Regen. Eng. Transl. Med. (2017) 3:32–50
DOI 10.1007/s40883-017-0025-z

REVIEW

Treatments of Meniscus Lesions of the Knee: Current Concepts and Future Perspectives

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Received: 13 December 2016 / Accepted: 1 February 2017 / Published online: 21 February 2017

Abstract
The present preference in the clinical management of meniscus lesions is to preserve it by repairing whenever possible or substituting the tissue. Still, meniscectomy continues to be one of the most frequent orthopedic procedures regardless of the fact that it may lead to a series of early degenerative events in the knee. Surgical and technological advances enabled to extend the indications for meniscus repair. The outcome of meniscus repair is influenced by several factors. Classification of meniscus lesions remains a challenge while there have been some attempts in building consensus around it. Substitution of meniscus tissue has been performed to avoid or minimize the possible degenerative effects occurring in the absence of meniscus. Meniscus allograft transplantation has demonstrated its use as a replacement strategy of large lesions. In partial lesions, the use of acellular scaffolds has provided an improved clinical outcome when the insertional horns and the peripheral rim are preserved. However, the current scaffolds have shown some limitations, and the neotissue is different from the native meniscus. Tissue engineers thus envision going beyond the partial meniscus regeneration. Nowadays, it is aimed to develop a new generation of meniscal implants for total meniscus regeneration, which not only meet the biomechanical requirements but also the biological requirements both in the short- and long-term. Moreover, these might be patient/injury-specific regarding the size and shape as well as being cultivated with autologous cells and biologically enhanced. Herein, the clinical management of meniscus lesions and advanced tissue engineering strategies are reviewed.

Lay Summary
Meniscus injuries are the most frequent injuries in the knee. Given the increased understanding of the consequences of meniscectomy, which is still one of the most frequent orthopedic procedures, the clinical management of meniscus changed towards favoring repair or substitution. The future of meniscus substitution and regeneration is strongly supported by the clinical need. This study reviews the current concepts and provides future perspectives on the clinical management of meniscus lesions, and tissue engineering and regenerative medicine strategies to update and guide researchers and surgeons.

Keywords Meniscus, · Meniscus repair, · Meniscus lesion, · Meniscus tear, · Scaffold, · Tissue engineering

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Introduction

Today, in addition to the clinical studies, musculoskeletal lesions and in particular meniscus injuries have been studied

pre-clinically in many scientific domains including but not limited to application of different tissue engineering strategies and biologics, and gene therapy. The menisci are fundamental elements of a healthy knee [1, 2]. They are fibrocartilaginous tissues functioning between the tibial plateau and the femoral condyle with their C-like shape with a wedge-like cross-section [3, 4]. Menisci have a specific extracellular matrix [5, 6] and multiple cell types [7, 8]. These are complex tissues with particular biomechanics [9] and cell distribution [10]. Thus, the menisci are heterogeneous with segmental and regional variations according to its ultrastructure, biology, and function [10, 3, 9]. Besides, only a certain portion of the tissue receives blood supply. In adults, the peripheral vessels penetrate around 10 to 25% of the width of the lateral meniscus and 10 to 30% of the width of the medial meniscus [11]. This greatly determines the self-healing ability [12, 13].

Meniscus injuries are the most frequent injuries in the knee [14]. The lesions of the meniscus can have different types and patterns [15, 16] (Fig. 1), which are linked to different prognoses and treatments [12]. The removal of the meniscus from the knee brings significant consequences and can lead to early degenerations in the knee [17–20]. In the clinics, treatments for the meniscus injuries depend on the patient condition and the injury [21, 6]. The algorithm for treatment of meniscus lesions has significantly changed in the last decade [22, 23]. Given the extended understanding of the meniscus [3, 24, 25] and the consequences of meniscectomy [26], clinical management dramatically changed towards favoring repair or substitution [27, 22]. However, even today, meniscectomy is one of the most frequent orthopedic procedures performed worldwide [28]. When compared to partial meniscectomy, meniscus repair has generally improved the clinical outcome and/or lowered the risk for subsequent osteoarthritis [24]. Therefore, the meniscus tissue shall be preserved whenever possible. Nevertheless, suturing the meniscus has indications and limitations.

The difference between the medial and the lateral meniscus on knee kinematics should also be considered. The lateral meniscus is responsible for most of the load transfer within the lateral compartment [29]. However, in the medial compartment, the load transmission is more equally disseminated among the cartilage surfaces and the correspondent meniscus [30]. The lateral meniscus holds up to 70% of the load transmission in the lateral compartment while the medial meniscus is responsible for 50% within its respective compartment [31]. The lateral meniscus is more mobile, while the more static medial meniscus is known to play an additional secondary role as joint stabilizer contributing to resist the anterior tibial displacement, agonist with anterior cruciate ligament (ACL) [29].

The basic science knowledge related to the menisci is of the highest importance once it has provided an improved understanding of healing mechanisms and will surely keep influencing the indications and outcome for tissue repair and substitution [3, 32] Tissue engineering and regenerative medicine (TERM) promises to change the clinical practice in a broad perspective, and dealing with meniscus lesions is not an exception [33–35].

In 2014, Beaufils et al. [36] published an important chapter on "How to Share Guidelines in Daily Practice on Meniscus Repair, Degenerate Meniscus lesion, and Meniscectomy" in the European Society of Sports Traumatology, Knee Surgery and Arthroscopy (ESSKA) Instructional Course Lecture Book within the scope of the 16th ESSKA Congress in 2014 which discussed how guidelines, recommendations, may promote meniscus preservation. In 2015, the International Meniscus Reconstruction Experts Forum consensus statement on the MAT practice was published [37] where a more standardized approach to indications, surgical methods, and postoperative care was outlined as recommendations to achieve a better patient outcome. Moreover, the ESSKA board initiated in 2014 the "ESSKA meniscus consensus initiative" under the leadership of Philippe Beaufils and Roland Becker. This initiative aims the build a European consensus on the meniscus lesion treatments. The report of this project in published recently in 2016 [38] and can be found online in the ESSKA's website: http://www.esska.org/. In the report, an algorithm for the treatment of degenerative meniscus lesions, and a description of non-operative treatment for degenerative meniscus lesions are provided; moreover, answers for the following critical questions were also provided:

- What is a degenerative meniscus lesion?
- Which MRI criteria characterize a degenerative meniscus lesion?
- What is the prevalence of degenerative meniscus lesions?
- Do degenerative meniscus lesions cause knee symptoms?
- What are the consequences by a degenerative meniscus lesion in the knee?
- Are degenerative meniscus lesions a cause or consequence of knee osteoarthritis?
- What is the role of knee radiographs in the assessment of middle-aged or older patients with a painful knee?
- What is the role of MRI in the assessment of middle-aged or older patients with a painful knee?
- How should we make the diagnosis of knee osteoarthritis on a daily practical basis?
- Does an unstable degenerative meniscus lesion cause knee symptoms?
- Are functional outcomes of arthroscopic partial meniscectomy and non-operative treatment different, based on osteoarthritic status?
- What is the patient population defined by the randomized controlled trial studies?
- What does non-operative treatment mean?
- What is the rate of conversion to surgery in those patients undergoing non-operative treatment?

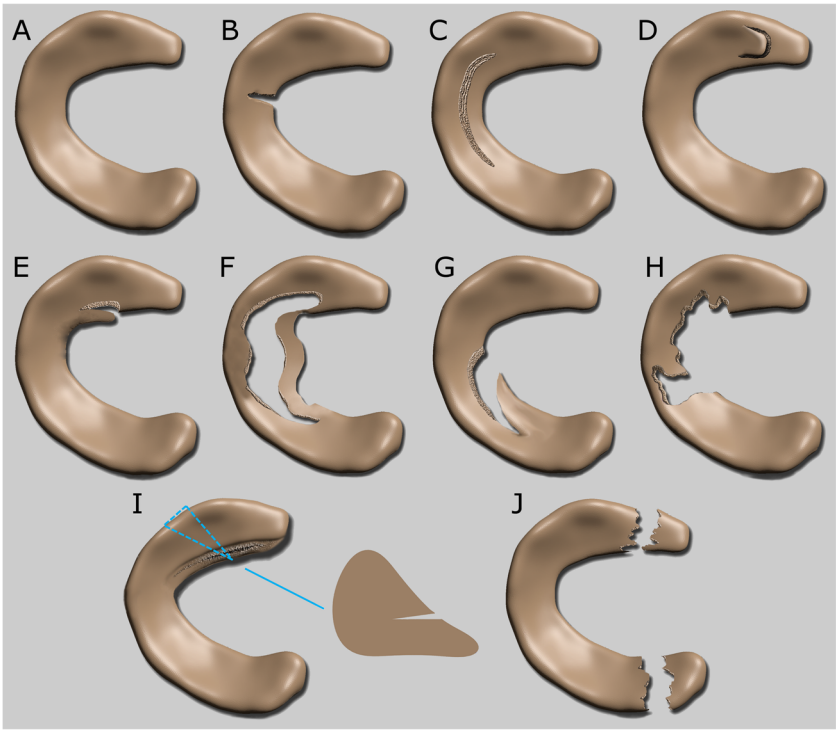

Fig. 1 Illustration of normal meniscus (*A*), and common types of meniscus tears: radial tear (*B*), longitudinal tear (*C*), horizontal flap (*D*), vertical flap (*E*), bucket-handle tear (*F*), oblique/parrot-beak lesion (*G*), complex degenerative (*H*), horizontal tear (*I*), root tears (*J*)

- Is the concept of an unstable meniscus useful for indicating meniscectomy (locking, clicking, MRI flap, etc.…)?
- What outcomes can be expected after arthroscopic partial meniscectomy?
- What is the rate of surgical complications after meniscus resection?
- What is the risk of osteoarthritis after meniscus resection?
- Is there a place for arthroscopic lavage (or lavage-debridement: arthroscopic procedure including degenerative (meniscal/chondral) and/or synovial tissue debridement?) for osteoarthritic knees?
- When should arthroscopic partial meniscectomy be proposed?

Classification of Meniscus Lesions

Degenerative Versus Traumatic Lesions

The menisci function under compressive, radial tensile, and shear stresses [39–41]. These stresses may influence the meniscus and also the knee joint injuries. Patient's age is a relevant pathophysiological factor of meniscus lesions, even if lesions can occur in all age groups [28, 42, 36]. The characteristics of meniscus tissue vary according to age, tear pattern, and pathological conditions [43]. These include the water content, cells, extracellular matrix, collagen, and adhesion glycoproteins [43]. When dealing with the clinical management of meniscus lesions, it is critical for the treatment or prognosis, to distinct if the surgeon is dealing with a traumatic or degenerative tear [36]. However, such distinction is not always easy.

A traumatic meniscus tear is typically associated with an acute event capable of creating enough capacity to rupture the meniscus tissue [44]. The patterns more frequently connected to traumatic tears are longitudinal, bucket-handle, and radial tears [45]. However, most often, flap tears are also considered as traumatic. The types of meniscus tears are depicted in Fig. 1. High-energy trauma leading to fractures around the knee can also be implicated in meniscus tears [46]. Conversely, degenerative meniscus lesions (Fig. 2a) have a considerably different nature. Some characteristic changes of a degenerative meniscus include cavitations, softened tissue, fibrillation, or complex tear patterns (Fig. 2b), among other degenerative changes [47]. The most representative types of such lesions are horizontal tears [48–50]. Even among younger populations, they often have a degenerative nature [48–50].

Nowadays, the root tears are also attracting more attention [51]. Posterior root tears and medial meniscus root tears are more often degenerative while the lateral ones are more usually traumatic, frequently combined to acute ACL rupture [52–54]. The typical clinical presentation of an acute meniscus tear usually includes sudden onset of pain and/or swelling of the joint. Mechanical symptoms are typically associated with unstable tears [55]. Mechanical symptoms include clicking, catching, or locking of the knee joint [55]. Supposedly, innocuous activities such as walking or squatting have also been linked to injuries of the menisci [56].

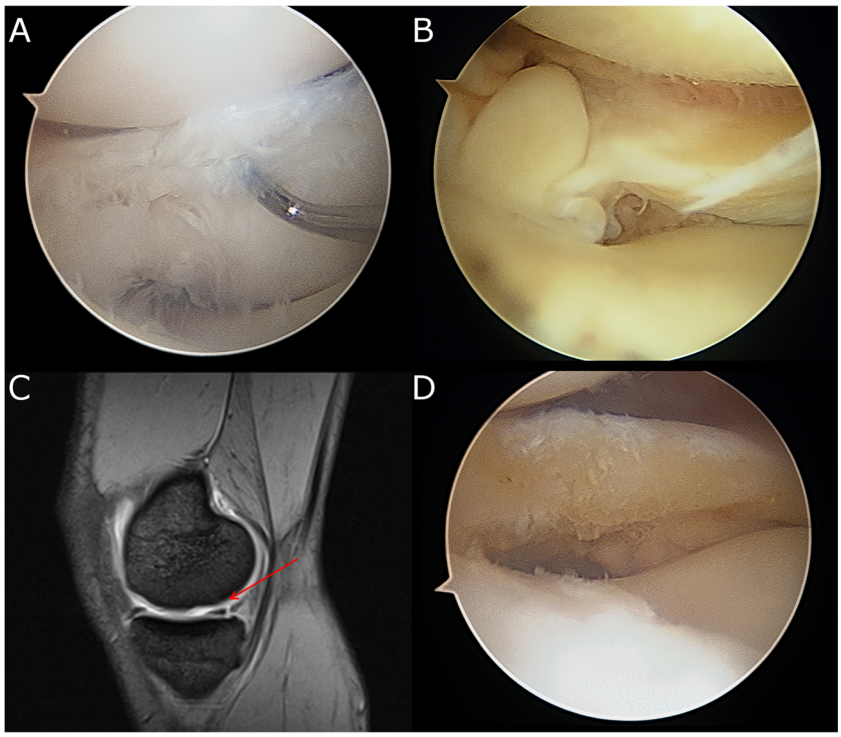

Fig. 2 Typical fibrillation of a degenerative meniscal lesion (**a**); complex tear combining flap and horizontal tear (**b**); MRI lateral view of longitudinal medial meniscus tear (*red arrow*) (**c**); final look after meniscectomy reducing the volume of meniscal tissue (**d**)

Another important issue to be considered is that a magnetic resonance imaging (MRI) indicating a meniscus injury does not necessarily mean that it requires direct treatment. A meniscus lesion is a common incidental finding on MRI in both symptomatic and asymptomatic knees [57], especially in older people. Age, clinical and radiographic findings of osteoarthritis [58, 59] and repetition of micro-trauma can play a role in the degeneration of the menisci, as well as the knee joint [60]. In all such situations, a diminished vascularization can be expected, and this might lead to further tissue degeneration [12, 36].

The global assessment of the knee joint is always required. It is highly debatable if the isolated treatment of any meniscus tear can be successful in the treatment of symptoms caused by global joint osteoarthritis [36]. However, it is well-known that the absence of meniscus tissue will accelerate the development of knee osteoarthritis [61]. Nevertheless, it must be furthered recognized that in some specific conditions, a degenerative meniscus lesion, asymptomatic for a long period, might suddenly become symptomatic after an acute traumatic event [36].

Assessment and Classification of Meniscus Lesions

When the presence of a meniscus tear is doubted, the patient's history and clinical examination are needed. For the diagnosis of a meniscus lesion, many different clinical tests exist [62]. However, these have a diagnostic accuracy only low to moderate. Standing x-ray protocol evaluation including frontal plane, lateral, skyline patella, and schuss view is helpful to study the lower limb alignment and for overall joint assessment. MRI has high accuracy regarding the preoperative evaluation of meniscus lesions (Fig. 2C) [63–65], especially when performed by a radiologist dedicated to musculoskeletal pathology [66, 67].

When two or more types of tears occurring in any plane are combined within the same meniscus, this is usually considered a "complex tear" [36]. Several classification methods have been proposed in order to assist in prognosis, treatment, and assessment of results from treatment [47]. Vascularity is frequently considered in classification systems due to its role in tissue healing. One of the most commonly used classification systems is from Cooper et al. [68] in which the meniscus is divided into circumferential zones: zone 0 corresponds to the meniscal-synovial junction, zone 1 corresponds to the outer third of the meniscus, zone 2 includes the middle third, and zone 3 is the central third of the meniscus. The International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (ISAKOS) committee has recently made a study on the meniscal tear classification combining the best available clinical and basic science knowledge [47]. For the radial classification, the committee recommended the classification in which the meniscus is divided into 3 anterior, middle, and posterior with the observed agreement of 68%; even though there was 87% of observed agreement on the division of the meniscus into anterior and posterior halves. Regarding the vascularity, the Committee adopted a modified version of the previously mentioned Cooper classification system that was based on the evidence of vascularity extending up to 3 mm into the meniscus. However, there was only 54% of observed agreement for estimation of the rim width. As it was hypothesized, that study showed that there is a sufficient

interobserver reliability on meniscal tear classification (in terms of the tear depth, location, tear pattern, length, quality of the tissue, and percentage of the meniscus excised), and the data of international clinical trials which aim to assess the outcomes of treatment for meniscal tears can be pooled. In addition to the contribution of that study to clinical management, it also aims to improve data gathering from clinical trials designed to evaluate the outcomes of different strategies [47] which has great importance too.

Treatments of Meniscus Lesions

Meniscectomy

Recent results favor meniscus repair over partial (Fig. 2d) or total meniscectomy concerning either clinical outcome and/or risk for subsequent osteoarthritis [36, 24]. Nevertheless, meniscectomy is still one of the most frequent causes for orthopedic surgery today [28]. The terms "partial," "subtotal," or "total" meniscectomy are used and aim to reflect the amount of tissue that is surgically removed. Though, the borders of each of these terms are not yet clearly identified [26].

Partial meniscectomy has shown higher risk of radiographic changes towards osteoarthritis compared to repair [24]. Concerning meniscectomy for traumatic tears, once more, a worse outcome has been described for the risk for osteoarthritis [15]. When a meniscectomy is required in case of an irreparable tear, it is known that preserving the biggest possible amount of tissue, particularly the peripheral, lowers the adverse effects in load transmission and contact area reduction [69–71].

There is a significant difference considering prognosis and outcome when managing a meniscus tear by meniscectomy on a stable compared to an unstable knee [26]. Worse results can be expected when performing isolated meniscectomies on unstable knees (ACL-deficient) [26]. Under such conditions, particularly for the medial meniscus, ACL repair should be addressed at the same time once the risk for subsequent meniscectomies is higher if the ACL is not effectively repaired [72, 73]. This risk is lower for stable lateral meniscus tears [64]. If the ACL repair is delayed more than 12 months after the ACL injury when compared to less than 12 months, a 3.5 overall odds ratio (a measure of association) for risk of subsequent medial meniscus tears has been established [74]. The timing of ACL repair has a lower influence on the risk of subsequent lateral meniscus tears [74]. Meniscectomy also has been considered to worsen the outcome of ACL repair [75, 76]. Such findings might be understood under the different kinematic roles of both menisci in the knee joint [20, 29].

The greater role of the lateral meniscus in load transmission most likely contributes to the increased risk for rapid chondrolysis after lateral meniscectomy when compared to medial meniscectomy [77, 78]. A worse outcome should be anticipated for lateral meniscectomy when compared to the medial [26]. Despite the previous considerations, some controversy remains once arthroscopic partial meniscectomy has been linked to some satisfactory outcome with faster return to activity compared to meniscus repair [79, 15]. In brief, meniscectomy remains as a valid option, while sometimes is still the "only" option. However, higher risk of complications, possibly a lower rate of return to the same level of activity especially after a lateral meniscectomy, and an increased risk of subsequent osteoarthritis must be carefully considered.

Meniscus Repair

The techniques for meniscal suture/repair have been advancing given the developments in medical devices and surgical techniques, complemented with improved biological and anatomical knowledge. Several repair techniques are available (Fig. 3), and can be selected according to the lesion pattern, surgeon's experience, and availability of resources. The techniques for meniscus repair comprise all-inside [80, 81], inside-out [82, 83], or outside-in [84, 85] approaches, which can be executed either alone or combined.

"All-inside" indicates that the devices for suture/repair are kept inside the joint at all time during the procedure (Fig. 4). Several biodegradable meniscus repair devices composed of the rigid poly-L-lactic-acid (PLLA) have been described for all-inside application [86]. These include arrows (Fig. 5a), screws [86], darts, and staples. However, there are some concerns related to degradability [86]. Despite some reported favorable outcome [87, 88], these devices are related to higher failure rates [89, 90] and higher number of complications including synovitis, inflammatory reaction, cyst formation, device failure/migration, and chondral damage [90]. The use of rigid meniscus repair devices such as polylactic acid or its derivatives has been linked with the loosening of fragments/bodies inside or outside the joint [91]. Such complications might be related to the structure and erratic degradation rates of such polymers [91]. Given the considerable prevalence of complications, these rigid devices have progressively lost their attractiveness.

The most frequently used all-inside techniques require suture combined with small anchors, which serve as holds, and a prettied slip knot [80]. They enable variable compression and retensioning of the suture. A depth-limiting sleeve on the inserter is commonly used to avoid excessive penetrations of the needle which has an inherent risk of iatrogenic complications (e.g. perforation of neurovascular structures) [92]. "Inside-out" indicates that the sutures usually linked to needles or suture passers come from the inner joint and perforate the meniscus towards the outside capsule where knots are tied (Fig. 5b). In "outside-in" (Fig. 5c), the sutures are introduced

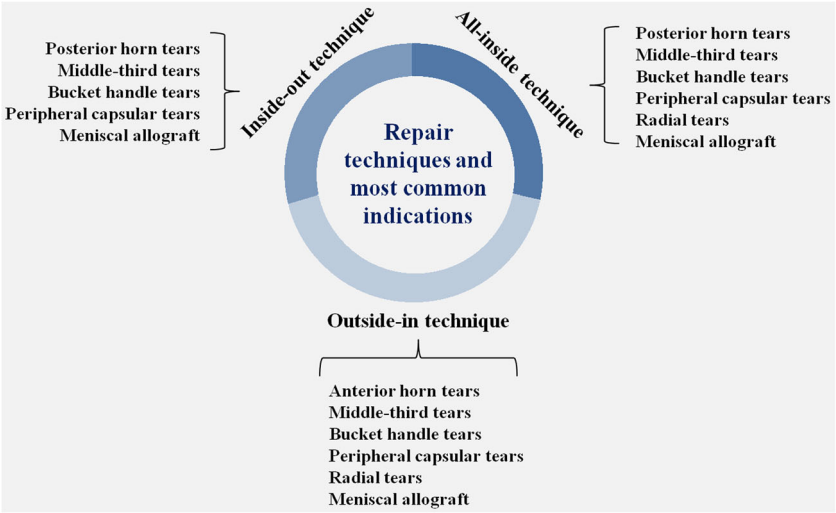

Fig. 3 Meniscus repair techniques and most common indications

percutaneously into the joint, perforated the meniscus, and finally, the sutures are brought again outside over the capsule beneath the subcutaneous tissue.

Vertical sutures are perpendicular to the circumferential fibers of the meniscus, and have higher pull-out resistance [93]. Horizontal sutures are parallel to those circumferential fibers. Regardless of the technique, vertical or horizontal mattress sutures can be achieved. Several technical attempts have been proposed in order to enhance the healing: sutures combined with grasping, trephination, or augmentation with fibrin clot [94]. The meniscal sutures are not exclusive of acute tears. Selected degenerative injuries including some horizontal cleavage tears are suitable for a successful repair [95]. Similarly, some degenerative meniscus root tears have also been repaired, consequently preserving the meniscal functions with all its inherent advantages [96].

The types of tears that are suitable for suture include horizontal lesions which are usually degenerative even in younger patients [48], vertical or longitudinal tears, bucket-handle, and some radial tears of the vascular region which are considered in the traumatic group [45]. The key to a successful outcome depends on the type and the location of the lesion, and certainly to the experience of the surgeon. Flap tears are frequently traumatic and are mostly considered irreparable. This type of lesions can also be found in irreparable complex degenerative lesions. The root tears can be repaired by trans-osseous tunnels [52] and all-inside techniques [97] if the remaining tissue is suitable for repair.

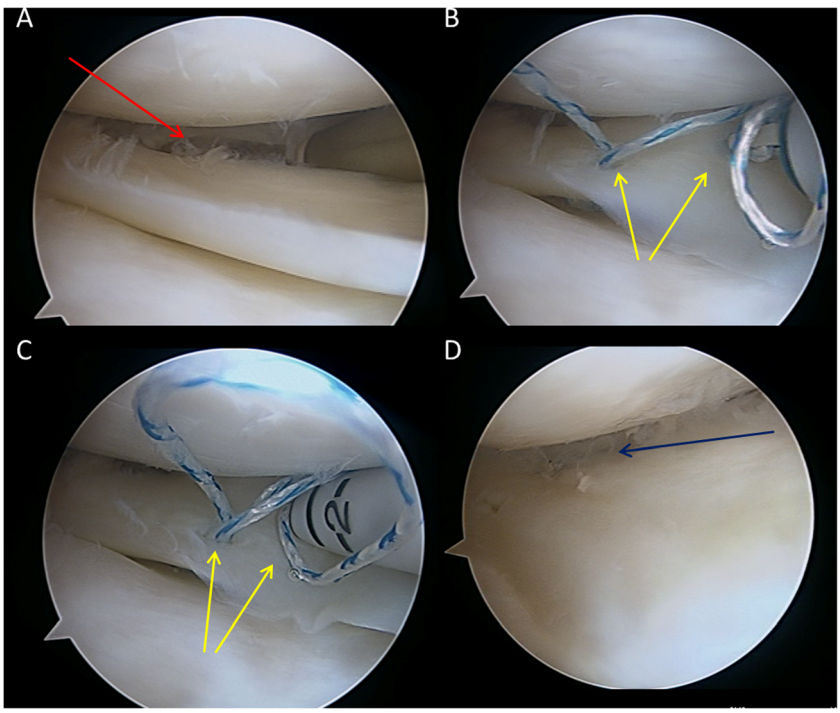

Fig. 4 Longitudinal meniscus tear (*red arrow*) (**a**); all-inside device delivering sutures (*yellow arrows*) which are passed through the meniscus (**b** and **c**); final look after tensioning the suture making the previous gap disappear (*blue arrow*) (**d**)

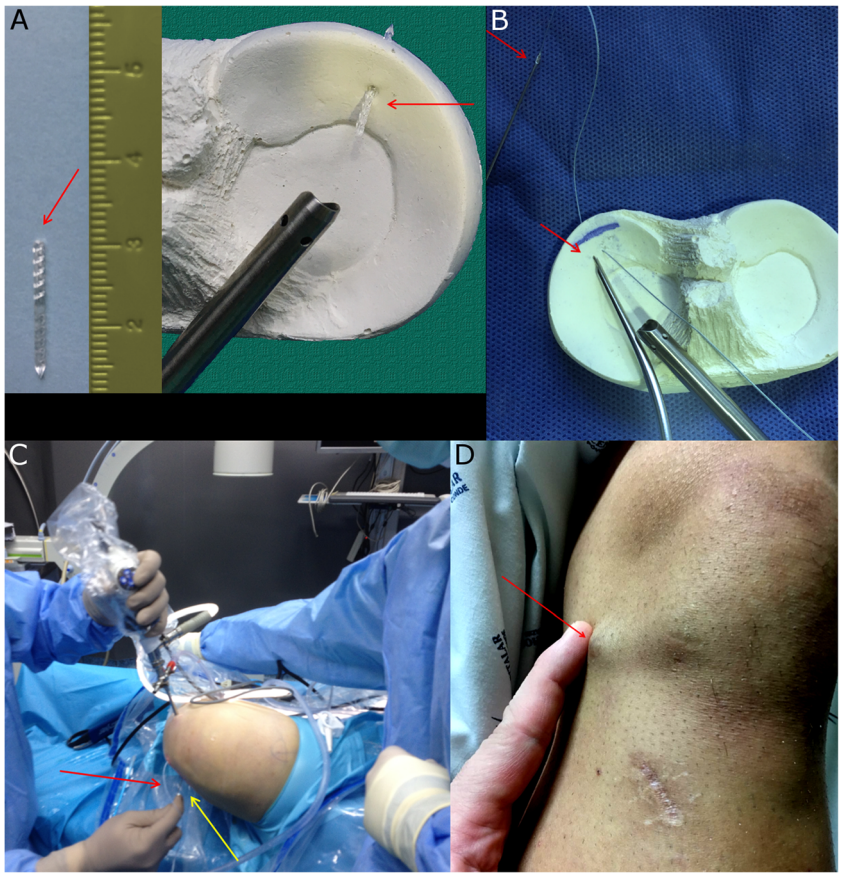

Fig. 5 Polylactic acid arrow (*red arrows*) for meniscal repair (on the left side of **a**), a model representing clinical application showing the arrow trespasses the meniscus (on the right side of (**a**); a model representing inside out delivery of needles with attached sutures (*red arrows*) through the meniscus (**b**); outside-in technique by using needles (*yellow arrow*) which pass the meniscus from the outside to the inside of the joint, these needles will serve as suture passers (*red arrow*) (**c**); granuloma after outside-in medial meniscus repair with a non-degradable suture (*red arrow*) (**d**)

Generally, the healing ratio after meniscus repair is considered to be complete healing in 60% of cases, 25% partial healing, and 15% failure [71]. Moreover, partially or incompletely healed menisci are often asymptomatic [98, 99]. After an arthroscopic meniscus repair, the failure rate ranges from 5 to 43.5%. However, in general, a failure rate around 15% is accepted by most authors [98]. Surgical repair of the posterior horn of either medial or lateral menisci is associated with some risk of iatrogenic damage to local neurovascular structures [100]. So, like any other surgery, complications are possible, and the experience of the surgeon is of major relevance. Regarding the all-inside devices [101], a low rate of complications can be possible. However, these might comprise loosening of the implant inside the joint, intra-articular deployment, suture failure, accidental cutting during tensioning, or bending of the device itself during its depletion. It is also possible to observe some superficial granulomas around sutures and/or rigid implants (Fig. 5d). Multiple factors must be considered for a meniscus lesion repair [15]. These include age, activity level, tear pattern, chronicity of the tears, combined injuries such as ACL injury, and the healing potential —vascularization. Meniscus repair in younger people provides better outcome comparing to older people [102].

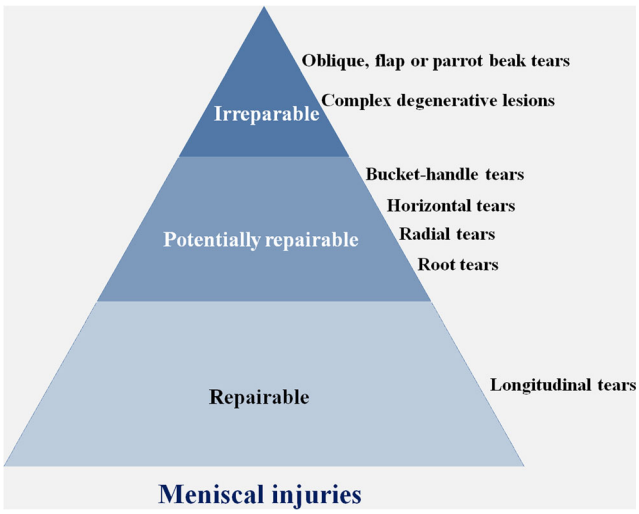

Fig. 6 Injury types of meniscus and general repair potential

The indications for potentially repairable meniscus lesions have extended including some tears which were previously considered as irreparable (Fig. 6). Another point is that the attempt of meniscus repair, even if it fails, does not seem to worsen the outcome of a subsequent meniscectomy [98]. It has also been demonstrated that the amount of tissue removed after a failed meniscal repair is not more than the one from the meniscectomy that would have been performed if meniscectomy had been the choice in the first surgery [98].

This fact also contributes to the increased tendency towards preservation and repair opposing to meniscectomy.

Substitution with Allografts

Meniscus allograft transplantation (MAT) has clearly proven to be a valid and reliable treatment when considering the consequences of severe meniscal loss [103–105]. The first description of such procedure happened in the 1970s as part of an osteochondral allograft resurfacing procedure in patients with posttraumatic osteoarthritis secondary to tibial plateau fractures [106, 107]. On the other hand, the first free MAT was performed in 1984 [108]. That was the beginning of a long journey, and since then it has been advocated for the treatment of patients with a symptomatic knee following a meniscectomy [109]. With time, it has undertaken some improvements, and a growing interest in recent years [104, 103].

There are several options for MAT procedures including graft management (fresh, fresh-frozen, cryopreserved, or freeze-dried) and fixation using bone blocks or only soft tissue without any clinical consensus regarding the best option. Concerning the fixation, multiple studies have shown comparable graft survival and outcomes between the two different fixation techniques [109, 104].

Two areas of intense research can be considered: the meniscus tissue itself, and its anchorage to the bone. The medial and lateral menisci have different morphologic characteristics which influence technical options. The medial meniscus root attachments are more separated than those of the lateral meniscus which are closer. For this reason, a medial MAT usually requires two bone tunnels in the tibia either the graft includes or not bone blocks; while for lateral MAT, it is more difficult to perform such tunnels due to a technical difficulty with the risk of coalescence. A bone slot/block technique (Figs. 7a–b) can be considered because it can allow preserving the native tibial root attachments of the graft [109].

The ideal candidate patients for MAT are young patients with a history of prior meniscectomy in a stable knee with neutral alignment and no severe chondral damage. Obesity and smoking are considered risk factors [109]. For appropriately selected patients, MAT has proven its efficacy in improving function and reduction of pain [104]. However, there are still some concerns to address regarding the graft longevity, prevention of osteoarthritis, and return to high demand activities [109].

Substitution with Commercial Scaffolds

The indications for MAT and partial meniscus substitution with scaffolds are different. Scaffold implantation requires that the meniscus roots and peripheral rim remain preserved while such requirements are not necessary for MAT [109]. On the other hand, partial meniscus substitution using mainly acellular scaffolds has been used with encouraging short-term clinical results for chronic partial meniscus lesions [110–112]. The restrictions to obtain suitable meniscus allografts in several countries, some concerns related to the transmission of infectious diseases, and the advances in TERM (Tissue engineering and regenerative medicine) have led to growing interest in the search for alternative options for meniscus substitution with scaffolds.

The concept of meniscal scaffolds was introduced in the 1990s [113]. Today, two scaffolds have been commercialized and used in Europe for clinical application [110]. One of them is the collagen meniscus implant or "CMI" (Ivy Sports Medicine, Lochhamer, Germany) which is based on type I bovine collagen matrix [113]. The other one is polycaprolactone-polyurethane scaffold and known as "Actifit" (Orteq Bioengineering, London, UK) (Fig. 7c) [114, 115]. Meniscus substitution by both implants has proven to be safe, without any apparent adverse effects [116, 117]. Moreover, both available implants have provided a positive clinical outcome in the treatment of partial medial and lateral meniscus lesions in terms of pain reduction and knee function. These short-term results refer to both the polyurethane-based at 2 years with the Actifit [112, 118, 119, 114] and at up to 10 years follow-up with the CMI [120, 111, 121]. The final tissue obtained has been recognized as different from the native meniscus in terms of mechanical properties extracellular matrix composition and organization [110]. Also, subsequent extrusion of the scaffold (extension beyond the tibial margin) is another concern [119]. Moreover, chondroprotection of the scaffold is a very critical need because the rationale of performing a substitution includes the avoidance of the consequences of meniscectomy. To overcome the limitations with both allografts and commercially available acellular scaffolds,

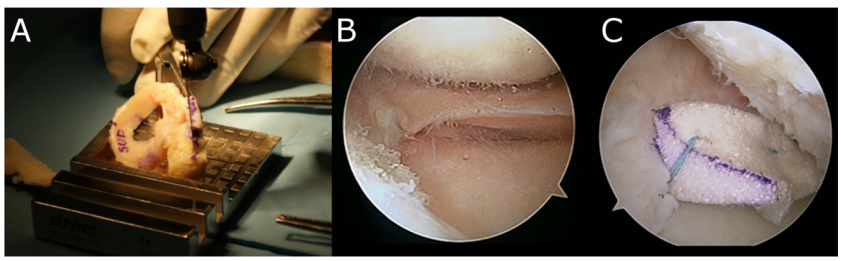

Fig. 7 Lateral meniscus allograft using bone slot technique (**a**); arthroscopic second look 5 years after implantation (**b**); the commercial polycaprolactone-polyurethane scaffold implanted in the medial compartment of a patient (**c**)

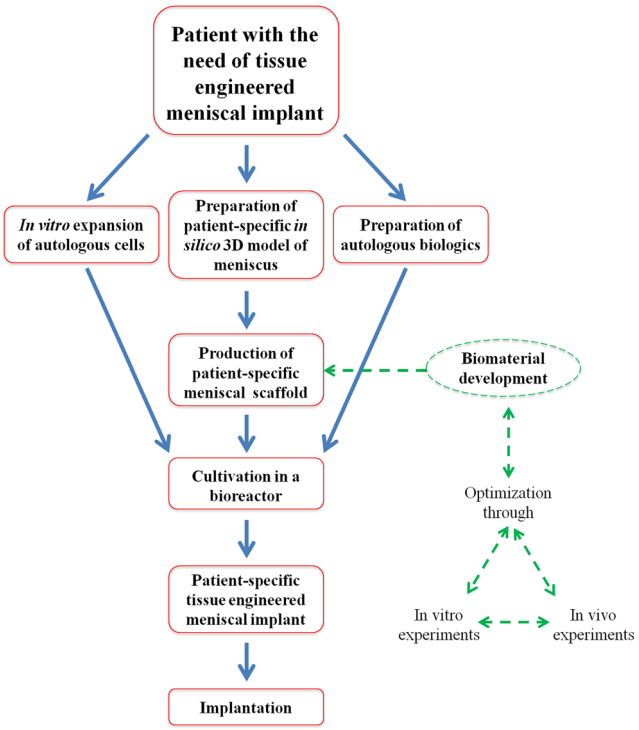

Fig. 8 A conceptual illustration of the key steps involved in meniscus tissue engineering. Autologous cells are isolated from the patient's biopsy that will receive the tissue engineered implant, and expanded in vitro to reach the needed number. The tissue regeneration can be enhanced by the use of biologics that are prepared from the same patient. The scaffold is manufactured in a patient-specific fashion with the use in silico 3D model of the tissue. Once the cells and the biologics are introduced into the scaffold, and the implant cultured preferably in a bioreactor, a new matrix will start to be formed inside the scaffold, and this construct, implant, is implanted into the patient. One of the critical steps, which is not yet proven to be achieved, is the development of the ideal biomaterial for meniscus tissue engineering. The development of biomaterials requires a long procedure that involves the optimization through the feedbacks received from both in vitro and in vivo experiments.

there is a great expectation from TERM for the development superior strategies.

Tissue Engineering and Regenerative Medicine

TERM promises to develop solutions for tissue regeneration typically by employing cells, scaffolding biomaterials, and signaling factors, either alone or in combination [122, 33]. An illustration of meniscus tissue engineering road map is depicted in Fig. 8. The major component of meniscus tissue engineering is the scaffold, i.e., when considering acellular strategies. The scaffold initially acts as a substitute for the missing native tissue, and hosts, and interacts with the cells that either seeded in vitro, and/or migrated into the scaffold in situ. Preferably, the autologous cells are isolated from the patient's biopsy that will receive the tissue engineered implant, and expanded in vitro to reach the needed number.

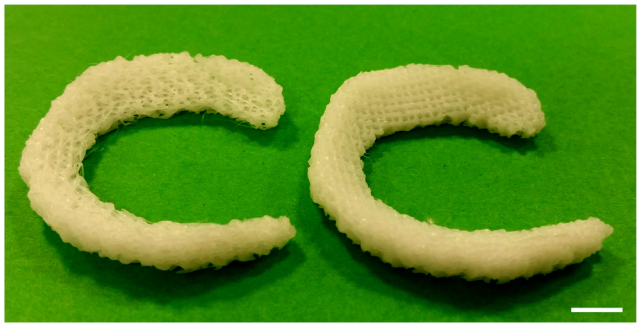

Fig. 9 3D-printed patient-specific scaffolds from polycaprolactone with different internal architectures using the 3D meniscus model that was obtained from the patent's high-quality MRI volumetric image dataset. The *scale bar* indicates 1 cm.

Mesenchymal stem cells have been used in regenerative strategies for the meniscus [123, 124] owing to their plasticity and multipotency and their function in tissue regeneration. The regeneration process can be improved by the use of autologous biologics.

The meniscus serves primarily as a biomechanical component of the knee. The size and shape of the scaffold are critical for the scaffold to function properly. With the use of medical imaging, the scaffold is manufactured in a patient-specific fashion (Fig. 9) from in silico 3D model of the tissue [125]. Once the cells and the biologics are introduced into the scaffold, and the implant cultured preferably in a bioreactor, the extracellular matrix will start to be synthesized inside the scaffold. Finally, the implant can be implanted into the patient.

One of the critical steps (or perhaps the most critical step) which is not yet proven to be achieved is the development of the ideal scaffold for meniscus tissue engineering. Many polymers have been studied as meniscal scaffold including but not limited to: collagen [126–129], poly(lactic acid) based [130–132], poly(glycolic acid) [133, 132], Poly (lactic-co-glycolic acid) [134, 135], polycaprolactone [136, 137], polycaprolactone/poly(ethyleneoxide) [138], hyaluronic acid/polycaprolactone [139–141], hyaluronic acid/gelatin [142, 123, 124], poly(glycolic acid)/hyaluronic acid [143], silk-based [144–146], gelatin/chitosan [147], vicryl [148], poly-(3-hydroxybutyrate-co-3-hydroxyvalerate [149], polyethylene terephthalate [150], and bacterial cellulose [151, 152]. Nevertheless, it is not possible to draw clear conclusions to define the *best* scaffold in contrast to the number of publications on this topic.

By default, no biomaterial is superior in overall than another one, and a certain biomaterial can be processed into a very wide range of different scaffolds by changing the parameters, or simply by using different manufacturing techniques including but not limited to: 3D printing technologies [125], freeze-drying [146], porogen leaching [146], electrospinning [153], and supercritical fluid foaming [154]. Thus, the number of scaffold options is not limited, although only two have successfully reached the clinics. Generally, synthetic polymers may present attractive features such as reproducibility,

mechanical strength, controllable biodegradation, and relative easiness for 3D printing. However, they may have relevant disadvantages regarding low bioactivity, hydrophobicity, and possibility of inflammation or immune response [155]. On the other hand, natural polymers may come with the advantage of superior bioactivity and 3D environment for cell adhesion and proliferation, while they may have their own disadvantages such as inferior mechanical properties, batch to batch variation, relatively less controllable degradation, and relatively uneasiness of 3D printing. Silk-based biomaterials have great potential for TERM applications [156, 157, 146]. Silks have promising biomechanical features, good biocompatibility and controlled rate of degradation [158, 146]. Several hydrogels [133, 159, 160] and decellularized meniscal scaffolds have also been investigated [161]. A pioneering strategy has been proposed in which the objective is to match the segmental vascularization of the meniscal scaffold [162]. The combinatorial use of distinct biomaterials showed promising results using a chick embryo model, as possibly the maintenance of phenotype of cells, and manage the blood vessels infiltration into the scaffold. Given the fact that the meniscus has partial blood supply limited to the outer periphery, this can be considered as a notable step forward to control neovascularization in meniscal scaffolds.

Nanobiomaterials have been studied for tissue engineering applications [163, 164] and can be fabricated with several methods into various structures including nanofibres [165, 138], nanoparticles [166], nanotubes [167], and nanofilms [168]. Nanotechnology can also be used to modify surfaces of biomaterials [169]. Nanobiomaterial production methods include electrospinning, self-assembly processes, phase separation, and various lithography-based methods. Having the biomaterial in nanoscale provides a highly increased surface area, surface roughness, and surface area to volume ratio yielding to an enhancement of physiochemical properties including surface topography, wettability, and energy. Thus, use of nanotechnology is an important tool to mimic the surface characteristics of natural tissues and to guide tissue regeneration [170].

Total meniscus substitution other than with an allograft is a bigger challenge compared to partial substitution. Besides, as mentioned above, degradable polymers have also been investigated; however, there is no biodegradable scaffold for total meniscus substitution in the market. In addition to the challenges with scaffolds for partial substitution, there are two more major challenges for the scaffolds for total substitution: (i) correct size and shape, and (ii) the attachments of the scaffold to the tibia. For the first challenge, Cengiz et al. [125] demonstrated how to make patient-specific meniscal implants from medical images. That study opens the door to the production of anatomically correct meniscal implants in two ways: (i) direct 3D production of the patient-specific implant through 3D printing and (ii) production of a patient-specific mold to be used for conventional production methods of biomaterials. Thus, as soon as the scaffolding biomaterial is developed, it can be produced in a patient-specific fashion. For the second challenge, the design of attachments of the non-degradable prosthesis can contribute to finding a solution, for example a non-degradable prosthesis made from polycarbonate-urethane which can be considered by the surgeon to be used for total meniscus substitution in selected cases if an allograft is not available [171, 172]. In the sheep model study of Lee et al. [173], anatomically correct polycaprolactone scaffolds were 3D-printed into anatomically correct scaffolds that were loaded with microspheres for the sequential release of connective tissue growth factor and transforming growth factor-β3 in a spatially and temporally controlled way. The release of growth factors provided instructive clues to induce endogenous cells to differentiate any produce zone-specific collagen types I and II to obtain a neotissue matrix and inhomogeneous mechanical properties that are similar to the native tissue [173]. This study has a clear significance regarding the manufacture of anatomically correct 3D-printed meniscus scaffolds, and the strategy of regenerating an inhomogeneous tissue which is the case of the meniscus.

The development of biomaterials and their experimentation requires a long procedure that involves the optimization through the feedbacks received from both in vitro and in vivo experiments. The not-yet-overcome challenges include the biomechanical and compositional dissimilarity of the new tissue to the native meniscus. As long as the scaffold meets the certain requirements of being a meniscus scaffold (such as suturability, biomechanical, and biological features), any scaffolding biomaterial has a degree of potential, and should be studied extensively in vitro, and in vivo. The researchers should consider the features is needed from a scaffold for meniscus regeneration, and should answer these questions positively:

- Is the scaffold correct in size and shape, or can be tailored at the time of surgery by the surgeon? (If not, then the implant will fail).
- Is the scaffold suturable? (If the scaffold does not hold the suture, then there is a very important problem) (This is one of the issues that can be found in scaffolds in the literature).
- Does the scaffold bear forces like compression, tension, and shear, and recover its shape after mechanical unloading? (If not, then the implant will fail).
- Does the scaffold have high porosity with interconnected pores that have a certain size range for cells to attach, proliferate, and migrate?
- Is the scaffold attractive to cells in terms of biology (This is one of the issues regarding the synthetic polymer-based implants).
- Is the degradation of the scaffold matched with neotissue formation? (This is one of the issues regarding the collagen-based implants).

- And, of course, does the scaffold meet the default requirements from biomaterials including the safety, biocompatibility, non-toxicity, allowance for cell adhesion, and proliferation?

The vast majority of the TERM research has been focused on scaffolds; however, recently, scaffold-free strategies have been demonstrated. The self-assembly definition of Athanasiou et al. [174] is "a scaffoldless technology that produces tissues that demonstrate spontaneous organization without external forces." Minimization of free energy via cell-cell interactions facilitates the self-assembly [174], where the cells act as a scaffold of each other and coalesce into a cohesive structure [175]. By its nature of being-scaffold-free, the self-assembly process has advantages over scaffolds by avoiding [175] biomaterial-induced inflammatory response, biomaterial degradation-related toxicity, stress-shielding, inhibition of cell migration, and issues with cell-to-cell communication that may limit the matrix remodeling of extracellular matrix. Self-assembly includes four major events [174]:

- High-density seeding of the cells into a non-adherent substrate
- Minimization of free energy through binding of cell adhesion receptors
- Cell migration and extracellular matrix synthesis
- Distinct regional matrix formation of and tissue maturation

Formation of chondro-like cellular aggregates with rabbit meniscus cells was shown in vitro through the formation of the cellular nodules between day 1 and day 3, nodular growth, highest at day 5, and nodular regression as of day 8 [176]. A ring-shaped well can be used for a tensile force to be provided upon the self-assembly and the contraction of the construct which can guide the fiber orientation too [177]. Catabolic enzymes and growth factors can be incorporated with the self-assembling process to achieve more maturated neotissue [178, 179].

Bioreactors are equipments that can regulate the conditions in vitro including mechanical stimulation, as well as the oxygen, pH, temperature, and nutrient supply to enhance the mass transfer between the media and the cultured cells [180–184]. Bioreactors are used for dynamic culturing instead of conventional static culturing. Moreover, they can provide a more uniform cell seeding. Given the meniscus being under mechanical stimulation during its normal function, introduction of mechanical and pressure stimulations appear to be more relevant than traditional static cell culture. A meniscus-specific bioreactor can provide a suitable stimulating environment for meniscus regeneration [185, 186]. A variety of bioreactors have been employed, including mechanical stimulation bioreactor [131, 187], rotating wall vessels [188], spinner flasks [150], and flow perfusion bioreactors [189].

Hydrostatic pressure has shown to be beneficial on both biomechanical and biochemical features of cellular scaffolds [190]. A dynamic compression bioreactor provided an increased collagen type I synthesis, and orientation of cells and collagen fibers [152]. After 2 weeks of culturing under a specific dynamic unconfined pattern for three times a week, a significant increase in matrix accumulation was observed [191]. However, at longer culturing periods, loss of matrix and mechanical properties occurred [191]. The effect of stimulation duration is also reported for spinner flasks, it was recommended up to a week because the level of glycosaminoglycans increases only a little after later time points, while the total level of collagens almost doubles [150]. Dynamic compression was beneficial for 2 weeks while 4 weeks did not bring any additional benefit [186]. Stimulations can be also combined, such as continuous perfusion and cyclic compression stimulation [187], or perfusion and on-off cyclic compression loading to enhance the functional properties of cellular scaffolds [192]. It was also shown that the pro-inflammatory gene expression in meniscus fibrochondrocytes can be regulated by biomechanical signals. Dynamic tensile forces can downregulate the pro-inflammatory responses by suppressing the interleukin-1β-induced inducible nitric oxide synthase gene expression, and synthesis of the pro-inflammatory mediators such as tumor necrosis factor-α, and matrix metalloproteinase-13 [193]. Besides, static and dynamic compression can affect differently the RNA levels of matrix proteins [194]. In some cases, the use of bioreactors was reported that they do not to provide a superior meniscus tissue formation as compared to traditional 2D static culturing methods. For example, the use of a rotating wall bioreactor did not significantly improve the cell growth and matrix production [133, 188]. This disagreement may be related to the difference of the study designs (e.g., used scaffolds, cells, growth factors, assay time points). The optimal stimulation regime for the meniscus is to be determined by the contribution of many future studies.

Animal experimentation has been performed to bridge the gap between in vitro and human use. In vivo experiments have two main consecutive objectives: (i) evaluation of safety and biocompatibility of biomaterials and inflammatory response and (ii) evaluation of the scaffolds' performance for meniscus regeneration. For the first objective, usually a mouse model is used and the biomaterial is implanted subcutaneously. Once the biomaterial is evaluated as safe, then the in vivo meniscus regeneration performance of the scaffold is evaluated with orthotopic models using relevant animal models. Table 1 shows the recent preclinical works of meniscus tissue engineering. The animal models used in meniscus tissue engineering include rabbit, dog, sheep, goat, pig, and horse [195, 196, 110]. Nevertheless, the cell morphology, and the extracellular matrix are different in animals and human [195]. Each model has its advantage and disadvantage in the validation of the

Table 1 Scaffolding biomaterials used in the recent preclinical meniscus tissue engineering studies, and the outcomes

Biomaterial	Cells	Animal model	Follow-up until	Reported outcome	Ref.
Collagen	Autologous mesenchymal stem cells	Horse	12 months	Treated defects were regenerated with fibrocartilaginous tissue formation; untreated lesions were partially repaired or not repaired	[126]
Collagen/hyaluronic acid scaffolds reinforced with poly(l-lactic acid)	–	Sheep	8 months	Rupture or progressive shape change of the scaffolds with severe narrowing. Inferior neotissue	[214]
Polycaprolactone	Rabbit mesenchymal stem cells	Rabbit	3 months	Meniscus-like tissue formation	[137]
Silk fibroin	–	Sheep	6 months	Loss of the scaffold in some cases. Similar cartilage degeneration as the control. No observed inflammation. Similar compressive properties as the native tissue	[144]
Collagen membrane	Injected autologous chondrocytes	Goat	6 months	The membrane application, with and without the cells, provided better results than the suture. Only a transient healing process with the use of collagen membrane without cells, and not sustained after 6 months. However, the inclusion of cells allowed a sustained tear healing after 6 months	[215]
Polylactic acid/polyglycolic acid	Human cartilage-derived morphogenetic protein-2 gene expressing dog myoblasts	Dog	3 months	Matrix production observed only with the scaffolds with the transfected cells	[216]
Collagen	–	Dog	17 months	Some cases had inflammation, but no infection. Formation of meniscus-like tissue infiltrated into the scaffold that incorporated into the native tissue. After 1 year, the histopathologic changes observed that is benign gradual assimilation of the scaffold into the native tissue with disintegration and gradual disappearance	[217]
Poly (L-co-D,L-lactic acid)/poly (caprolactone-triol)	Fibrochondrocytes from rabbit menisci	Rabbit	6 months	The scaffold adapted to the surrounding tissue without causing chronic inflammation, infection, and rejection. Neoformation of fibrocartilaginous tissue was achieved, while articular cartilage mainly preserved. However, no significant difference between cellular and acellular scaffolds was observed.	[218]
Hyaluronic acid/collagen derived	Autologous mesenchymal stem cells	Rabbit	3 months	The scaffolds seeded with stem cells and precultured in chondrogenic medium for 2 weeks before the implantation provides meniscus-like tissue formation	[123]
Hyaluronic acid/polycaprolactone	Autologous chondrocytes	Sheep	12 months	Cellular scaffolds provided increased fibrocartilaginous tissue formation, and higher tissue regeneration capacity. Excellent integration with surrounding tissues, connective tissue formation, and new vessel ingrowth	[141]
Poly (lactic-co-glycolic acid)	Autologous myoblasts cultured in a chondrogenic medium	Dog	3 months	The repair tissue was integrated with the surrounding tissue and mostly filled the defect, although it was fibrous and/or in some cases scar-like tissue. Thus, the tissue quality of the normal meniscus was not achieved	[134]

performance of a scaffold [195]. This is linked with the difference of animals and humans in kinematics and knee loading pattern, and the menisci are different regarding geometry, biomechanics, biocomposition, and cells. Moreover, surgical operations depend on the animal model, and easiness of handling and costs change. In general, menisci in the larger animal models are relatively more similar to human menisci regarding size. However, the use of a rat model has been also

reported [197]. Nevertheless, it is critically important to have a clinically relevant defect model as well as the chosen animal. The defect models of meniscectomy or tears are relevant. Although, some authors used punch defects [124, 198]. Before conducting an animal experimentation, several questions should be considered:

- Do in vitro and physicochemical results support further in vivo experiment?
- Is the biomaterial first shown to be safe using a small animal model?
- Is a relevant animal chosen for the scaffold and cells to be used?
- Is a relevant defect model chosen?
- Are the follow-up time points relevant?

Biologics are biologically active natural components that can enhance the tissue healing including growth factors [199, 200] and platelet-rich plasma (PRP). PRP is one of the attractive blood-derived biologics by being a great source of growth factors (including platelet-derived growth factor, endothelial growth factor, and transforming growth factor) and both anti- and pro-inflammatory cytokines (including interleukins 4, 8, 13, and 17; tumor necrosis factor-α; and interferon-α) that can influence the tissue healing [201–205]. Given the big differences in the study designs (including the preparation of PRP, and inclusion/type of cells and scaffolds) as well as the absence of standardization of the evaluation of the outcomes of the biological treatment studies, there are opposing views on the outcomes of PRP treatments [33]. Moreover, injection of PRP into the tissue is different than the use of PRP in a tissue-engineering strategy where PRP and cells are introduced into a scaffold, and cultivated in vitro.

The idea of gene therapy [206–208] is based on the transfer of exogenous genes or its complementary deoxyribonucleic acid into target somatic cells directly or using viral or non-viral methods. The study of Goto et al. [209] is a leading work on this strategy for meniscus while there are more recent studies [210–213]. In that study [209], the genetic transduction of a bacterial marker gene was done using either a retrovirus or an adenovirus as the vector. When retrovirus was used, the retrovirally transduced meniscus cells that were embedded into collagen gels were introduced to the meniscus defect. When adenovirus was used, a suspension of blood and adenovirus was prepared, and then a clot was introduced to the defect. They showed that the expression of genes could be observed for a minimum of 20 weeks in vitro, and a minimum of 3 and 6 weeks in rabbit and dog models, respectively [209]. Accordingly, new advanced treatments can be developed through the transfer of genes to regulate the synthesis of growth factors, and both meniscus regeneration and degeneration might be managed [33].

Conclusions

There has been a progressive increase in indications for meniscus repair opposing to meniscectomy thanks to the understanding of the meniscus functions and the consequences of the absence of meniscus in the knee joint. Nevertheless, meniscectomy has been providing a satisfactory outcome for treatment of irreparable meniscus lesions, while meniscus repair has proven to be satisfactory in appropriately selected cases. Still, meniscectomy keeps being a very frequent procedure. Technological and surgical developments provided an increase in the indications for meniscus repair. Some injuries that were previously considered as irreparable such as horizontal cleavage tears, radial tears, and root tears, are today considered as potentially reparable. When repair is not possible, meniscus substitution by allografts or acellular scaffolds provides favorable clinical outcome when correct indications are considered. Preoperative planning is required for more efficient classification, subsequent prognosis, and treatment. Moreover, the surgeons should be trained for several repair options.

The future of meniscus substitution is strongly supported by the clinical need. TERM promises the development of new scaffolding biomaterials together with other technologic advances, biological and genetic enhancements. Nevertheless, the ideal meniscal implant has not been yet developed. The main outstanding challenges in meniscus regeneration that are greatly linked include:

- An implant that successfully functions as a healthy meniscus because the ultimate rationale of substitution includes the chondroprotection and prevention of osteoarthritis, i.e., the avoidance of the consequences of meniscectomy
- A clear success in the concurrent satisfaction of the biological, biomechanical, and surgical requirements including suturability of the implant
- A clear success in obtaining a fully mature tissue that is similar to the healthy meniscus in terms of extracellular matrix composition and organization, thus, also function in the knee joint
- A clear success on the development of (i) non-uniform implants because menisci are not uniform biologically and biomechanically, and (ii) distinct implants for medial and lateral meniscus since they are not the same regarding the biomechanics and biology

The biological and biomechanical requirements are linked with implant's patient-specificity regarding the cells, biologics, and implant geometry. To achieve such a success, active participation of meniscus surgeons is of the essence in the process of scaffold and drug delivery systems (e.g., nanoparticles) development, in vitro experiments, and preclinical in vivo trials.

Acknowledgements This article is a result of the project FROnTHERA (NORTE-01-0145-FEDER-000023), supported by Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF). 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).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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