. *Acta Radiol* 2017;58:464–471.
- 72. Pollard ME, Kang Q, Berg EE.** Radiographic sizing for meniscal transplantation. *Arthroscopy* 1995;11:684–687.
- 73. De Bruycker M, Verdonk PCM, Verdonk RC.** Meniscal allograft transplantation: a meta-analysis. *SICOT J* 2017;3:33.
- 74. Dangelmajer S, Familiari F, Simonetta R, Kaymakoglu M, Huri G.** Meniscal transplants and scaffolds: a systematic review of the literature. *Knee Surg Relat Res* 2017;29:3–10.
- 75. Koh YG, Moon HK, Kim YC, Park YS, Jo SB, Kwon SK.** Comparison of medial and lateral meniscal transplantation with regard to extrusion of the allograft, and its correlation with clinical outcome. *J Bone Joint Surg Br* 2012;94:190–193.
- 76. Jang SH, Kim JG, Ha JG, Shim JC.** Reducing the size of the meniscal allograft decreases the percentage of extrusion after meniscal allograft transplantation. *Arthroscopy* 2011;27:914–922.
- 77. Tuca M, Luderowski E, Rodeo S.** Meniscal transplant in children. *Curr Opin Pediatr* 2016;28:47–54.
- 78. Zaffagnini S, Grassi A, Marcheggiani Muccioli GM, et al.** Is sport activity possible after arthroscopic meniscal allograft transplantation? Midterm results in active patients. *Am J Sports Med* 2016;44:625–632.
- 79. Alentorn-Geli E, Vazquez RS, Diaz PA, Cusco X, Cugat R.** Arthroscopic meniscal transplants in soccer players: outcomes at 2- to 5-year follow-up. *Clin J Sport Med* 2010;20:340–343.
- 80. Marcacci M, Marcheggiani Muccioli GM, Grassi A, et al.** Arthroscopic meniscus allograft transplantation in male professional soccer players: a 36-month follow-up study. *Am J Sports Med* 2014;42:382–388.
- 81. Yoon KH, Lee SH, Park SY, Jung GY, Chung KY.** Meniscus allograft transplantation for discoid lateral meniscus: clinical comparison between discoid lateral meniscus and nondiscoid lateral meniscus. *Arthroscopy* 2014;30:724–730.
- 82. Riboh JC, Tilton AK, Cvetanovich GL, Campbell KA, Cole BJ.** Meniscal allograft transplantation in the adolescent population. *Arthroscopy* 2016 Jun;32:1133–1140.
- 83. Kocher MS, Tepolt FA, Vavken P.** Meniscus transplantation in skeletally immature patients. *J Pediatr Orthop B* 2016;25:343–348.
- 84. Bendich I, Rubenstein W, Mustafa Diab M, Feeley B.** Evaluating meniscus allograft transplant using a cost-effectiveness threshold analysis. *Knee* 2018;25:1171–1180.
- 85. Pereira H, Frias AM, Oliveira JM, Espregueira-Mendes J, Reis RL.** Tissue engineering and regenerative medicine strategies in meniscus lesions. *Arthroscopy* 2011;27:1706–1719.
- 86. Verdonk P, Beaufils P, Bellemans J, Djian P, Heinrichs EL, Huysse W, 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 Apr;40:844–853.
- 87. Verdonk R, Verdonk P, Huysse W, Forsyth R, Heinrichs EL.** Tissue ingrowth after implantation of a novel, biodegradable polyurethane scaffold for treatment of partial meniscal lesions. *Am J Sports Med* 2011 Apr;39:774–782.
- 88. Zaffagnini S, Grassi A, Marcheggiani Muccioli GM, Holsten D, Bulgheroni P, Monllau JC, et al.** Two-year clinical results of lateral collagen meniscus implant: a multicenter study. *Arthroscopy* 2015;31:1269–1278.
- 89. Zaffagnini S, Grassi A, Marcheggiani Muccioli GM, et al.** MRI evaluation of a collagen meniscus implant: a systematic review. *Knee Surg Sports Traumatol Arthrosc* 2015;23:3228–3237.
- 90. Bouyarmane H, Beaufils P, Pujol N, et al.** Polyurethane scaffold in lateral meniscus segmental defects: clinical outcomes at 24 months follow-up. *Orthop Traumatol Surg Res* 2014;100:153–157.
- 91. Rodkey WG, DeHaven KE, Montgomery WH III, et al.** Comparison of the collagen meniscus implant with partial meniscectomy: a prospective randomized trial. *J Bone Joint Surg Am* 2008;90:1413–1426.
- 92. Monllau JC, Gelber PE, Abat F, et al.** Outcome after partial medial meniscus substitution with the collagen meniscal implant at a minimum of 10 years' follow-up. *Arthroscopy* 2011;27:933–943.
- 93. Zaffagnini S, Marcheggiani Muccioli GM, Lopomo N, et al.** Prospective long-term outcomes of the medial collagen meniscus implant versus partial medial meniscectomy: a minimum 10-year follow-up study. *Am J Sports Med* 2011;39:977–985.
- 94. Warth RJ, Rodkey WG.** Resorbable collagen scaffolds for the treatment of meniscus defects: a systematic review. *Arthroscopy* 2015 May;31:927–941.
- 95. Bulgheroni E, Grassi A, Campagnolo M, Bulgheroni P, Mudhigere A, Gobbi A.** Comparative study of collagen versus synthetic-based meniscal scaffolds in treating meniscal deficiency in young active population. *Cartilage* 2016;7:29–38.
- 96. Dholander A, Verdonk P, Verdonk R.** Treatment of painful, irreparable partial meniscal defects with a polyurethane scaffold: midterm clinical outcomes and survival analysis. *Am J Sports Med* 2016;44:2615–2621.
- 97. Houck DA, Kraeutler MJ, Belk JW, McCarty EC, Bravman JT.** Similar clinical outcomes following collagen or polyurethane meniscal scaffold implantation: a systematic review. *Knee Surg Sports Traumatol Arthrosc* 2018;26:2259–2269.

- 98. Monllau JC, Poggioli F, Erquicia J, et al.** Magnetic resonance imaging and functional outcomes after a polyurethane meniscal scaffold implantation: minimum 5-year follow-up. *Arthroscopy* 2018;34:1621–1627.
- 99. Shin YS, Lee HN, Sim HB, Kim HJ, Lee DH.** Polyurethane meniscal scaffolds lead to better clinical outcomes but worse articular cartilage status and greater absolute meniscal extrusion. *Knee Surg Sports Traumatol Arthrosc* 2018;26:2227–2238.
- 100. Gelber PE, Isart A, Erquicia JI, Pelfort X, Tey-Pons M, Monllau JC.** Partial meniscus substitution with a polyurethane scaffold does not improve outcome after an open-wedge high tibial osteotomy. *Knee Surg Sports Traumatol Arthrosc* 2015;23:334–339.
- 101. Gelber PE, Petrica AM, Isart A, Mari-Molina R, Monllau JC.** The magnetic resonance aspect of a polyurethane meniscal scaffold is worse in advanced cartilage defects without deterioration of clinical outcomes after a minimum two-year follow-up. *Knee* 2015;22:389–394.
- 102. Bulgheroni P, Bulgheroni E, Regazzola G, Mazzola C.** Polyurethane scaffold for the treatment of partial meniscal tears: clinical results with a minimum two-year follow-up. *Joints* 2014;1:161–166.
- 103. Zaffagnini S, Giordano G, Vascellari A, et al.** Arthroscopic collagen meniscus implant results at 6 to 8 years follow up. *Knee Surg Sports Traumatol Arthrosc* 2007;15:175–183.
- 104. Verdonk R, Verdonk P, Huyse W, Forsyth R, Heinrichs E-L.** Tissue ingrowth after implantation of a novel, biodegradable polyurethane scaffold for treatment of partial meniscal lesions. *Am J Sports Med* 2011;39:774–782.
- 105. Genovese E, Angeretti MG, Ronga M, et al.** Follow-up of collagen meniscus implants by MRI. *Radiol Med (Torino)* 2007;112:1036–1048.
- 106. Joobar R, Schmitz N, Annable L, Boksa P.** Publication bias: what are the challenges and can they be overcome? *J Psychiatry Neurosci* 2012;37:149–152.
- 107. Zaffagnini S, Marcheggiani Muccioli GM, Grassi A, et al.** Arthroscopic lateral collagen meniscus implant in a professional soccer player. *Knee Surg Sports Traumatol Arthrosc* 2011;19:1740–1743.
- 108. Vrancken AC, Buma P, van Tienen TG.** Synthetic meniscus replacement: a review. *Int Orthop* 2013;37:291–299.
- 109. Verhaeghe L, Boeren K.** A rare complication after synthetic meniscus replacement. *J Belg Soc Radiol.* 2018;102:63.
- 110. Cengiz IF, Oliveira JM, Ochi M, Nakamae A, Adachi N, Reis RL.** Biologic. In: *Treatment for meniscal repair: injuries and health problems in football*. Berlin, Heidelberg: Springer, 2017:679–686.
- 111. Pereira H, Cengiz IF, Silva-Correia J, Oliveira JM, Reis RL, Espregueira-Mendes J.** *Human meniscus: from biology to tissue engineering strategies*. Sports Injuries. Berlin, Heidelberg: Springer, 2015:1089–1102.
- 112. Cucchiari M, Schmidt K, Frisch J, Kohn D, Madry H.** Overexpression of TGF- β via rAAV-mediated gene transfer promotes the healing of human meniscal lesions ex vivo on explanted menisci. *Am J Sports Med* 2015;43:1197–1205.
- 113. Zaffagnini S, Cucchiari M, de Girolamo L, et al.** Gene therapy, growth factors, mesenchymal cells, new trends and future perspective. In: Hulet C, Pereira H, Peretti G, Denti M, eds. *Surgery of the meniscus*. Berlin, Heidelberg: Springer, 2016:559–575.
- 114. Cengiz IF, Oliveira JM, Reis RL.** *PRP therapy: osteochondral tissue engineering*. Berlin, Heidelberg: Springer, 2018:241–253.
- 115. Angele P, Johnstone B, Kujat R, et al.** Stem cell based tissue engineering for meniscus repair. *J Biomed Mater Res A* 2008;85:445–455.
- 116. Baker BM, Nathan AS, Huffman GR, Mauck RL.** Tissue engineering with meniscus cells derived from surgical debris. *Osteoarthritis Cartilage* 2009;17:336–345.
- 117. Barry F, Murphy M.** Mesenchymal stem cells in joint disease and repair. *Nat Rev Rheumatol* 2013;9:584–594.
- 118. Vangsness CT, Jr., Farr J, 2nd, 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;96:90–98.
- 119. Hansmann J, Groeber F, Kahlig A, Kleinhans C, Walles H.** Bioreactors in tissue engineering: principles, applications and commercial constraints. *Biotechnol J* 2013;8:298–307.
- 120. Cengiz IF, Oliveira JM, Reis RL.** *Tissue engineering and regenerative medicine strategies for the treatment of osteochondral lesions, in 3D Multiscale Physiological Human*. London: Springer; 2014:25–47.
- 121. Cengiz IF, Oliveira JM, Reis RL.** Micro-CT – a digital 3D microstructural voyage into scaffolds: a systematic review of the reported methods and results. *Biomater Res* 2018;22:26.
- 122. González-Fernández ML, Pérez-Castrillo S, Sánchez-Lázaro JA, et al.** Assessment of regeneration in meniscal lesions by use of mesenchymal stem cells derived from equine bone marrow and adipose tissue. *Am J Vet Res* 2016;77:779–788.
- 123. Heo J, Koh RH, Shim W, Kim HD, Yim H-G, Hwang NS.** Riboflavin-induced photo-crosslinking of collagen hydrogel and its application in meniscus tissue engineering. *Drug Deliv Transl Res* 2016;6:148–158.
- 124. Mueller SM, Shortkroff S, Schneider TO, Breinan HA, Yannas IV, Spector M.** Meniscus cells seeded in type I and type II collagen-GAG matrices in vitro. *Biomaterials* 1999;20:701–709.
- 125. Puetzer JL, Bonassar LJ.** Physiologically distributed loading patterns drive the formation of zonally organized collagen structures in tissue engineered meniscus. *Tissue Eng Part A* 2016;22:907–916.
- 126. Gunja NJ, Athanasiou KA.** Additive and synergistic effects of bFGF and hypoxia on leporine meniscus cell-seeded PLLA scaffolds. *J Tissue Eng Regen Med* 2010;4:115–122.
- 127. Gunja NJ, Uthamanthil RK, Athanasiou KA.** Effects of TGF- β 1 and hydrostatic pressure on meniscus cell-seeded scaffolds. *Biomaterials* 2009;30:565–573.
- 128. Warnock JJ, Fox DB, Stoker AM, et al.** Culture of equine fibroblast-like synoviocytes on synthetic tissue scaffolds towards meniscal tissue engineering: a preliminary cell-seeding study. *PeerJ* 2014;2:e353.
- 129. Aufderheide AC, Athanasiou KA.** Comparison of scaffolds and culture conditions for tissue engineering of the knee meniscus. *Tissue Eng* 2005;11:1095–1104.
- 130. Gu Y, Zhu W, Hao Y, Lu L, Chen Y, Wang Y.** Repair of meniscal defect using an induced myoblast-loaded polyglycolic acid mesh in a canine model. *Exp Ther Med* 2012;3:293–298.
- 131. Kwak HS, Nam J, Lee Jh, Kim HJ, Yoo JJ.** Meniscal repair in vivo using human chondrocyte-seeded PLGA mesh scaffold pretreated with platelet-rich plasma. *J Tissue Eng Regen Med* 2017;11:471–480.
- 132. Zhang Z-Z, Jiang D, Ding J-X, et al.** Role of scaffold mean pore size in meniscus regeneration. *Acta Biomater* 2016;43:314–326.
- 133. Chiari C, Koller U, Dorotka R, et al.** A tissue engineering approach to meniscus regeneration in a sheep model. *Osteoarthritis Cartilage* 2006;14:1056–1065.

- 134. Fisher MB, Henning EA, Söegaard N, Bostrom M, Esterhai JL, Mauck RL.** Engineering meniscus structure and function via multi-layered mesenchymal stem cell-seeded nanofibrous scaffolds. *J Biomech* 2015;48:1412–1419.
- 135. Kon E, Filardo G, Tschon M, et al.** Tissue engineering for total meniscal substitution: animal study in sheep model—results at 12 months. *Tissue Eng Part A* 2012;18:1573–1582.
- 136. Zellner J, Hierl K, Mueller M, et al.** Stem cell-based tissue-engineering for treatment of meniscal tears in the avascular zone. *J Biomed Mater Res B Appl Biomater* 2013;101:1133–1142.
- 137. Zellner J, Mueller M, Berner A, et al.** Role of mesenchymal stem cells in tissue engineering of meniscus. *J Biomed Mater Res A* 2010;94:1150–1161.
- 138. Freymann U, Endres M, Neumann K, Scholman H-J, Morawietz L, Kaps C.** Expanded human meniscus-derived cells in 3-D polymer-hyaluronan scaffolds for meniscus repair. *Acta Biomater* 2012;8:677–685.
- 139. Gruchenberg K, Ignatius A, Friemert B, et al.** In vivo performance of a novel silk fibroin scaffold for partial meniscal replacement in a sheep model. *Knee Surg Sports Traumatol Arthrosc* 2015;23:2218–2229.
- 140. Mandal BB, Park S-H, Gil ES, Kaplan DL.** Multilayered silk scaffolds for meniscus tissue engineering. *Biomaterials* 2011;32:639–651.
- 141. Yan L-P, Oliveira JM, Oliveira AL, Caridade SG, Mano JF, Reis RL.** Macro/microporous silk fibroin scaffolds with potential for articular cartilage and meniscus tissue engineering applications. *Acta Biomater* 2012;8:289–301.
- 142. Sarem M, Moztaaradeh F, Mozafari M, Shastri VP.** Optimization strategies on the structural modeling of gelatin/chitosan scaffolds to mimic human meniscus tissue. *Mater Sci Eng C* 2013;33:4777–4785.
- 143. Bodin A, Concaro S, Brittberg M, Gatenholm P.** Bacterial cellulose as a potential meniscus implant. *J Tissue Eng Regen Med* 2007;1:406–408.
- 144. Martínez H, Brackmann C, Enejder A, Gatenholm P.** Mechanical stimulation of fibroblasts in micro-channeled bacterial cellulose scaffolds enhances production of oriented collagen fibers. *J Biomed Mater Res A* 2012;100:948–957.
- 145. Weinand C, Peretti GM, Adams SB Jr, Randolph MA, Savvidis E, Gill TJ.** Healing potential of transplanted allogeneic chondrocytes of three different sources in lesions of the avascular zone of the meniscus: a pilot study. *Arch Orthop Trauma Surg* 2006;126:599–605.
- 146. Baker BM, Gee AO, Sheth NP, et al.** Meniscus tissue engineering on the nanoscale: from basic principles to clinical application. *J Knee Surg* 2009;22:45–59.
- 147. Perán M, García MA, Lopez-Ruiz E, Jiménez G, Marchal JA.** How can nanotechnology help to repair the body? *Advances in cardiac, skin, bone, cartilage and nerve tissue regeneration. Materials (Basel)* 2013;6:1333–1359.
- 148. Baker BM, Mauck RL.** The effect of nanofiber alignment on the maturation of engineered meniscus constructs. *Biomaterials* 2007;28:1967–1977.
- 149. Baker BM, Nathan AS, Gee AO, Mauck RL.** The influence of an aligned nanofibrous topography on human mesenchymal stem cell fibrochondrogenesis. *Biomaterials* 2010;31:6190–6200.
- 150. Subbiah R, Veerapandian M, Yun KS.** Nanoparticles: functionalization and multifunctional applications in biomedical sciences. *Curr Med Chem* 2010;17:4559–4577.
- 151. Harrison BS, Atala A.** Carbon nanotube applications for tissue engineering. *Biomaterials* 2007;28:344–353.
- 152. Haynie DT, Zhang L, Zhao W, Rudra JS.** Protein-inspired multilayer nanofilms: science, technology and medicine. *Nanomedicine (Lond)* 2006;2:150–157.
- 153. Thorvaldsson A, Stenhamre H, Gatenholm P, Walkenström P.** Electrospinning of highly porous scaffolds for cartilage regeneration. *Biomacromolecules* 2008;9:1044–1049.
- 154. Gu Y, Wang Y, Dai H, Lu L, Cheng Y, Zhu W.** Chondrogenic differentiation of canine myoblasts induced by cartilage-derived morphogenetic protein-2 and transforming growth factor- β 1 in vitro. *Mol Med Rep* 2012;5:767–772.
- 155. 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;13:1103–1112.
- 156. Amable PR, Carias RBV, Teixeira MVT, et al.** Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors. *Stem Cell Res Ther* 2013;4:67.
- 157. Everts PA, Knappe JT, Weibrich G, et al.** Platelet-rich plasma and platelet gel: a review. *J Extra Corpor Technol* 2006;38:174–187.
- 158. Laver L, Marom N, Dnyanesh L, Mei-Dan O, Espregueira-Mendes J, Gobbi A.** PRP for degenerative cartilage disease: a systematic review of clinical studies. *Cartilage* 2017 Oct;8:341–364.
- 159. Marx RE.** Platelet-rich plasma (PRP): what is PRP and what is not PRP? *Implant Dent* 2001;10:225–228.
- 160. Marx RE.** Platelet-rich plasma: evidence to support its use. *J Oral Maxillofac Surg* 2004;62:489–496.
- 161. Bacelar AH, Cengiz IF, Silva-Correia J, Sousa RA, Oliveira JM, Reisa RL.** ‘Smart’ hydrogels in tissue engineering and regenerative medicine applications. In: Khang G, ed. *Handbook of intelligent scaffolds for regenerative medicine*. Singapore. Pan Stanford Publishing, 2017:327–361.
- 162. Silva-Correia J, Gloria A, Oliveira MB, Mano JF, Oliveira JM, Ambrosio L, et al.** Rheological and mechanical properties of acellular and cell-laden methacrylated gellan gum hydrogels. *J Biomed Mater Res A* 2013;101:3438–3446.
- 163. Oliveira J, Pereira H, Yan L, Silva-Correia J, Oliveira A, Espregueira-Mendes J, et al.** inventors. Scaffold that enables segmental vascularization for the engineering of complex tissues and methods of making the same, PT Patent 106174, Priority date: 16/12/2013, 26-08-2013 2013.
- 164. Lee CH, Rodeo SA, Fortier LA, Lu C, Eriskin C, Mao JJ.** Protein-releasing polymeric scaffolds induce fibrochondrocytic differentiation of endogenous cells for knee meniscus regeneration in sheep. *Sci Transl Med* 2014 Dec 10;6:266ra171.
- 165. Gatt CJ, Patel JM, Merriam AR, Culp B, Dunn MG.** ‘A load-sharing tissue-engineered meniscus scaffold: one-year outcome’, Scientific Session Presentation, American Orthopaedic Society for Sports Medicine Annual Meeting. Seattle WA. Jul 2014.
- 166. Gelber PE, Gonzalez G, Torres R, Garcia Giralto N, Caceres E, Monllau JC.** Cryopreservation does not alter the ultrastructure of the meniscus. *Knee Surg Sports Traumatol Arthrosc* 2009;17:639–644.