Review Article

The Meniscus and Meniscal Scaffolds for Partial Meniscal Replacements

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Abstract

The meniscus is the most common damaged structure of the knee, accounting for almost one million cases of knee surgeries performed annually in the United States alone. A complete meniscectomy (complete meniscus removal) was the most common procedure performed in 1889 and was the standard procedure in the next 80 years. However, follow-up radiographic studies from the late 1960s to 1980s reported a high frequency of post-meniscectomy osteoarthritis of the knee.

The meniscus functions to transmit load, absorb shock, stabilize the knee joint and nourish the joint. A complete integrity of the meniscus is crucial in maintaining the normal biomechanics of the knee and preventing the onset of premature or traumatic osteoarthritis. 3D Printing of silicone allows arthroscopic replacement of damaged menisci, either totally or partially, enabling the patient to return to work and sports almost instantaneously after surgery.

This review summarizes the meniscal structure, biomechanical properties, meniscal lesions, the characteristics and clinical outcomes of various biodegradable synthetic and biological meniscal scaffolds.

Meniscal Structure and Biomechanical Properties

Meniscal Anatomy

The menisci are a pair of fibrocartilaginous cushions which sits on the tibial plateau in the knee joint. They act as knee cushions which transmit body weight evenly across the knee joints, thus minimizing contact stresses between femur and tibia and damages to the articular surfaces. Meniscal injuries predisposed the knees to developing premature osteoarthritis (Figure 1).
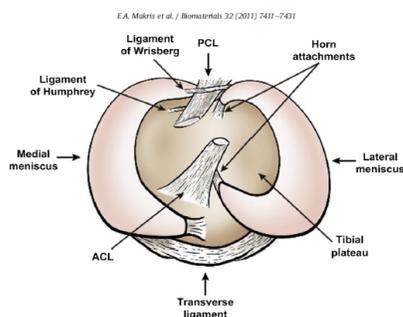

Figure 1: Anatomy of the meniscus.

The meniscus is divided into 3 zones, the outermost vascular red-red zone, middle red-white zone and the innermost avascular white-white zone. Cells are spindled-shaped in the outermost red-red zone while chondrocyte-like in the innermost white-white region.

The meniscus obtains its limited blood supply from the perimeniscal capillary plexus within the synovial and capsular tissues of knee. These plexus, extending for one to three millimeters over the articular surfaces of menisci, are branches of the inferior and superior branches of the lateral and medial geniculate arteries.

The vascular supply to meniscus is age dependent. In adult, tears which occur at the most vascularized, peripheral 3 mm of the menisci are most amenable to repair and cellular regeneration, as opposed to the generally avascular tears, greater than 5 mm from the menisci-synovial junction, which are not reparable. For both the medial and lateral menisci, the vascular penetration is about 10-30% (Figure 2).
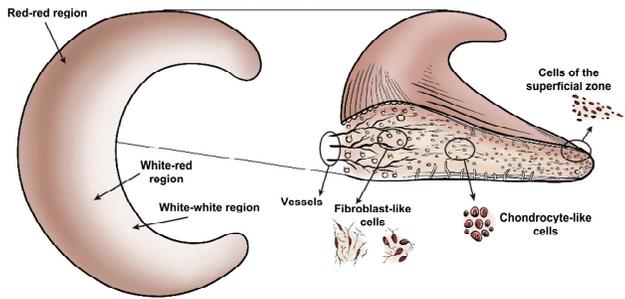
Figure 2: Regional variations in vascularisation and cell population of the meniscus.

## Meniscal Composition and Cell Characteristics

The meniscus has a highly heterogenous mix of ECM and cellular distribution. Meniscal ECM is categorized by region. More than 80% of the red-red region is composed of type I collagen by dry weight and the remaining comprises collagen types II, III, IV, VI and XVIII.

In the white-white region, total collagen comprises 70% of dry weight, with collagen types II and Types I accounting for 60% and 40%, respectively (Figure 2).

Meniscal Lesions and Development of Knee OA

Meniscal injuries eventually can lead to knee OA and knee OA induces further meniscal tears, thus propagating the vicious cycle. An injured meniscus triggers the synovium to release various inflammatory cytokines, which further induce degenerative changes within the matrix body and cause meniscal extrusion from the knee joint. These extrusions increase the stress on the tibial cartilage and further aggravate the injury [1].

Similarly, the collagen fibers are arranged randomly in the most superficial region, radially in the middle layer and circumferentially in the innermost layer. The circumferential fibers provide hoop-stress against the compressive loads exerted across the knee-joint (Figure 3). The circumferentially arranged fibers have a tensile strength of 50 to 300 MPa, while the radially arranged fibers have a tensile strength of 3 to 70 MPa.
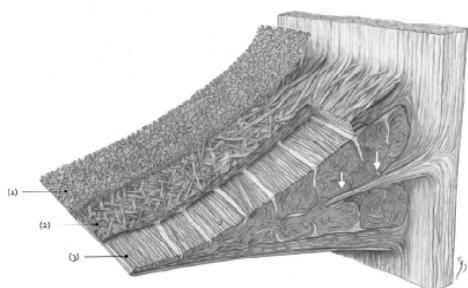
Figure 3: Ultrastructure of collagen fibers within meniscus.

Meniscal Injury Patterns

All meniscal lesions can be classified into eight categories according to the Casscells classification, namely i) Vertical longitudinal (bucket handle, ii) Vertical transverse (radial), iii) Horizontal tear (cleavage), iv) Oblique tear (flap), v) detachment of meniscal horns, vi) complex tear, vii) Degenerative and viii) miscellaneous (discoid),

However, for therapeutic purposes, the meniscal injuries can simply be classified clinically into peripheral meniscal lesions and central avascular lesions. The pattern of meniscal lesions is also age-dependent. Traumatic injuries in the young and athletes usually result in longitudinal tear patterns or vertical radial full thickness tears pattern. These tears usually occur in the vascular red-red zones and are therefore more amenable to repair. On the contrary, degenerative tears in the elderly are usually horizontal, intra-substance and complex in nature. These lesions are less amenable to repair [2].

Meniscal Treatment Options

Conventional treatments include meniscal repairs, partial meniscectomies, total meniscectomies, partial meniscal substitute replacements, porous meniscal implants or total artificial meniscal replacements, allograft and autograft meniscal transplantations [3-8].

A partial meniscectomy is usually performed for irreparable or degenerative meniscal lesions. However, the procedure reduces the contact area between the femoral condyle and tibial platform, thus predisposing the knee to osteoarthritis [9].

Consequently, more emphasis is placed on meniscal repair and reconstruction techniques. Repair procedures range from inside-out, outside-in and all inside techniques [10].

Meanwhile, reconstructive strategies restoring meniscal functions such as meniscal allografts, Small Intestinal Submucosa (SIS) implants and autogenous tendon grafts have also been experimented [11-13].

The first free meniscal allograft transplantation, performed by MIlachowski and Wirth in 1984, reduces pain and improves knee functions in relatively young patients after a short follow-up. However, its chondroprotective effects have not been proven. Concerns of disease transmission, graft shrinkage and deteriorating material properties have hindered its widespread use [14-16]. Similarly, the SIS and autogenous tendon grafts have not obtained satisfactory results [17,18].

Mechanical Properties and Force Transduction of Meniscus

From table 1, the posteromedial region of the meniscus has

the lowest compressive properties and tensile modulus. These results, together with the relative immobility of the posterior horns of the meniscus as shown above, would explain the frequent occurrences of most clinical traumatic tears in these regions.

Study	Compressive Aggregate Modulus MPa	Tensile Properties Stiffness MPa
Medial Superior	Human Meniscus Sweigart et al.	Circumferential fibers (lateral meniscus)
Anterior	0.15 +/- 0.03	124.58+/-39.51
Central	0.10 +/- 0.03	91.31 +/- 23.04
Posterior	0.11 +/- 0.02	143.73+/-38.91
Medial Inferior	(Medial meniscus)	
Anterior	0.16 +/- 0.05	106.21+/-77.95
Central	0.11 +/- 0.04	77.95+/-25.09
Posterior	0.09 +/- 0.03	82.36+/-22.23

Table 1: Posteromedial region of the meniscus has the lowest compressive properties and tensile modulus.

The Effect of Knee Flexion on Knee Contact Area and Joint Forces

By occupying 60% of the total contact areas between femur and tibia, the menisci distribute forces evenly the underlying articular cartilage, thus minimizing point contact. The contact area decreases 4%, with simultaneous increase in contact forces, for every 30 degrees of knee flexion.

The menisci bear 40 to 50% of the total transmitted load across the knee joint in extension and 85% of the total transmitted load across the knee joint at 90 degrees flexion. In full knee flexion, the lateral meniscus and medial menisci transmit 100% and 50% of the load respectively.

The meniscal motion allows maximal congruency during knee flexion and helps to protect the menisci from injury. In the study by Vedi V et al. [19], meniscal movement was studied using a dynamic MRI: With weight bearing, the anterior horn of medial meniscus moves through a mean of 7.1 mm, the posterior horn moves 3.9 mm and 3.6 mm of mediolateral radial displacement. With weight bearing, the anterior horn of the lateral meniscus moves 9.5 mm, the posterior horn moves 5.6 mm and there was 3.7 mm of radial displacement. This relative immobility of the posterior horn of the medial meniscus may account for its susceptibility to injuries and tears. With sufficient stress, usually rotatory nature in a weight bearing, flexed knee, either meniscus may be torn insubstance or from its peripheral attachment [20,21].

Being a secondary knee stabilizer, the menisci confer some stability to the normal knees and especially the ligament-deficient knees. The menisci are connected anteriorly by the transverse ligament and attached peripherally to the capsular ligament on the medial and lateral side of the knee joint and its horns to the inter-area of the tibia.

The Effect of Meniscectomy (Removal of Meniscus) on Contact Forces

Both Paletta and Kurosawa et al. reported a 50% decrease in total contact area and corresponding 200 % to 300% increase in peak local contact load, following a total meniscectomy. Correspondingly, partial (16to34%) meniscectomy leads to a greater than 350% increase in contact forces on the articular cartilage [8,22].

Meniscal Scaffolds

4 types of Materials for Meniscal Scaffold Fabrication

Tissue-derived materials: Tissue-derived materials including periosteal tissue, small intestine submucosa, acellular porcine meniscal tissue and de-acellularized tissue or Extracellular Matrix (ECM). These materials, being biocompatible and bioactive, provide a natural environment for cell adhesion, migration and ECM deposition. The disadvantages are limited supply and poor mechanical properties.

Chondrocytes seeded SIS scaffolds, when compared to those in Polylactic Co-Glycolic Acid (PLGA) scaffolds, yielded higher sulfated GAG and hydroxyproline content. In contrast to human, fetal bovine and crosslinked dermis isolates, SIS also demonstrated preferential retention, infiltration and viability of the canine meniscal cells. Besides the disadvantages mentioned above, optimal pore sizes of 100 to 150 microns are difficult to achieve with SIS.

Decellularized meniscal scaffolds provide suitable cellular microenvironment and meniscal geometry. Decellularised meniscal scaffold can be firstly obtained using a complex procedure which comprises freeze thawing, SDS and disinfection, as described by Stapleton et al. [23] Stabile et al. [24] subsequently applied oxidation to improve scaffold porosity and Maier et al. [25] used enzymatic process to reduce immunogenicity of the scaffold. Finally, growth factors and recombinant human BMPs were used to induce and improve chondrocyte migration into the scaffolds.

Azhim et al. [26] has also used a neoteric sonication decellularization system to fabricate a bovine meniscal scaffold. Despite having good mechanical properties, the sonication process significantly changes the native ECM and collagen fibers arrangement.

ECM Matrix Components: ECM matrix components are naturally derived substances such as collagen, proteoglycans and elastin. Regen Biologics pressure-heat molded a bovine Achilles

tendon into Mena flex-a Collagen Meniscal Implant (CMI). A 10-year follow-up study showed pain relief and functional improvement in knee joints. However, the shrinking and remodeling processes of these allografts may eventually compromise the mechanical strength of the implant. Its chondroprotective effect has yet to be proven.

Mena flex (CMI) CMI is a purified type I collagen isolated from bovine Archilles tendon, the remaining is composed of GAGs including chondroitin sulfate and hyaluronic acid. It is chemically cross-linked with formaldehyde and sterilized using gamma-radiation.

Comparative follow-up clinical studies, with duration ranging from 3 months to 10 years, supporting and validating the use of CMI scaffolds have also been performed and will be described below.

Stone KR et al. initially showed that CMI supports new tissue ingrowth, is assimilated into the new tissue and is gradually being replaced with immature collagen over 3 to 6 months in a phase I clinical feasibility study. [62] Reguzzoni subsequently observed at 6 months the development of parallel lacunae walls with collagen fibrils, blood vessels and fibroblasts-like cells after posterior horn CMI use [15]. Rodkey, in a 2-year clinical follow-up of 8 CMI patients, validated CMI's ability to support new tissue regeneration and symptomatic improvement [28].

Bulgheroni showed improvement in Lysholm and Tegner scores in mid-term results in 28 patients receiving CMI implants and knee scores were unchanged between 2 and 5 years after surgery. Radiographic evaluation also showed no failure at 5 years [29]. Steadman and Rodkey at 5.8 years follow-up reported improvement in mean Lysholm and Tegner Activity Scores. MRI evaluation did not demonstrate any chondral surface degeneration. Biopsies evaluation also did not reveal any evidence of infection, inflammation or immune reaction. On second look arthroscopy, it was estimated 60% of meniscal defect was filled by the scaffold [30].

A summary of various absorbable and permanent materials used in fabricating meniscal scaffolds is presented in Tables (1, 2).

A summary of various clinical outcomes, complications and reoperations of various scaffolds is presented in Table 3.

Table 1. Properties of different types of materials used in engineered meniscal scaffolds.

Materials	Properties				
	Mechanics			Bioactivity	Logistics
	Mechanical Properties (Elastic Modulus)	Anisotropy	Geometry (Biomimetic)		
Tissue-derived Materials	Periosteal tissue: 8–12 MPa SIS: 12–25 MPa Porcine meniscus: 110–200 MPa	Highly anisotropic	Highly biomimetic	High	Low
ECM Components	250–500 kPa	Anisotropic	Biomimetic	High	Medium
Synthetic Polymers	200–5000 MPa	Highly anisotropic	Depends on the fabrication method	Low	High
Hydrogels	0.01–10 MPa	Isotropic	Depends on the fabrication method	Medium	High

Table 2: Properties of Different Types of Materials Used in Engineered Meniscal Scaffolds.

Monllau et al. in a 10-year follow-up of 25 patient with implanted CMI, reported better pain relief and functional improvement, with significant improvement in Lysholm and VAS pain scores [31]. Zaffagnini, in a prospective 10-year follow-up long-term outcomes study of the medial collagen meniscus implant versus partial medial meniscectomy, demonstrated the former group having significantly lower VAS pain scores and higher objective IKDC, Tegner index, SF-36 and Physical Health Index [32]. Moher et al. also reported improvement on all clinical scores (Lysholm, Tegner, IKDC, VAS Pain score) at 2 years when CMI was used in the lateral joint space [33].

The only CMI prospective multicenter randomized control trial, comparing the clinical results of CMI with partial meniscectomy at 4.9 years follow-up in 311 patients, was conducted by Rodkey et al. [28]. The patients were first divided into an acute and chronic group. The former had no prior surgery while the latter had previous surgery to the involved meniscus. The patients in both the acute and chronic groups were then randomized to undergo either CMI surgery or partial medial meniscectomy treatment (control). In the chronic group, positive biopsies result of CMI obtained one-year post surgery showed that the implant scaffold was able to direct the formation of meniscus-like matrix by the

host. Patients in the CMI group also regained more activity and required fewer reoperations than the partial medial meniscectomy control group. However, these improved clinical outcomes were not reflected in the acute group [28].

Stone et al. used Bovine Archilles tendon to manufacture co-polymeric collagen-based scaffolds to repair subtotal meniscectomy in dogs without seeding cells. Scaffold implanted group showed substantial meniscal like regeneration in 63% of joints [34]. These very important findings suggest a need for a new meniscal scaffold which can function in the acute setting.

Synthetic Polymers: Polyurethane (PU), Polyglycolic Acid (PGA), Polylactic Co-Glycolic Acid (PLGA) and Polycaprolactone (PCL) are amongst the most commonly used absorbable synthetic materials in the fabrication of meniscal scaffolds [35]. They can be customized to various geometry, fiber diameter, porosity, pore size, biomechanical strength and degradation rate [35].

However, their hydrophobic properties, aseptic inflammation, immune responses and side effects from degradation byproducts limit their applications. For example, diisocyanato from degradation of PU is toxic. The degradation of PLGA generates acidic byproducts, which cause inflammatory responses and damage local tissues [36].

Polyurethane is a highly porous, thermoplastic and biocompatible elastomer template which can bridge torn tissue in the red-red zone of the meniscus. Its relatively long degradation time of 4 years makes it ideal for use in tissue engineering. The arthroscopic appearance, cellular distribution, scaffold bioactivity and mechanical properties of the meniscal scaffolds can be accurately replicated, as shown in the following studies by Verdonk and Esposito.

Verdonk examined the arthroscopic appearance of the acellular polyurethane scaffold replacement in 52 patients who had partial meniscectomy. Cartilage stability was observed in 92.5% of the patients. 3 had cartilage degeneration and 9 had scaffold failure due to arthroscopic fixation failures [19].

Esposito et al. reinforced PLDLA with PCL in a 90 to 10 ratio (w/w) [37]. The polyester polymer scaffold was seeded with fibro chondrocytes, implanted into NZ white rabbits and anchored at the anterior and posterior horns using nylon sutures. At 12 and 24 weeks, the PLDLA/PCL scaffold showed similar circumferential and radial distribution of the fibrocartilage fibers as those in the native meniscus.

Actifit is a novel, synthetic, acellular, bio absorbable, acellular, highly porous (80%) scaffold, used clinically to treat partial meniscal lesions. It comprises PCL (80%) and PU (20%). PCL can take up to 5 years to degrade by hydrolysis of the ester bonds within it. PU either gets phagocytosed or integrates into the

surrounding tissues over a long period. The interconnected pores encourage vessel ingrowth and meniscus regeneration. Thus far, both preclinical and clinical studies have supported the use of Actifit PU scaffolds. In the preclinical canine studies, Tienan and Klompmaker et al. showed scaffold integration with the peripheral capsule and complete pore infiltration with vascularized tissues without causing foreign body reaction [38,39].

Verdonk et al. in the first clinical study of 52 patients with PU scaffold implanted after partial meniscectomy, showed 81.4% (35 of 43 implanted menisci) had tissue ingrowth at 3 months with dynamic contrast-enhanced MRI. Cartilage status remained stable. At 2-year follow up there was statistical significant improvement in all clinical scores including Knee Injury and Osteoarthritis Outcome (KOOS), Lysholm, VAS and IKDC scores [19]. Meanwhile, Baynat also showed normal chondrocytic penetration into the Actifit scaffold one-year post implantation. All patients also resumed their daily and sporting activities 2 years after surgery [40]. In another one-year follow-up by Efe et al. of 10 patients with PU meniscal scaffolds, there was also significant improvement in KOOS and Knee Society Scores [41]. MRI also showed stable scaffold architecture and preserved articular cartilage. At 2 years, there was consistent improvement in all patient-reported outcome scores. One case of scaffold resorption and scaffold extrusion did not affect overall clinical outcome.

Spencer et al. reported satisfactory outcome after a follow-up of 19.1 months in 23 patients with both CMI (12 patients) and Actifit (11 patient) implants. The Actifit group had greater than 50% infill of regenerative tissue in 80% of the cases that underwent second-look arthroscopy at 1 year [42]. Kon et al. reported improved knee outcomes using the IKDC and Tegner scores 2 years after surgery. However, different clinical outcomes were observed in patients with knee pain caused by different knee pathologies requiring combined surgeries such as microfracture, chondro abrasion, osteochondral scaffold implant or osteotomy [36,43]. Thus, it is essential to standardize patient groups when making comparisons.

In contrast to most mainstream studies looking at both medial and lateral knee compartments, Bouyarmane et al. specifically looked at the lateral knee compartment in 54 patients. Pain (VAS) and function outcome scores (IKDC and KOOS) also improved at 2 years, showing the safe and effective use on the lateral side [44]. Compared to the 12 out of 15 review studies detailing the use of CMI in partial meniscal repair, conducted in different settings by Rodkey et al. [45], Stone et al. [34], Steadman and Rodkey [10], Reguzzoni et al. [15], Zaffagnini et al. [46], Bulgheroni et al. [29], Monllau et al. [31] and Spencer et al. [23], the use of Actifit polyurethrane scaffold was only reported by the 3 remaining studies by Efe et al. [41], Verdonk et al. [47] and Spencer [21,24].

Nevertheless, partial replacements using both CMI and Actifit have achieved significant and encouraging clinical results when compared with baseline values or controls. There is, however, no statistical or clinical significant difference between the beneficial effects seen in both CMI and Actifit groups. Other biopolymers which have been used for meniscal scaffolds include Silk fibroin, bacterial cellulose, Micro-Channeled Cellulose Scaffold (MCCS) and platelet-rich plasma. SF Silk are fibrous proteins commonly used in the tissue engineering of articular cartilage, ligaments and bones. Silk are selected for their biosafety profile, biocompatibility, versatility and biodegradability.

Mandal used silk fibroin from *Bombyx mori* silkworm cocoons to produce a multilayer, multi-porous meniscal scaffold, with fibroblasts seeded outside and chondrocytes seeded inside. The final scaffold product has an architectural morphology and cellular distribution like that of the native meniscus [48].

Although compressive and tensile moduli increase over time, they remain inferior to native meniscus. The durability of the porous scaffold in sheep specimen with medial meniscal defect has been shown by Gruchenberg to last for at least 6 months, without any macroscopic or histologic abnormalities [49].

Yan et al. prepared SF which was leached with granular NaCl and freeze dried to produce porous scaffolds ranging from 8-16% SF by weight. 16% SF scaffolds have less porosity and interconnectivity but superior mechanical strength. The observed compressive modulus for the 16% SF scaffold was 15.14 +/-1/7 MPa, comparable to that of a natural meniscus [50]. Bodin et al. used bacterial cellulose, a polysaccharide synthesized by *Gluconacetobacter xylinus*, in blood vessel, cartilage and bone tissue engineering. Bacterial cellulose was shown to be biocompatible, biomechanically superior, highly hygroscopic and crystalline [51]. Its compressive modulus at 10% strain (1.8kPa) was five times better than that of collagen meniscal implant. (0.23 kPa).

Martinez et al. showed that Micro-Channeled Cellulose Scaffold (MCCS) allow seeded fibroblasts to adhere and migrate within the microchannels, facilitated the radial alignment of collagen fibers with cell proliferation significantly higher in the MCCS than in the unmodified cellulose scaffold [52]. Finally, Ishida et al. showed the combination of PRP and gelatin enhances meniscal regeneration [53].

Hydrogels: Hydrogels are hydrophilic colloids constructed by a network of crosslinked natural or synthetic polymer chains. They have been selected for their safety profile, viscoelasticity and biocompatibility. Their physical properties, non-cytotoxic features and versatile properties allow for cell mixing and growth factors loading. However, hydrogels are not mechanically strong or bioactive [54]. Thus, Double-Network (DN) hydrogels were developed, which can offer excellent mechanical properties-even

with the water content exceeding 90%- and a dynamic stiffness value comparable to that of the swine meniscus [11]. Some crosslinking agents such as glutaraldehyde enhance the biological stability but suppress the implants' immunogenicity and lead to over-crosslinking and cytotoxicity [31].

Kobayashi et al. has shown encouraging results in the rabbit meniscus-deficient knee studies when comparisons were made between the PVA-H menisci implanted group and the meniscectomy group. In contrast to the PVA-H meniscus group which has normal articular cartilage and implant even after 2 years post-surgery, the meniscectomy group has osteoarthritis set in just one year and continue to progress [55,56]. Using projection stereolithography, Grogan et al. constructed a 3D methacrylated gelatin (GelMA) meniscal scaffold which has collagen alignment and was able to direct cell growth 3 weeks post meniscal cell seeding [57]. Sarem et al. fabricated macroporous multilayered gelatin G/chitosan Cs scaffold. Cs in conjunction with G, enhances bioactivity of Cs and improves G hydrophilicity of water retention and nutrient transfer [58].

Cell Sources for Meniscal Scaffolds

Both Mesenchymal Stem Cells (MSCs) and Costal Chondrocytes (CC) have been used in the study of meniscal scaffolds. MSCs can be harvested from various adult tissues and differentiate into cells of different lineages like bone, muscle, cartilage, tendon, ligaments and other connective tissues. MSCs can be seeded into the scaffolds to produce new matrices to repair meniscal defects and complement type I collagen sponges, decellularized meniscus and hyaluronan/ gelatin composites CC can be harvested easily and expanded *in vitro* to generate large quantities of fibrocartilaginous matrix with GAGs, collagen type I and II Different studies have not shown uniform results of cellular seeding on the final architecture, morphology and biomechanical properties of the meniscal scaffolds. Koller et al. increased the bioactivity of HA/PCL scaffold by adding PET (Polyethylene Terephthalate) [59]. Koller also bonded PGA with PLGA (75:25) to produce meniscus-like scaffold [60]. After seeding of allogenic meniscal cells, the regenerated neomenisci had similar biomechanical properties as the native menisci. However, it was unclear whether unseeded meniscal scaffolds could attain the same properties as seeded meniscal scaffolds.

Baker and Mauck, on the one hand, were able to electrospin biomechanically similar scaffolds which were able to direct cell growth [61] Similarly, electrospinned circumferential AL scaffolds by Fischer was able to direct circumferential cellular arrangement, similar to that seen in native meniscus, after bovine stem cells seeding.

On the contrary, Chiari et al. using HA and PCL scaffolds to repair total and partial sheep meniscus defects, demonstrated that

despite the absence of cells, the implant retained its morphology and remained in position for 6 weeks, with successful implant integration into native tissues [62].

Meniscal Allograft Transplantation

Meniscal allografts have similar biomechanical properties as the native meniscus but are compounded by problems of disease transmission and immune rejection. In the landmark study by Van Der Straeten et al. from 1989 till 2013, 329 Meniscal Allograft Transplantation (MAT) were performed in 313 patients. Clinical and radiographic results and MAT survival were evaluated retrospectively. The mean patient age at surgery was 33 years and 60% were male patients. 156 cases had healthy to mildly damaged cartilage. 130 cases had moderately to severely damage cartilage. 118 patients had concurrent procedures including cartilage procedures, osteotomy or ACL-Reconstruction.

The survivorship of the transplanted meniscal allograft is determined by the age of patient, condition of articular cartilage and concurrent surgical procedures at the time of index surgery. Cumulative allograft survivorship was 15.1% at 24 years. The allograft survivorship in patients younger than 35 years old at surgery was significantly higher (24.1%) compared to those in patients older than 35 years old (8.0%). More allografts survived (43.0%) in knees with healthy or mildly damaged cartilage, when compared to those in knees with moderately to severely damaged cartilage (6.6%).

None of the meniscal allograft survived at 24 years in cases with simultaneous osteotomy. In addition, 61% of patients underwent at least one additional surgery (1-11) for clinical symptoms after MAT [63]. Finally, MAT did not delay or prevent tibiofemoral OA progression. 19.2% were converted to a knee prosthesis at a mean of 10.3 years. Patients younger than 35 with healthy or mild cartilage damage may benefit from MAT for relief of symptoms (survivorship 51.9% at 20.2 years), but with a high number of surgical re-interventions.

Common Fabrication Technologies for Meniscal Tissue Engineering (table 3)

Table 2. Common fabrication technologies used in meniscal tissue engineering.

Scaffold Structure	Fabrication Method	Pros & Cons
Sponge scaffold	Particulate leaching	(+) highly porous scaffolds with porosity values up to 93% (−) only used to produce thin membranes up to 3 mm thick
	Gas foaming	(+) organic solvent-free process (−) a structure with largely unconnected pores (−) non-porous external surface
	Freeze drying	(+) highly porous scaffolds with porosity values >90% (+) reduction of toxic solvents use (+) elimination of time-consuming drying and leaching processes of porogen components (−) instability of the emulsion (−) difficulty in controlling the pore size and porosity
	Phase separation	(+) highly porous scaffolds with porosity values >90% (−) limited range of pore size (<200 um) (−) difficult to control the micro- and macro-structure of the scaffold
Non-woven fibrous scaffold	Electrospinning	(+) nanofibrous architectures (+) wide range of fiber diameters (+) wide range of polymers can be used (−) used solvents can be toxic (−) limited capability to fabricate biomimetic structure
Oriented/woven fibrous scaffold	FDM/PED	(+) layer by layer architecture (+) ability to fabricate complex structures (−) low resolution (−) limited range of materials
	EHD-jetting	(+) layer-by-layer architecture (+) ability to fabricate complex structures (−) used solvents can be toxic

Table 3: Common Fabrication Technologies Used in Meniscal Tissue Engineering.

Commercially Available Meniscal Scaffolds

Three types of biodegradable and biocompatible scaffolds are available commercially to replace partial meniscus defects: 1) Mena flex CMI from ReGen Biologics, Inc. (ReGen Biologics, Inc, Cary, NC, USA), 2) Actifit® scaffold from Orteq Ltd. (Orteq Ltd., London, UK), and 3) NU surface® Meniscus Implant from Active Implants (Active Implants, LLC., Memphis, TN, USA).

Mena flex CMI and Actifit® scaffold are partial meniscal substitutes with equivalents in histological, radiological and clinical evaluations [11]. They have received the Conformité Européenne (CE) mark in Europe whereas the US Food and Drug

Administration (FDA) believes that additional data are needed to confirm their efficacy on chondral degradation and prevention of osteoarthritis development [41]. NUsurface® Meniscus Implant is the first total meniscal substitute and has been used in Europe under CE Mark since 2008 and in Israel since 2011 [2]. It is currently undergoing SUN Clinical Trial in the United States.

Future Prospects for Meniscal Scaffold

Current artificial meniscal implants, such as CMI and Actifit, have only been able to address chronic meniscal injuries but not acute ones. Future trends of mensical scaffolds research should focus not only on conferring the ability to customize, detect, respond and alter load-bearing properties with time and varying angles of flexion, but also integrating self-healing properties into the scaffolds, independent of cell-seeding. As the meniscus is relatively acellular, further studies are required to ascertain the exact contribution of cellular seeding to mechanical strength in the early stage of repair the final meniscus scaffolds should allow instantaneous weight bearing and arthroscopic meniscal replacement to facilitate surgery, speedy rehabilitation and return to work for patients.

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