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Review

A review of strategies for development of tissue engineered meniscal implants

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ABSTRACT

The meniscus is a key stabilizing tissue of the knee that facilitates proper tracking and movement of the knee joint and absorbs stresses related to physical activity. This review article describes the biology, structure, and functions of the human knee meniscus, common tears and repair approaches, and current research and development approaches using modern methods to fabricate a scaffold or tissue engineered meniscal replacement. Meniscal tears are quite common, often resulting from sports or physical training, though injury can result without specific contact during normal physical activity such as bending or squatting. Meniscal injuries often require surgical intervention to repair, restore basic functionality and relieve pain, and severe damage may warrant reconstruction using allograft transplants or commercial implant devices. Ongoing research is attempting to develop alternative scaffold and tissue engineered devices using modern fabrication techniques including three-dimensional (3D) printing which can fabricate a patient-specific meniscus replacement. An ideal meniscal substitute should have mechanical properties that are close to that of natural human meniscus, and also be easily adapted for surgical procedures and fixation. A better understanding of the organization and structure of the meniscus as well as its potential points of failure will lead to improved design approaches to generate a suitable and functional replacement.

1. Introduction

The medial and lateral menisci of the knee are fibrocartilage tissues that serve important functions for knee stabilization, load distribution and cushioning of mechanical impact forces [1-4]. Tears of the meniscus are common and can impair physical activities involving the knee, and will lead to the onset of osteoarthritis if left untreated or unrepaired [5-8]. This review describes the development, structure, and function of the meniscus along with meniscal tears and repair approaches. Finally, the literature describing progress in current approaches to develop improved or novel treatments and meniscal replacement devices using tissue engineering and 3D printing is summarized with an emphasis on research published in the last 10 years, though older relevant research is included. The goal of developing improved functional human meniscal replacement devices and FDA-approved tissue therapies may come from combining an understanding of the biology, biochemistry and biomechanics of the meniscus with modern biofabrication techniques.

1.1. Meniscus developmental biology and maturation

Development of the meniscus begins in utero, with the condensation of mesenchymal cells forming the bulk of the tissue [1]. The immature meniscus is completely vascularized, though the presence of antiangiogenic factors may potentially prime the tissue for the development of the different vascular zones [9]. As the tissue develops the collagen content increases, particularly in the circumferential direction. However, unlike the organized collagen network seen in adult menisci, the fetal meniscus collagen arrangement is essentially random [10]. Movement of the fetus in utero is well documented, and the resulting biomechanical forces are believed to be critical for musculoskeletal development and maturation [11-13]. The importance of biomechanical stress and strain for normal fetal meniscal development is supported by embryonic immobilization studies in chicks that have revealed failure of later meniscal development and ultimately degradation [14]. Over the course of gestation, meniscal cellularity and vascularization continue to decrease [15]. After birth, vasculature can still be observed throughout the meniscus,

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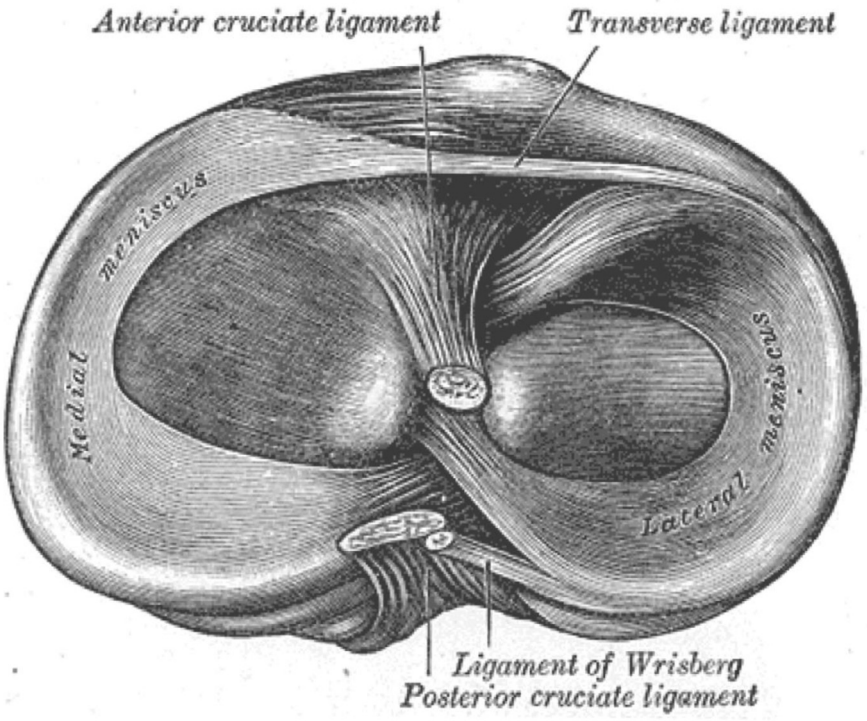

Fig. 1. Knee menisci (Gray's illustrations). Case courtesy of Assoc. Prof. Craig Hacking, Radiopaedia.org, rID: 84971.

but is noticeably less present in the inner tissue. As the knee joint develops through childhood, the meniscus increases in size and extracellular matrix (ECM) complexity, particularly as the collagen matrix becomes more organized [16]. By early adulthood, tissue vascularization is limited to the peripheral one-third of the tissue, with the inner one-third of the tissue completely avascular [16]. This decrease in vascularity is believed to be linked to the distribution of endostatin, a potent angiogenic inhibitor, over time. More specifically, with aging, endostatin has been shown to increase within the inner meniscus and decrease in the periphery of the meniscus [17].

1.2. Meniscal mechanobiology and structure

Human menisci are two wedge-shaped, semilunar discs that form a pocket to stabilize and cushion the impact between the lateral/medial femoral condyles and the tibial plateau during the course of normal leg movement (Fig. 1) [16]. By absorbing compressive forces due to normal movement, the meniscus maintains stability and reduces joint friction [1, 3, 4]. The lateral meniscus is nearly circular and covers more area of tibial plateau than the C-shaped medial [18]. A network of ligaments function in concert to stabilize the meniscus and knee joint during loading conditions experienced during extension or flexion of the joint [16, 19-22]. In order to absorb joint loading, the menisci are not firmly fixed along their entire structure on the tibia and can follow knee translation during motion. However, the ends of the meniscus, the anterior and posterior horns, are tightly anchored to the tibia by ligamentous extensions forming the meniscal root attachment [23]. The medial meniscus posterior horn is anchored to the posterior intercondylar fossa with a shared attachment point of the posterior meniscocapsular and meniscotibial ligaments [20] and in front of the posterior cruciate ligament insertion point on the tibia. The anterior horn attachment to the tibia surface is variable with up to four tibial insertion points with connections to the anterior cruciate attachment and the transverse ligament [4, 22, 24]. The width of the medial meniscus is approximately 7.6 mm at anterior horn, 9.3 mm at midbody and 12.6 mm at the posterior horn [20]. The midbody of the medial meniscus is connected to the joint capsule via the deep medial collateral ligament which helps restrict motion [4]. The posterior horn of the lateral meniscus is connected to the tibia with a complex organization of three popliteomeniscal fascicles, posterolateral capsule, meniscotibial ligament, and the anterior and posterior meniscofemoral ligaments [19, 25]. The width is approximately 7.5 mm at the anterior horn and 10.4 mm at the midbody and posterior horn [19]. The less commonly torn lateral meniscus has a larger range of motion than the medial meniscus which results from the close proximity of the attachments of the anterior and posterior horns as well as fewer capsular attachment points [4].

Each meniscus serves a different function where the medial meniscus is important for maintaining anterior-posterior knee stability [26, 27] and the lateral meniscus helps maintain rotatory stability [28]. The differences in biomechanical function, tibial attachment biology, stress loads, and contact areas necessitate that repair procedures, particularly in the horn and root zones are unique to each attachment [19, 20, 29-31]. During normal movement activities such as walking, the knee joint experiences mechanical force loading up to 5 times that of the normal body weight [32]. During knee extension, an estimated 40–60% of the exerted force is directly transmitted to the meniscus, increasing to 90% during knee flexion [33]. Most of this load increase impacts the posterior horn, which is among the most common tear sites found in the medial meniscus [29, 30]. The axial force transmitted to the meniscus is converted to tensile strain through tissue deformation and the induction of hoop stresses throughout the ECM [1]. Force transmission is aided by the viscoelastic properties conferred by the interplay between the solid collagen/proteoglycan matrix and the fluid water component of the tissue. Force application, such as standing or taking a step, causes an immediate elastic response within the tissue due to the hydrostatic pressure present in the fluid component [34]. While still under load, the meniscus continues to slowly deform at a controlled rate due to the solid matrix resisting a higher proportion of the force, resulting in a functional tissue creep response [34]. Though the load is effectively distributed in healthy tissue, contact stress is significantly increased in knee joints with meniscal tears [5].

The meniscus is composed of an ordered network of collagen (22% wet weight), glycosaminoglycans (GAGs; 0.8% wet weight) and water (72% wet weight) [35], arrayed to efficiently transmit force throughout

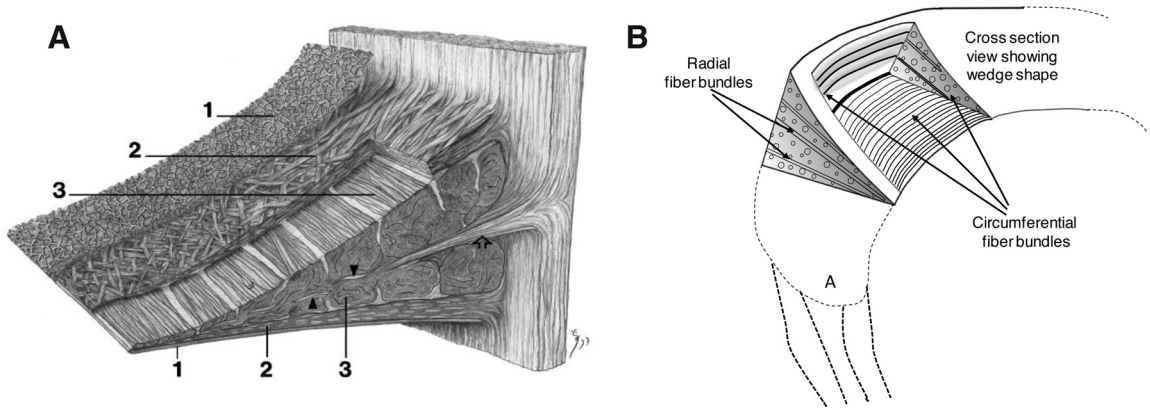

Fig. 2. A. Illustration showing collagen fiber orientation within the meniscus based on electron microscopy. 1, superficial network; 2, lamellar layer; 3, central main layer where collagen fibrils have circumferential orientation. Arrowheads, interwoven radial collagen fibrils; open arrow, connective tissue penetrating from joint capsule. Reprinted with permission from Petersen and Tillmann [37]. B. Cut away view illustration showing collagen fiber orientation within the meniscus near the anterior horn. The meniscus contains circumferential collagen fiber bundles interspersed with radial "tie fiber" collagen fibers. A, Anterior horn shaded to show approximate footprint. The dashed lines on the right indicate the continuing meniscus shape.

the tissue (Fig. 2). This combination of proteins and sugars forming the meniscus extracellular matrix facilitate uptake of significant amounts of water [36]. The surface layer of the meniscus is primarily composed of randomly oriented collagen I fibers, with the inner layers comprised of both collagen I and collagen II [37]. In the inner meniscus, collagen fibers are oriented circumferentially [38], imparting tensile strength and transmission of compression forces into hoop stress around the periphery of the tissue (Fig. 2B). Radial collagen tie fibers, arranged perpendicular to the meniscal plane, confer structural integrity and stiffness to the tissue under load bearing conditions [39]. Joint movement and the application of mechanical forces are important for continued development, reorganization and maintenance of the collagen network [15].

In addition to the ordered collagen structure, proteoglycans and GAGs present in the adult meniscus contribute significantly to tissue mechanical properties [40]. Sulfated GAGs are an important component of the meniscus, with the main types consisting of chondroitin-sulfate (60% of GAG weight), dermatan sulfate (20–30% of GAG weight), and keratin sulfate (15% of GAG weight) [3]. Though all three GAGs are found throughout the tissue, they are present in higher quantities in the inner region of the tissue. Aggrecan, biglycan, and decorin proteoglycans are also found throughout the meniscus, and follow similar distribution patterns to the GAG network [41]. The extensive proteoglycan and GAG network present in the tissue is instrumental in the ability to resist compressive loads [40]. The extremely high negative charge present on these molecules attracts counter-ions, drawing water into the tissue [42]. The pressure exerted by the hydrated tissue effectively counters compressive loads applied to the tissue, allowing the force to be redistributed and preventing structural damage.

Traditionally, the meniscus has been divided into three zones of vascularization: a vascular red-red zone, a semi-vascular red-white zone, and an avascular white-white zone [43]. The red-red zone is located at the outer edge of the meniscus and is attached to the joint capsule, with roughly 10–30% of the tissue periphery supporting blood vessel growth. A recent study of adults of <35 years old found the maximum degree of vascular penetration was up to 42–48% into each meniscus [44]. Partial vascularization of the middle tissue section is referred to as the red-white zone, due to the limited presence of cells and vessels in this region. The deep meniscal region is completely avascular, devoid of any blood vessels or neural cells [3]. The degree of vascularization appears to be directly related to the healing capacity of each zone; the red-red zone has the highest capacity for self-regeneration, whereas the white-white zone is highly susceptible to permanent damage and degenerative lesions [43]. Resident cells within the white-white zone absorb nutrition and clear waste through synovial diffusion, potentially due to joint motion [43].

The classification of cells within the meniscus is largely based on morphology and tissue function, with three generally accepted cell identities: fibroblasts, fibrochondrocytes, and progenitor cells [45]. Cells located in the outer red-red zone of the meniscus typically have an oval shape and function similar to fibroblasts, namely secreting extracellular matrix proteins, and are surrounded by collagen I [46]. Cells within the intermediate and inner white-white zone appear round, and are embedded within ECM consisting primarily of collagen II and GAGs. The cellular morphology and ECM composition surrounding these cells is more indicative of hyaline cartilage, and thus these cells have been classified as fibrochondrocytes [45]. Recently, a third CD34+ cell group has also been identified at the superficial (surface) area of the meniscus. These cells present with flat, spindle-like morphology and exhibit stem cell like characteristics. It is theorized that these cells may be involved in the regenerative properties of the meniscal red-red zone, with some studies showing cellular migration to damaged tissue [47].

2. Meniscal injuries

Tears of the meniscus resulting from trauma or repetitive abnormal stresses are among the most commonly diagnosed knee injuries, with a yearly incidence of approximately 61 per 100,000 people [48, 49]. They usually occur due to knee twisting during physical activity, particularly if full body weight is applied, and during sudden stops, starts and aggressive pivoting. Squatting and deep knee flexion is another common mechanism that can lead to torn menisci. Athletes and military members have high frequencies of meniscal tears, with military service members having ten times the incidence of tears compared to civilians [50, 51]. The symptoms range from popping, catching and clicking sensations, swelling and to pain with deep knee flexion. Asymptomatic meniscal tears have also been described [52], and are correlated with osteoarthritis [53]. Radiographs that rely on differences in x-ray density cannot accurately differentiate meniscus from adjacent soft tissues [54]. However, osteoarthritic changes to bone, swelling of the joint space or loss of joint space can be identified on x-rays and suggest an underlying injury to the meniscus and ligamentous attachments of the knee. MRI, which can provide excellent characterization of soft tissues, is the mainstay for diagnosis of meniscal tears [54, 55]. In addition, the gold standard for diagnosing meniscal tears is direct observation with arthroscopy [56].

Meniscal tears are generally classified according to their orientation, directionality and can be partial or full thickness [8, 57]. The 2019 ESSKA meniscus consensus added more definition to meniscal tears [58,

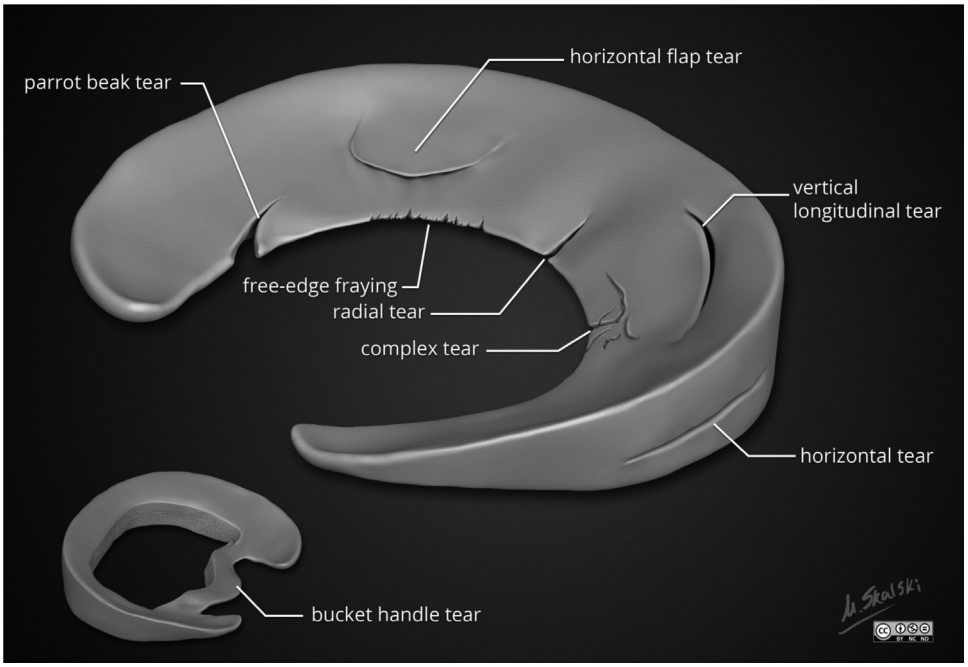

Fig. 3. Illustration of different meniscal tears. Case/image courtesy of Dr. Matt Skalski, Radiopaedia.org, rID: 55569.

59]. They suggest dividing the meniscus into three equal-sized radial zones (anterior, mid body and posterior) and three equal width circumferential zones labeled 1, 2 or 3 starting from the outer rim [60]. The latter classifications are more objective and replace the previous convention of red-red, red-white and white-white. There are vertical tears in the longitudinal direction, and in the radial direction from the medial rim toward the lateral rim, or complex tears encompassing multiple directions (Fig. 3). Vertical longitudinal tears usually occur between the circumferential collagen fibers, and as such may not necessarily disrupt the mechanical functions of the knee [61]. However, and more commonly found in the medial meniscus, large longitudinal vertical tears can progress to completion and twist to form a "bucket handle" tear which can displace or flip similar to a bucket handle [62]. Bucket handle tears typically lead to knee instability, pain and locking of the knee joint. Medial meniscus tears are frequently associated with anterior cruciate ligament tears [31]. Horizontal tears are sometimes asymptomatic, are typically degenerative and most often occur between horizontal layers of collagen fibers of the medial meniscus [63, 64]. Parrot beak or oblique tears and radial tears disrupt the circumferential collagen fiber arrangement and compromise the ability to handle loads, and are typically not repairable [8, 65]. Tears in and around the anterior or posterior horn and root attachments are also common [66, 67]. These tears can be quite damaging since secure attachment at the meniscal horns is critical for load distribution [68], and if left untreated degenerative osteoarthritis will develop [69, 70]. Finally, a class of meniscal damage that is sometimes under diagnosed due to its location in a blind spot when observing through standard arthroscopic portals are ramp lesions [71-73]. These are longitudinal tears of the peripheral attachment of the posterior horn of the medial meniscus often associated with ACL rupture, and were originally defined as being no longer than 2.5 cm in length [74]. Left undiagnosed and untreated, ramp lesions increase the failure risk of ACL grafts, have increased probability of further meniscal damage, and like other meniscal injuries, increase risk of osteoarthritis [73].

3. Tear treatment options

The following sections describe methods to surgically repair or treat damaged meniscus tissue including the use of allograft transplants and artificial meniscus implants. Treatment methods of torn menisci have changed and improved as better understanding, surgical techniques and instruments, and data are developed. The importance of the meniscus to knee joint stability, shock absorption and load transmission mandates that, when feasible, the meniscus should be saved or repaired rather than resected [58, 59]. Historically a complete meniscectomy was performed, though this procedure was later linked to rapid onset of degenerative osteoarthritis [57, 75]. Fortunately, a variety of surgical repair options that notably spare meniscal tissue are currently possible, and several techniques are discussed here.

3.1. Repair methods

Nearly 1 million meniscal surgical procedures are performed annually in the United States [49, 76]. The surgical treatment varies depending on the type of damage present (Fig. 3) and includes partial meniscectomy, repair, or reconstructions using implants or allograft transplants [7]. Tears in the outer 1/3 (e.g., the red-red zone) are the most likely to heal without surgical intervention owing to the vascularity of this region. In addition, self-repair is possibly aided by mesenchymal stem cells (MSCs) recruited to the injury site, as greater numbers of MSCs are detectable in synovial fluid following meniscal injury compared to normal knees [77]. Arthroscopic surgeries are the most common repair approach [8, 78] and include inside-out repairs ([79], outside-in repairs [80, 81], all-inside repairs [82], and transtibial repairs of the meniscal root [67, 70, 83]. These techniques are frequently used to repair damage in the red-red zone or red-white zone and are defined by the direction of the sutures (e.g., introduction from outside the joint capsule and into the meniscus for outside-in, *etc.*). All-inside meniscus repairs are becoming more common [84], are ideal for posterior horn tears, and require absorbable sutures and fixation devices. The inside-out method is best for repairs on the mid-body and posterior parts of the meniscus, with functional outcome and failure rates similar to the all-inside process [85]. Outside-in methods are ideal for anterior horn and mid-body tears, due to preferential access to the afflicted region. Each method has similar complication risks that include failure to heal, neurovascular damage and knee stiffness. The outside-in method takes the longest time to complete but has the highest success rate [84]. Meniscal root tears are typically repaired using suture anchors (direct fixation) and

indirect fixation using sutures pulled through a transtibial tunnel [70, 83, 86]. In general, vertical longitudinal tears are quite repairable [87], while oblique, radial and bucket handle tears have less likelihood of successful repair [88].

In an attempt to augment and increase repair success, some surgeons improve the flow of blood to the repair by trephination and abrading the red-red zone to allow for infiltration of blood, cells and growth factors [89]. Additionally, platelet rich plasma (PRP), which is abundant in growth factors and anti-inflammatories, is used [90]. Fibrin clots have been used to augment repair of degenerative complex horizontal tears of the medial meniscus with clinical healing observed in 75% of patients in short term follow up [91]. The physical state of the clot allow for more precise placement at the tear site compared to PRP [92], and fibrin clots enhance healing ability and tissue regeneration in avascular (white-white zone) of menisci [93, 94]. Each of these supplemental methods is an attempt to counteract the low vascularity and cellularity of the tissue and the corresponding poor healing ability of cartilaginous tissue of the meniscus. The benefits of these augmentations are not always entirely clear as clinical studies report conflicting results on healing outcomes, particularly with the use of PRP [90]. However, the success of these results are influenced by the type of tear, and among other factors, patient age. [89, 90, 95, 96].

If the tear and patient are not amenable to repairs, partial meniscectomy is an option. The procedure has been performed for many years and has a low risk of surgical complications [97]. Although patients report satisfaction with the results, it is well documented that meniscectomy results in an increase in contact stress and often leads to the development of osteoarthritis [5, 61, 98] .

3.2. Meniscus allograft transplant

For certain patients, including those with complete meniscectomy, a meniscal allograft transplant is an effective treatment option [99-104]. The donor graft is typically frozen after harvest, and the freeze thaw process is assumed to kill any cells present without significantly disrupting the organized collagen structures. The choice of preservation method does, however, affect meniscal mechanical properties [101, 105]. The graft must be appropriately sized to ensure best outcomes and are typically matched through Pollard's radiographic method or by close matching of sex, weight and height (reviewed by [100]). There is no true agreement on the degree of graft size mismatch tolerated, but it is clear that oversized and undersized grafts increase contact forces on either the articular cartilage or the meniscus itself and this negatively effects knee function [106]. Dienst et al. concluded that a size difference of ±10% of the original meniscus size should yield acceptable results and that it is better to choose an allograft that is slightly too large rather than too small [106].

In addition to size matching, secure fixation of both the anterior and posterior horn of the allograft is critical to ensure that mechanical properties remain close to normal. [107, 108]. Allografts are frequently transplanted with bone plugs for medial meniscal allografts or bone bridges for lateral allografts harvested from a cadaveric donor [109-111]. These methods preserve the critical attachment points in the meniscal roots between bone, ligament and meniscus in the donor material and obviate the need for surgeons to reconstruct this strong attachment point in the recipient. The bone plugs allow for fairly routine healing and integration of the bone graft site, show better results than soft tissue fixation with joint contact pressures [112], and in most cases patients are able to resume preinjury activity levels [113]. Alhalki et al. determined in a cadaveric study that the contact mechanics of grafts using bone plugs were close to normal, and that the addition of peripheral sutures had no significant effects on the mechanics, which suggests that strong meniscal horn anchorage in allografts are the most essential to preserving or regaining functional knee mechanics [107]. Furthermore, the environment and root attachment for each horn of the medial and lateral meniscus are each mechanically unique which adds complexity to any repair [114, 115]. As with meniscal repairs, the success of allograft transplants is defined by pain relief and improvement of knee function and motion for the patient, as well as delaying or preventing the onset of osteoarthritis. Reports suggest that allograft transplants improve knee functionality in the short and intermediate term [113, 116].

3.3. Artificial meniscus implants

The acquisition of the appropriately sized matched donor meniscus can be difficult and expensive, with the potential to introduce biological pathogens to the recipient. In an attempt to circumvent these risks and limitations, synthetic, laboratory-produced solutions have been developed. One such example is the Collagen Meniscus Implant (CMI, Stryker Corporation, Kalamazoo, MI, USA) [117], a Class 2 medical device first approved by the United States FDA in 2008 in a 510(k) process and composed of a bovine cartilage, chondroitin sulfate and hyaluronic acid-based scaffold that was designed as a resorbable temporary structure that would stabilize the knee joint and promote cell infiltration and growth, with the end result yielding a fully developed and restored meniscus [117-119]. The CMI is fabricated by first precipitating the components and layering the precipitate into a mold after which the material is lyophilized and cross-linked with formaldehyde [117]. The resulting material is highly porous, and electron microscopy reveals the CMI structure is a herringbone-like pattern that are 500 μm long and with 80 μm wide grooves [120]. The CMI surface pores have diameters from 60 to 90 μm and appear to be a fibrillar network in stratified layers. However, the collagen network of the CMI is essentially random and lacks the natural anisotropic circumferential and radial fiber alignments seen in the meniscus.

Though the CMI approximates an entire meniscus, it is FDA cleared to replace only portions of the medial meniscus and not for a complete meniscal replacement. In doing so, the patient needs a healthy meniscal rim complete with anterior and posterior roots to fix the implant. In addition, the defect in the patient must extend into the red-red or the red-white zone of the meniscus (or be resected and prepared to expose the zones) in order to provide sufficient vascularization and access to cells for repopulating the CMI. Initial studies showed that 6 months post implantation in human patients, ingrowth of cells into the CMI occurred [117, 118]. Histologically, the CMI had begun to be replaced by cells similar to meniscus fibrochondrocytes, new collagen was evident and distinct from the CMI, and no inflammation or infection was present, though no detailed characterization of the cells were reported [117, 118, 120]. In addition, significant implant structure was still present, but cellularization of the implants appeared to be progressive with improved results after 1 year and accompanied by diminished implant size [118], suggesting that the remodeling of the repaired meniscus is a slow process. A sheep study using CMI showed that the nascent cell population was more like scar tissue than meniscal tissue; however, CMI seeded with fibrochondrocytes before implantation showed much improved vascularization, remodeling, and cellularity [121], which suggests that using a scaffold loaded with cells such as fibrochondrocytes, chondrocytes, or MSCs may offer a better approach for meniscal healing and regeneration compared with just a scaffold alone. Long term follow up with CMI recipients using physical examinations for functionality and MRI scans indicate that pain relief and improved knee operation persist for at least 10 years [122-124] and remodeling of the implant occurs for up to 5 years post-surgery [125]. Interestingly, radiography showed none of the CMIs maintained their initial size, 11% were complete resorbed and 89% were partially resorbed [123, 126]. [127]It is unclear if the reported shrinking size of the CMI over time was implant contraction or compression or if it was a biological absorption concomitant with cellular colonization and remodeling. Second look arthroscopies or biopsy may answer this question. A recently published follow up study on a small number of recipients concluded that CMI provided pain relief and good knee function for 20 years post implantation, though some os-

teoarthritis progression was noted [127]. These data are encouraging, and additional recipients need to be studied for long term follow up.

A different approach to meniscus injury treatment is the NUsurface device (Active Implants, LLC, Memphis, TN USA), a disk-shaped artificial meniscus composed of circumferentially strengthened polycarbonate-urethane with embedded high tensile ultra-high molecular weight polyethylene fibers [128]. This implant is approved for use in some European countries and Israel, and is being investigated for safety and effectiveness in ongoing United States clinical trials (The SUN Clinical Trial, The VENUS Clinical Study; ClinicalTrials.gov). This artificial meniscus is neither resorbable nor biocompatible and was designed for implantation without any fixation requirement. However, the lack of fixation led to an incident where the implant migrated from the proper location into the suprapatallar space and resulted in knee lock up [129]. The ongoing clinical trials should determine if this issue remains problematic.

The NUsurface artificial meniscus design was dictated by desired mechanical behavior and optimized with 3D finite element simulations of material properties and contact mechanics of the knee joint [128]. The final design was chosen to have optimal pressure distribution in the knee relative to natural meniscus, and also for ease of manufacturing. An extensive study showed that the implant was a non-linear viscoelastic material, was flexible and deformable under low compressive load, but became stiffer and resisted deformation under higher compressive loads. This was attributed to the circumferential reinforcing fibers transitioning from a slack native state to aligning and tensing during deformation [130]. The synthetic meniscus was capable of withstanding 5 million dynamic gait loading cycles without failure and exhibited only superficial surface damage [131]. Furthermore, in a study with cadaveric knees, Shemesh et al. concluded that the NUsurface implant restored mechanical function in knees with damaged medial menisci to levels typical in healthy knees, and with no alteration to the contact pressures or area of the lateral meniscus [132]..

Finally, ACTIfit (Orteq Sports Medicine Ltd., London, UK) is a polyurethane and poly(ε-caprolactone) (PCL) based device that is a biodegradable, porous scaffold approved for use in Europe [133]. It is similar to CMI in shape and implantation strategy for replacing part of the damaged meniscus as long as the rim and horns are intact. Studies show that host cells repopulate the device and that it is capable of restoring knee function [133-136]. A recent 5-year European clinical study of 155 patients indicated that ACTIfit improved knee joint function and decreased pain. [137]. However, 23 implants failed during the study with 10 breakages, 7 replaced with allograft transplants, and 6 subjected to knee arthroplasty. The US FDA has recently given ACTIfit a Breakthrough Device Designation.

4. Development of scaffolds and tissue engineered models for meniscal repair

In addition to implants already approved for medical use in patients worldwide, there are numerous studies in the research and development phase to design tissue engineered implants as well as practical alternatives made with artificial materials. Tissue engineering brings high expectations for discovery of new regenerative medicine therapies. Various materials, including synthetic polymers, hydrogels, and tissue-derived ECM as well as MSCs and other cell types have been used recently to produce scaffolds or tissue engineered models for meniscus regeneration or replacement [138-144] (Table 1). Furthermore, novel fabrication techniques such as 3D printing and electrospinning promise to play a significant role for future orthopedic device design including personalized medicine where customized manufacture of individual patient-specific replacement tissues and devices are possible [145]. The following sections describe materials and additives used to build meniscal structures that have been tested in vitro and in animal models as well as different scaffold fabrication techniques.

4.1. Materials used for meniscal scaffolds and models

Specific properties and features are required of materials used in meniscal and other tissue substitutes (reviewed in [146]). For example, scaffold material stiffness and composition is known to influence the outcome of lineage differentiation of mesenchymal stem cells [147-154]. The geometric and architectural features of the material such as the pore size and percentage and micro surface roughness and height are also important for cell adhesion, infiltration and proliferation [155-159], and collagen fiber length and stiffness together influence cell surface tension which is needed for proliferation and migration [160]. In addition, the materials must either be biocompatible or be capable of being functionally modified to promote cell growth and to avoid introducing cytotoxicity [161, 162]. In some cases, it is desired that the scaffold is resorbed and replaced with natural cells and extracellular matrix. In these instances, it is important to understand the rate of in vivo resorption relative to that of recellularization and remodeling and to note any potential toxicity of the degradation products in the body.

Often synthetic materials such PCL, poly(lactic acid-co-glycolic acid) (PLGA), poly-L-lactide (PLLA), and others [142, 143, 163, 164] are used. PCL is appealing to use in scaffolds because devices made from it have been approved by the FDA, it's ~60 °C melting point makes it easy to work with and it is metabolized into non-harmful CO_2 and H_2O [165]. Scaffolds may also be composed of natural molecules such as collagen, gelatin, hyaluronic acid, agarose and other hydrogels [166], and in some instances scaffolds are composed of ECM from decellularized meniscus tissue [167, 168]. Hydrogels are polymer networks that absorb and retain water due to the presence of hydrophilic groups [169]. Their crosslinked network stems from hydrogen bonds, hydrophobic interactions, and covalent bonds that convey stability in water while maintaining a three-dimensional structure. In general, most protein hydrogels and other natural polymers provide an environment that encourages cell adhesion, growth and differentiation, but lack stiffness and mechanical strength [170]. Thermoplastics are a useful aid to mechanical stability and scaffold structural integrity, but are not always preferred substrates for cell growth [169, 171].

Decellularized extracellular matrix (DECM) has been used as a cell-instructive building block for tissue engineering in many projects [172-175], including meniscus [168, 176-181], where it's use was first reported by Maier et al. in 2007 for ovine specimens [182], Stapleton et al. for porcine meniscus [181] and Sandmann et al. in 2009 for human meniscal tissue [183]. The ECM components such as collagen, fibronectin, laminin, elastin, proteoglycans, and the localized growth factors present are involved in maintaining the native-like environment of the cells growing both in vitro or in vivo [184]. Gentle removal of the cells preserves the complexity of structured matrix to serve as a scaffold [17, 181, 185] while retaining instructive cues for cellular repopulation and gain of functionality in the tissue engineered model, and thus may be more promising to use than other biomaterials. DECM scaffolds may offer clinical value in treating meniscal tears by acting as a biomechanically relevant material to replace damaged tissue removed during partial meniscectomy [185], however nearly all the published work on DECM scaffolds as meniscal replacements are in vitro studies. Thus, additional pre-clinical animal studies are required to evaluate if DECM scaffolds provide a suitable long-term solution for repair of damaged human meniscus tissue. Another limitation is the potential for significant loss of GAGs during decellularization [17, 181, 186]. Furthermore, the dense microstructure of both native and decellularized meniscus hinders cell mobility, invasion and proliferation. Macropore sizes in the range of 150–500 μm seem to be ideal for cellular infiltration [159], and infiltration is improved following treatment with histone deacetylase inhibitors to reduce the stiffness of the cell nucleus to make deformation easier during cell translocation [187]. Matrix-degrading enzymes may also be used, in order to render the meniscus matrix environment closer to a fetal-like state, which is known to have better repair capa-

Table 1
Recent publications on meniscal substitute research.

Material used	Fabrication method	Biological Additives	Results	Notables	Cross-linker	Methods	Reference
Fabrication by molding							
Collagen I	Molding	Meniscal fibrochondrocytes	Collagen, gag content, tensile and equilibrium moduli increased with time.	~50% uniform contraction of the meniscus		Culture the cells and meniscus structure in chondrogenic media for 4 weeks.	[208]
Collagen I	Molding	Meniscal Fibrochondrocytes	Immobilized constructs retained their dimensions over the culture period unlike unclamped samples. Collagen fiber remodeling resulted in developing circumferential and radial alignment leading to anisotropy with a 2–3x circumferential moduli relative to radial moduli.			Collagen meniscal structures and cells were immobilized at the extended horn region and cultured for up to 8 weeks in growth media.	[233]
Collagen I	Molding	Meniscal Fibrochondrocytes	Development of aligned collagen fibers proceeded faster and was accompanied by improved GAG and collagen content and native-like equilibrium modulus, and improved tensile properties.			Collagen meniscal structures and cells were immobilized at the extended horn region and cultured for up to 4 weeks in growth media with axial loading applied.	[234]
Collagen I	molding	MSCs, meniscal fibrochondrocytes	MSCs led to higher level of GAG compared with fibrochondrocytes but the collagen structure was not as good.	High levels of GAG production correlated with reduced collagen fiber diameter.		Collagen meniscal structures and cells were immobilized at the extended horn region and cultured for up to 4 weeks in growth media.	[239]
Collagen I	molding	Meniscal fibrochondrocytes	Molding collagen into tubing loaded with bone plugs formed a scaffold with three regions: bone, bone-collagen, and collagen, showing collagen and bone can be integrated together into a simplified test model for meniscus-to-bone enthesis. Clamped samples had continuous collagen fibers that spanned the collagen and bone regions and did not contract in the longitudinal axis like unclamped samples, and are more like that found in native enthesis.			The integration of fibrochondrocyte seeded collagen gels to decellularized bone plugs was studied as an enthesis model system for up to 4 weeks in modified growth media. It was also determined if immobilization in the bone plug surface effects collagen organization at the soft tissue to bone interface.	[245]
DECM	molding	Meniscus cells	Meniscus cells invaded scaffolds with 16% W/V ECM density. Genipin cross-linking led to higher GAG content and cell numbers, and improved shear strength of repair		genipin	Determine the effects of ECM density and genipin cross linking on cell proliferation and differentiation within the ECM scaffold.	[168]
DECM	molding	hMSCs	Meniscal cells invaded the peripheral region of the unseeded plugs within 7 days of explant culture but required 28 days to cellularize the inner regions of the plug. MSC-seeded 8% density scaffolds retained more cells and had higher DNA and GAG content after 28 days.			DECM from meniscus was powdered, rehydrated to 8% W/V and molded. Cylindrical plugs were placed into porcine menisci and cultured as an explant in MSC growth media with ascorbate	[178]
DECM	Molding/ freeze drying	SF-MSCs, TGFβ3, IGF1	TGF-β3 and IGF1 induced production of the cartilaginous matrix and upregulated the expression of aggrecan, collagens I and II. SF MSCs had a round morphology in the DCM scaffolds in the presence of the growth factors. SF MSCs had better characteristics compared to bone marrow MSCs for meniscus tissue engineering applications by undergoing fibrochondrogenesis with less hypertrophic differentiation (based on collagen X). Larger-scale fibrocartilaginous matrix was generated by SF-MSCs seeded on meniscal DECM scaffolds with TGF-β3 and IGF-1.			Synovial fluid (SF) MSCs were cultured on DECM scaffolds with and without the addition of growth factors in serum free chondrogenic media for up to 3 weeks.	[194]

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Table 1 (*continued*)

Material used	Fabrication method	Biological Additives	Results	Notables	Cross-linker	Methods	Reference
DECM	molding	MSCs, TGFβ3	Serum-free media with TGF-β and dexamethasone promoted MSC proliferation and increased the production of meniscus ECM components, collagens and proteoglycans and promoted integrative repair of meniscus tissue explants			Test properties of cell seeded DECM (8% w/v) scaffolds cultured in different combinations of serum, Dexamethasone, and TGF-β. Evaluate the effects of these media on the tissue biochemical properties and the shear strength of repair in menisci explant models.	[246]
DECM, PEG-DA	molding	MSCs	qPCR showed that collagen I was upregulated in gels made with outer region DECM, while collagen II and aggrecan were upregulated in gels made with inner region DECM.		LAP	Cells, DECM from either the inner or outer meniscal region and PEGDA were mixed to form a hydrogel, and placed in chondrogenic cell culture media.	[180]
GelMA, HaMA	molding	chondrocytes	A bioreactor system was developed that applied defined uni- and biaxial mechanical stimulation to chondrocyte-containing hydrogels. 14-day static preculture was necessary in order to detect upregulation of chondrogenic markers after loading. Short duration loading ~1 hr. led to better results compared to 12 hr. loading cycles.		Irgacure 2959	The effects of different mechanical loads applied to cells in hydrogels and grown in chondrogenic media were evaluated.	[237]
GelMA	molding	ADSCs, TGFβ3	ADSCs encapsulated in GelMA and preloaded with TGF-b3 at 2 mg/mL undergo chondrogenic differentiation and, when injected and cross linked into a radial meniscal tear, resulted in repair, based on histology and mechanics.	For direct repair of meniscal tears in situ	LAP	Cross linked gelatin was seeded with cells and TGFB was investigated in an in vitro meniscal tear model, where tears were made and then healing ability of the cells and hydrogel was assessed for up to 8 weeks in culture following injecting and crosslinking in the tear.	[197]
PCL, carbon nanofibers	molding	Meniscal cells	When compared to human meniscus samples and control scaffolds lacking nanofibers, these nanocomposite scaffolds have better static and dynamic mechanical properties. Meniscal cells attached to the honeycomb surface and proliferated. Scaffolds were subcutaneously implanted rabbits, and biochemical and immunohistochemistry analysis showed biocompatibility.			PCL scaffolds were prepared with different concentrations of carbon nanofibers and evaluated based on physical and biological properties. Biotin, chondroitin, proline and glucose were also added to the scaffolds which were then freeze dried.	[247]
CMI	Commercial product made by molding/freeze drying	MSCs	Perfusion and mechanicalstimulation positively effect MSC proliferation and differentiation while seeded on a collagen meniscus implant. Equilibrium modulus improved 2.5-fold with growth under compression.			Cells were seeded on a CMI and grown in static conditions or a bioreactor with perfusion and/or cyclic compression.	[232]
Fabrication by electrospinning							
Collagen I	electrospinning		A custom electrospinning printer was designed and built to produce organized single lines of collagen nanofibers with cylindrical morphology. 40% acetic acid was the best solvent to produce solid cylindrical collagen fibers of 1–2 micro diameter.			Acetic acid concentration, relative humidity and voltage parameters were optimized for direct-write electrospinning collagen nanofibers for building scaffolds.	[248]
Collagen I, chondroitin sulfate, hyaluronic acid, PLGA	Freeze dried foam and electrospinning	Meniscal fibrochondrocytes	Cells proliferated on scaffolds for up to 3 weeks, but were slow to invade the interior. Compressive modulus reached 12 kPa after 45 days in culture		EDC/NHS	Culture the cells and scaffold for up to 45 days.	[210]

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Table 1 (*continued*)

Material used	Fabrication method	Biological Additives	Results	Notables	Cross-linker	Methods	Reference
Collagen I, chondroitin sulfate, hyaluronic acid, PLGA	Freeze dried foam and electrospinning	Meniscal fibrochondrocytes	Best results in samples seeded with cells prior to implantation. In all cases scaffolds were resorbed over time and inflammatory cells were observed. Chondrocytes and fibrocartilage tissue were present along with connective tissue		EDC/NHS	Culture the cells and scaffold for 10 days and implant into rabbit knees for 3 or 10 weeks.	[209]
PMMA, PCL, PLA, Collagen I	electrospinning		One formula (FM3) had the best compressive (255 MPa) and tensile moduli (11.6 MPa). No sign of infection was observed in the xenograft and neovascularization was detected along with granuloma indicating invasion of the foreign materials by macrophages.			Different formulations of Collagen and polymers were blended and electrospun onto negative shaped meniscal mandrels with random, aligned or radial fibers. A meniscus replicate was produced with different fiber alignment in different regions and sections of the meniscus were implanted into rat renal capsules for up to 4 weeks.	[249]
PCL, PEO, hyaluronate	electrospinning	PDGF-AB, collagenase	In vitro and in vivo data demonstrate that chemoattractants alone do not increase cell migration without also modifying local ECM microenvironment with collagenase to make it more porous.			PCL scaffold was combined with water soluble poly (ethylene oxide) (PEO) fibers that allowed for rapid release of collagenase followed by slower degrading HA fibers that released PDGF over several weeks. A meniscal fragment containing the scaffold was subcutaneously implanted into nude rats.	[189]
PCl, PEO	electrospinning	Meniscal fibrochondrocytes	Softening of the nucleus improves migration through microporous membranes, electrospun scaffolds, tissue sections and the subcutaneous meniscal implant. Nuclear properties and cell function recover after treatment.			PCL scaffold was combined with water soluble PEO fibers that allowed for rapid release of HDAC inhibitors to decrease meniscal cell nuclear stiffness. A meniscal fragment containing the scaffold was subcutaneously implanted into nude rats.	[187]
DECM, PCL	electrospinning	Meniscal fibrochondrocytes	Tensile modulus of aligned fibers peaked at ~330 Mpa and was significantly higher than the randomly aligned fibers (90 Mpa). Scaffolds also supported cell attachment though there was no correlation with ECM content.			Electrospun filaments were analyzed for mechanical properties and cell attachment.	[191]
Fabrication with 3D Printing							
Silk, gelatin	3D printing	Meniscal fibrochondrocytes	Biocompatibility was excellent. Fibrochondrocyte gene expression was maintained for 3 weeks. Compressive moduli was similar to native meniscus.		EDC/NHS	3D print human meniscus shaped scaffolds with three layers of grid, concentric and lamellar infill patterns.	[227]
Collagen I	3D printing	MSCs	Successfully reproduced the shape of the patient meniscus and cell were viable.	No attempt to mimic collagen architecture		Patient specific model created from MRI and printed with collagen I.	[214]
Collagen I, alginate, agarose	3D printing	Chondrocytes	Collagen or agarose each increased mechanical strength of alginate gels. Collagen/alginate gels were better at inducing cell attachment, proliferation, GAG production and cartilage gene expression, and better maintained chondrocyte phenotype.		$CaCl_2$	3D printed hydrogels and cells were evaluated by analysis of swelling ratio and mechanical properties and assessment of cell viability, morphology, and cartilage gene expression.	[250]
Collagen I, hyaluronic acid, p(DTD DD)	Molding, 3D printing and fiber weaving		Demonstrated that a fiber-reinforced scaffold acts as a functional meniscus replacement and had a protective effect on the articular cartilage through 32 weeks.			A polymer fiber–reinforced collagen sponge meniscus scaffold was evaluated mechanically and histologically after up to 32 weeks of implantation in an ovine total meniscectomy model.	[251]

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Table 1 (*continued*)

Material used	Fabrication method	Biological Additives	Results	Notables	Cross-linker	Methods	Reference
poly(desaminotyrosyl-tyrosine dodecyl ester dodecanoate), (p(DTD DD) collagen I, hyaluronate	3D printing and infusion		Compressive moduli and tensile stiffness comparable to native. When transplanted into a partial meniscus defect in an in vitro test using sheep hind limbs, it restored near normal knee contact stress.			3D-printing circumferential and radial filaments of poly(desaminotyrosyl-tyrosine dodecyl ester dodecanoate) and infused with collagen-hyaluronan. Mechanical properties were evaluated in an in vitro knee model system.	[228]
Collagen I, hyaluronic acid, p(DTD DD)	3D printing		Scaffolds were infiltrated with cells that generated dense fibrocartilage-like tissue with significant collagen and GAG deposition. The stability of the surgical fixation was variable, with three partially displaced and five completely displaced implants at 12 weeks and three correctly placed, four partially displaced, and two completely displaced implants at 24 weeks.		EDC/NHS	Biomechanically functional, collagen-hyaluronan infused, printed polymeric scaffold was implanted into 18 sheep for up to 24 weeks to assess the scaffold's fixation, cellular response, tissue generation, integration to the host tissue, and effect on the surrounding articular cartilage.	[229]
PCL, GelMA, Agarose	3D printing	Meniscal fibrochondrocytes	Dynamic stimulation resulted in increased collagen II in the inner region, and increased collagen I in the outer region.		Irgacure 2959	Meniscus shaped PCL scaffold printed and then coated with agarose and GelMA in the inner and outer regions. Constructs with cells were incubated in chondrogenic media for 6 weeks. Dynamic biaxial strain that increased in magnitude from the outer region (2% axial strain and 1% radial strain) towards the inner region (10% axial strain and 5% radial strain) was applied between weeks 4 and 8, at 1 Hz, for 1 h/day and 5 days/week	[224]
PCL, GelMA, GelMA-agarose	3D printing	Meniscal fibrochondrocytes	Circumferential PCL strands promoted elongation and alignment of fibrochondrocytes. These resemble native meniscus with more Collagen I in the outer zone and more Collagen II in the inner zone.		Irgacure 2959	Circumferentially oriented PCL filaments were printed in a meniscus shape, and then the inner and outer zones were coated with fibrochondrocytes in GelMA-Agarose and GelMA, respectively.	[226]
GelMA, HaMA, agarose, PCL	3D printing, molding	Meniscal fibrochondrocytes	GelMA and agarose allowed better cell viability than other hydrogels and PCL promoted better proliferation. Agarose, GelMA, HaMA, and GelMA- HaMA hydrogels induced a higher production of ECM than PCL. GelMA, on which cells adhered strongly, exhibited a high level of collagen production. Agarose and HaMA, on which cells adhered weakly and assumed a round morphology, exhibited a high level of GAG production.		Irgacure 2959	Different hydrogels, and 3D printed PCL were tested for in vitro meniscal regeneration in static and dynamic culture in chondrogenic media.	[252]
PCL, DECM, alginate	Molding, 3D printing	ADSCs, TGFβ3, CTGF	Alginate and ECM hydrogels derived from inner and outer regions of the meniscus stimulated chondrogenesis and fibrochondrogenesis, respectively. These were further improved after culture with TGFβ3 and CTGF, respectively. The hydrogel was 3D bioprinted in alternating strands with PCL which resulted in an equilibrium modulus of ~1000 kPa.		$CaCl_2$	Alginate hydrogels were mixed with DECM from inner or outer meniscus zone along with ADSCs and cultured with TGFβ3 and CTGF media. Gels were mixed with PCL for 3D printing.	[199]

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Table 1 (*continued*)

Material used	Fabrication method	Biological Additives	Results	Notables	Cross-linker	Methods	Reference
DECM, PCL	3D printing and molding	Meniscal fibro-chondrocytes	After 6 months, the best results were from the combination of PCL, ECM and cells where the collagen content was close to native, GAG content was 75% of native control group, and tensile modulus and compressive moduli were 85% and 60% of control.			PCL filaments extruded in circumferential and radial directions to simulate meniscal collagen fiber arrangements and a hybrid scaffold was created after injection of meniscus DECM. Constructs were seeded with fibrochondrocytes and implanted into a rabbit meniscal defect model.	[179]
PCL	3D printing	MSCs, CTGF, TGFβ3	MSCs subjected to growth factor and dynamic loading showed zonal differentiation into fibrochondrocyte-like cells with collagen I and II synthesis. In rabbits, evaluation at 24 weeks revealed zone-specific matrix phenotypes that resembled native tissue. The outer zone had an aligned fibrous matrix containing COL 1, and the inner zone was cartilaginous containing COL-2 and proteoglycans. In vivo, the implants developed native like ECM structure and mechanical properties approaching native meniscus.			Test effects of dynamic compressive-tensile loading and growth factors on MSCs seeded on a PCL scaffold. Mechanical and biological properties were evaluated in vitro for 4 weeks and in vivo for 24 weeks.	[201]
PCL	3D printing	MSCs	Cell seeded scaffolds increased fibrocartilage regeneration with the presence of collagens I, II, III and proteoglycans. In addition, there was less tibia and femur cartilage degeneration in the cell seeded implants compared with meniscectomy or scaffold only.			PCL scaffolds were seeded with cells for 24 h and implanted into a rabbit knee for up to 24 weeks.	[192]
PCL	3D printing		Infill structure (tool path) affected the compressive modulus.	No hydrogel was used		Used a patient specific meniscus model and varied the tool paths while printing to generate 2 different geometries based on variants of cross hatch infill patterns, and evaluated the porosity and compressive modulus.	[213]
PCL	3D printing	MSCs	Mean pore size of 3D-printed PCL scaffold influenced MSC behavior, GAG and collagen II production and biomechanics. Scaffolds with a mean pore size of 215μm had better tensile and compressive moduli and were optimal for cell attachment and ECM production. No inflammation was detected in vivo, and vascular infiltration was detected in the outer zone of the implant.			PCL scaffolds were fabricated with 3 different pore sizes, and MSC attachment, GAG production and mechanical properties were measured. Scaffolds were implanted in rabbit knees for 12 weeks.	[157]
PCL	3D printing		Meniscus scaffolds were produced with an architecture of circumferential and radial fibers. Suture tabs were incorporated to facilitate fixation at the meniscal horns and the coronary attachments. These scaffolds were designed to have 100% pore interconnectivity and 61% porosity. The equilibrium compressive modulus at 10% strain of the scaffold was 18.8 ± 3.1 MPa and ultimate load in a suture pull-out test on the anterior horn suture tab was 32 N.			A 3D printed meniscus scaffold was made with PCL using several different architectures.	[163]

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Table 1 (*continued*)

Material used	Fabrication method	Biological Additives	Results	Notables	Cross-linker	Methods	Reference
PCL, PLGA	3D printing	TGFβ3, CTGF	PCL meniscal scaffolds supported variable regeneration of fibrous and fibrochondrocytic tissue. There were no significant visual differences in the regenerated meniscal tissue with and without growth factors present. PCL degraded over time but remnants were still detectable at 12 months. 82% of the implants partially extruded out of place.	No fixation at the meniscal horns		Scaffolds with and without GF microspheres were implanted into sheep for up to 12 months. Implants were sutured to remaining meniscus and joint capsule.	[198]
PCL, PLGA μspheres	3D printing	SF MSCs, TGFβ3, CTGF	After 6 weeks in vitro, CTGF and TGFβ3 induced zone-specific expression of collagen I and II, from SF MSCs, and resembled native meniscus. Regenerated sheep meniscus tissue had zone-specific cell phenotypes similar to native meniscus, where the outer zone contained fibroblast-like cells; chondrocyte-like cells in the inner zone; and mixed fibroblast- and chondrocyte-like cells in the intermediate zone. Young's modulus was higher in the CTGF→TGFβ3 scaffold group and the native menisci than in the empty μS group.			Anatomically shaped meniscus were 3D printed with PCL with circumferential fibers. Microspheres containing CTGF and TGFβ3 μS were tethered to the outer and inner regions of the meniscus scaffold, where they released rapidly or slowly over 42 days, respectively in culture on a monolayer of SF MSCs, or in sheep.	[200]
Cellulose nanocrystal, phenyl acrylate, acrylamide	3D printing		A single network copolymer hydrogel was printed and tested. The synergistic effect of the hydrophobic (PA) and hydrophilic (acrylamide) components induced a significant increase in tensile strength (~4.4 MPa) and compressive strength (~20 MPa).		Irgacure 2959	hydrogel containing cellulose nanocrystal (CNC), and different ratios of phenyl acrylate (PA) and acrylamide was developed to print an artificial meniscus.	[253]
PLL nanofibers, alginate	3D printing	ADSCs	Compared to alginate hydrogel alone, the PLA aided cell proliferation.		$CaCl_2$	Patient specific meniscus model 3d bioprinted and placed in chondrogenic media.	[225]
PLGA μspheres, fibrin	Not applicable	Synovial MSCs, TGFβ3, CTGF	1000 ng/ml CTGF and slow TGFβ3 release (0.3 ng/day) effectively heal the meniscus tear, based on histology, alignment of collagen fibers, and tensile modulus.	For direct repair of meniscal tears in situ		Release rate of TGFβ3 was controlled by varying compositions of PLGA microspheres, and CTGF was encapsulated in fibrin glue. Meniscus explants with tears were cultured for 8 weeks on top of MSCs to determine how dose and rate of release influence tear healing.	[195]
Fibrin gel, PLGA μspheres	Not applicable	SF MSCs, TGFβ3, CTGF	Short-term release of CTGF recruited SF MSCs into the incision site and formed an integrated fibrous matrix. Sustain-released of TGFβ3 led to remodeling of the intermediate fibrous matrix into fibrocartilaginous matrix, fully integrating incised meniscal tissues with improved functional properties both in explants and in rabbits.			Healing was evaluated using a meniscal explant model derived from the inner avascular region and cultured on a SF MSC monolayer in chondrogenic media for up to 6 weeks. Also tested in avascular regions of rabbit menisci in vivo for up to 6 weeks.	[196]
DECM	Not applicable	Chondrocytes	Decellularized meniscus maintained collagen architecture and mechanical properties.	60% loss of GAGs during decellularization		Meniscal tissue was gently decellularized.	[181]

bility [187-190]. Thus, the balance between using structured DECM to supply instructive cellular cues while retaining the physical integrity of a functional support and maintaining porosity conducive to cellular migration and repopulation is important for the success of tissue engineered meniscal substitutes.

Two recent studies [168, 178] used minimally processed porcine DECM to mold scaffolds of different densities. Porosity decreased with increasing ECM percentage but all pores were larger than typical cell diameters. In an in vitro meniscus injury repair model using 3 mm diameter scaffold plugs, it was observed that meniscal cells invaded the

peripheral region of the unseeded plugs within 7 days but required 28 days until the inner regions of the plug were cellularized. MSC-seeded 8% density (w/v) scaffolds retained more cells and had higher DNA and GAG content after 28 days [178]. Meniscus cells were able to invade scaffolds with 16% ECM density. The addition of genipin cross-linking resulted in higher GAG content and cell numbers, and improved the shear strength of repair [168]. Their data suggest that the 16% w/v, cross-linked DECM scaffolds may be an approach to continue pursuing in an effort to develop laboratory generated meniscal repair solutions.

In a different approach, porcine DECM was combined with PCL to fabricate random and aligned nanofibers using electrospinning [191]. The tensile modulus of aligned fibers peaked at ~330 MPa and was significantly higher than the 90 MPa measured for the randomly aligned fibers. These scaffolds also supported cell attachment though there was no correlation with ECM content. This study, like most involving electrospinning, suffers from limitations in that only very thin fiber mats (<1 mm) can be deposited thus precluding production of a physiologically relevant 5–10 mm thick meniscus tissue implant.

The addition of morphogenic growth factors (GF) can improve cell viability, differentiation, and infiltration in meniscal scaffolds [189, 192-201]. In some cases, meniscal devices were suspended in cell culture media containing cartilage grown factors such as transforming growth factor beta (TGFβ), connective tissue growth factor (CTGF), insulin-like growth factors (IGF) or others to facilitate chondrogenic and fibrochondrogenic differentiation of stromal type stem cells [199, 201, 202]. In other studies, the growth factors are mixed within the hydrogel [197], and finally, growth factors were applied with fibrin glue and PLGA microspheres to patch meniscal tears [195, 196]. Mohanraj et al. published an intriguing PLGA microsphere GF delivery approach where the microspheres were designed to release TGFB3 cargo based on mechanical loading thresholds [203]. This approach may have value for repair of load bearing tissues including the meniscus. Several studies found the use of TGFβ3 alone was insufficient to induce effective meniscal healing [200, 204]. Thus, more in-depth approaches investigated the combination of TGFβ3 and CTGF where the GF release occurred in a more temporally controlled manner in defined meniscal zones [195, 196, 198, 200]. In one instance, a 3D printed PCL meniscus scaffold with circumferential fibers and interconnecting microchannels contained TGFβ3 and CTGF encapsulated within PLGA microspheres physically tethered to the inner and outer meniscal zones [200]. The PLGA components determined the release kinetics and allowed for rapid release of CTGF and controlled release of the TGFβ3 over 42 days. The scaffolds were cultured for up to 8 weeks directly on a monolayer of synovial MSCs in an explant model system. The acellular meniscus was invaded by the MSCs and developed GAG-rich fibrocartilage type tissue with aligned collagen fibers and improved tensile modulus; The most favorable results were observed with a high concentration of CTGF and slowly releasing TGFβ3.

4.2. Meniscal substitutes and scaffolds fabricated using traditional methods

Scaffolds for tissue engineering are often fabricated by molding and occasionally in combination with other methods such as electrospinning [205]. Simple molded scaffolds of PCL or PCL/Pluronic F127 with and without a collagen coating support MSC growth and chondrogenic differentiation in vitro [206]. More complex meniscal shaped scaffolds were fabricated from polyglycolic acid (PGA) fiber meshes by bonding adjacent PGA fibers with PLGA [207]. Rabbit meniscal cells were seeded on scaffolds which were then implanted in rabbits following medial meniscectomy. The implant shape was maintained over 36 weeks in vivo only when seeded with cells. Histologically, the cells resembled organized fibrochondrocytes, and collagen I, II and proteoglycans were detected. However, the total amount of collagen measured in the implant recovered after 36 weeks was approximately half that of natural meniscus, though collagen content was slightly higher in the middle sections, and the Young's Modulus in the middle and posterior sections of the recovered implant was 4 times less than natural tissue, indicating that these scaffolds are not yet as strong as native menisci [207].

Pure bovine collagen I and fibrochondrocytes were shaped using an anatomically correct meniscal mold [208]. Compared to alginate-based meniscus scaffolds, the collagen menisci contracted significantly over time in culture, though this could be mitigated somewhat using high concentration collagen (20 mg/ml). The collagen and GAG content and the tensile modulus increased with longer culture but ultimately the collagen organization and mechanical strength were less than that of the native meniscus [208].

Collagen foams have been used to produce scaffolds [209, 210]. In this work, Halili et al. stacked 3 layers of collagen foam interspersed with electrospun mats of PLGA and collagen I fibers and with the top collagen foam layer also containing chondroitin sulfate and hyaluronic acid. The mechanical properties could be tuned by changing the foam preparation methods as well as by seeding the scaffold with rabbit meniscal cells, which improved the compressive properties [210]. Replacement of the medial meniscus in a rabbit model with these scaffolds demonstrated the most favorable results were detected in samples seeded with cells prior to implantation. In all cases the scaffolds were resorbed or degraded over time and inflammatory cells were observed at the tissue site, but some chondrocytes and fibrocartilage tissue were present along with unstructured connective tissue [209].

4.3. Meniscal substitutes and scaffolds fabricated with three-dimensional printing

3D printing is becoming a more common method to produce meniscal scaffolds and replacements due to the ability to precisely control print head tool paths and architectural geometry of the object [211, 212]. This method can be used to fabricate a 3D structure specified via computer aided designs using hydrogels, synthetic polymers or ceramics and are sometimes supplemented with morphogenic proteins, and/or cells (bioprinting) [211]. Typically, a 3D printed object is manufactured layer by layer with precise control over the printhead tool path. 3D medical image datasets derived from CT and/or MRI can be used to reconstruct the patient's exact meniscus for 3D printing [213, 214]. Alternatively, a more generalized meniscus structure similar in form to the CMI can be 3D printed and be ready to be shaped as needed by the orthopedic surgeon (Fig. 4). Bioinks used for 3D bioprinting have similar requirements as scaffold materials and, in addition they must have the proper viscosity to be printable. However, hydrogels like collagen need to be held at cooler temperatures during extrusion printing to avoid thermally induced gelling, and this low viscosity solution lacks the essential structural properties to maintain shape fidelity during printing. Thus, unlike thermoplastics which are easily printed via extrusion, and retain their dimensions as each layer is extruded, collagen ink extrusions frequently sag as subsequent layers are deposited which ultimately compromises print quality by limiting the print height and decreasing shape fidelity. The use of support baths made of gelatin and agarose have greatly aided the printing of collagen and hydrogels by acting as fluid gels [215-217]. The inherent viscosity of the fluid gel holds the newly extruded ink in place until it gels or is crosslinked while, owing to fast viscoelastic recovery, yielding enough to allow the extrusion tip to move through without significant resistance. Indeed, extrusion filaments with diameters as small as 20μm have been successfully printed in support baths [218]. 3D bioprinting also comes with risks of cell damage from the shear stress, hydrostatic pressure, and compressive and tensile forces, and not all cell types will be affected in the same way [219]. In addition, shear and mechanical stresses can initiate cell differentiation in mesenchymal stem cells and other cell types. [148, 220-222]. Furthermore, although chemical photoinitiating agents such as lithium phenyl-2,4,6-trimethylbenzoylphosphinate (LAP) and Irgacure 2959 are often used in bioinks and methacrylated hydrogels for crosslinking to improve strength and mechanical properties, they can be a source of cytotoxicity and genotoxicity mediated by free radical photoproducts of

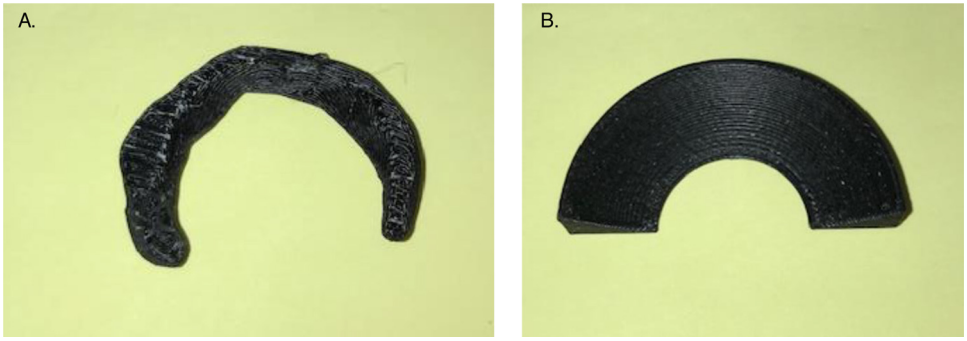

Fig. 4. 3D printed meniscus examples. Menisci designs were 3D printed in thermoplastic polymer as examples to illustrate two different approaches for replacement menisci. A. Anatomical design printed from a reconstruction based on MRI of a human patient, B. Generalized design that can be trimmed to fit different defect shapes prior to surgical implantation.

photoinitiator activation, direct chemical toxicity, and through the UV light source needed for crosslinking [223].

Several recent studies describe anatomically shaped meniscal devices produced by 3D printing [163, 192, 199, 201, 213, 224-227], including those fabricated based on human knee MRI reconstructions [213, 214, 225]. One study produced an architectural mimic bioprinted with MSCs and high concentration collagen I but with no attempt to recreate the microstructures of the meniscal collagen fiber arrangement [214]. Narayanan et al. used bioink composed of alginate, polylactic acid (PLA) nanofibers and human adipose-derived stem cells where they found that, compared to alginate hydrogel alone, the PLA allowed for better cell proliferation [225]. Finally, Cengiz et al. 3D printed with PCL without cells or ECM components and varied the tool paths to generate 2 different geometries based on variants of cross hatch grid patterns, and evaluated the porosity and compressive modulus [213]. These papers are proof of concept for the process of reconstructing and fabricating an exact copy of a patient's meniscus and serve as starting points for building more biologically relevant tissue engineered models.

A blend of silk fibroin and gelatin was used to 3D print human meniscus shaped scaffolds with three layers of grid, concentric and lamellar infill patterns [227]. The scaffolds were lyophilized and crosslinked with EDC/NHS and seeded with porcine fibrochondrocytes. Biocompatibility was excellent and no cytotoxicity was evident, and fibrochondrocyte gene expression was maintained for 3 weeks. In addition, the compressive moduli was similar to native meniscus.

In a study that factored native meniscal microstructure into the design, a resorbable poly(desaminotyrosyl-tyrosine dodecyl ester dodecanoate) meniscus-shaped scaffold was 3D printed with a circumferential and radial fiber network and then the void spaces were infused with collagen I and hyaluronic acid [228]. This meniscal replacement had compressive moduli and tensile stiffness comparable to native sheep meniscus (1.33±0.51 mPa, and 127.6 ± 47.6 N/mm, respectively), and when transplanted into a partial meniscus defect in an in vitro test using sheep hind limbs, they found it helped restore near normal knee contact stress. Subsequently, the scaffold was tested in a sheep 80% posterior meniscectomy defect model [229]. Unfortunately, the majority of the scaffolds were displaced from the initial location. However, fibrocartilage-like tissue infiltration and vascularization were observed, though the overall collagen and GAG content was less than found in native meniscus. Importantly, the data indicate that the biodegradable polyarylate polymer is apparently nontoxic [230, 231]. These in vivo results also highlight the critical nature of fixation of artificial and tissue engineered meniscal implants in order to be maintained in place and integrate in the repair site within the damaged meniscus, as materials that cannot hold up to sutures and surgical manipulation will lead to poor outcomes. Additional approaches were published where circumferentially oriented PCL filaments were printed in a meniscus shape, and then the inner and outer zones were coated with fibrochondrocytes in methacrylated gelatin (GelMa)-Agarose (fibrogenic material) and GelMa (chondrogenic material), respectively [224, 226]. Biochemically these resemble native meniscus with more Collagen I in the outer zone and more Collagen II in the inner zone. Similarly, Chen, et al. extruded PCL filaments in circumferential and radial directions to simulate meniscal collagen fiber arrangements and a hybrid scaffold was created after injection of meniscus DECM [179]. The constructs were seeded with fibrochondrocytes and implanted into a rabbit meniscal defect model. After 6 months, the best results were from the combination of PCL, ECM and cells where the collagen content was close to native, GAG content was 75% of native control group, and tensile modulus and compressive moduli were 85% and 60% of control [179].

5. Application of mechanical force to improve mechanical properties of meniscal substitutes

Some of the published data for tissue engineering meniscal repair scaffolds and devices describe meniscal structures that have an anatomical shape, or contain cells found in natural meniscus tissue. However, many of these engineered menisci-type devices lack the mechanical properties in compression and tension that are required to functionally replace or repair a damaged meniscus in the body [208, 214]. For the anisotropic native meniscus, tensile properties vary with position within the structure as a result of collagen fiber densities and orientation, properties that are absent in a homogeneous printed or molded meniscal replacement constructs. Fortunately, and reminiscent of the natural development and maturation of meniscal tissue in vivo [16], the application of resistance or mechanical force to cell seeded engineered structures leads to better biochemical properties, remodeling of the ECM, and development of a more anisotropic structure that better matches the desired mechanical properties [232-238]. To achieve this, bioreactors have been developed to deliver long and short term cyclic applications of compression, shear, and/or hydrostatic forces [16]. In a series of papers, Bonassar and colleagues demonstrated that by immobilizing the horn regions of a molded meniscus consisting of collagen I and fibrochondrocytes for up to 8 weeks, collagen fibers developed circumferential and radial alignments, and there was an overall improvement in equilibrium and tensile moduli. This elegant approach mimics the in vivo meniscal horn attachments and takes advantage of the contractile properties of fibroblasts, which are constrained due to horn area anchorage, and transforms the contractile force tension into hoop stress that facilitates collagen fiber alignment [233, 234]. Similarly, the use of MSCs in this system improved GAG and collagen production though the collagen fiber organization was better with fibrochondrocytes [239]. Despite these gains, the mechanical properties ultimately fell short of native meniscus. However, by applying physiologically relevant axial loading in a bioreactor in combination with meniscal horn immobilization, the development of aligned collagen fibers proceeded faster and was accompanied by improved GAG and collagen content, native-like equilibrium modulus, and improved tensile properties [234].

Another study found that MSCs seeded on CMI subjected to cyclic compression and perfusion had better proliferation and equilibrium modulus compared to uncompressed samples [232]. Similarly, tissue-based, scaffold-free menisci were created naturally by culturing only

chondrocytes and meniscal cells in a mold with chondrogenic media [167, 236]. Simultaneous tensile and compressive loading stimulation was applied for 1 h each day from days 10–14 with 30 cycles of 1-minute stimulation and 1 min of rest. This stimulation increased collagen and GAG content, and relaxation, instantaneous, and circumferential tensile moduli each showed several fold-improvement, while radial tensile modulus was 6 times better than unstimulated tissue constructs. These studies suggest that in order to develop a tissue engineered meniscal substitute that exhibits mechanical properties and anisotropy that simulates native meniscus, it is necessary to have a combination of materials and cells along with the application of mechanical loading to facilitate collagen remodeling and deposition.

6. Summary

There are several challenges that must be met in developing a human meniscal substitute: the mechanical properties and behaviors must approximate those of native tissue, novel devices must be suitable for fixation to the knee joint capsule, the remaining meniscus and/or the ligaments, tendons and bone near the meniscal horns, and the implant must be either biocompatible and permit cellular infiltration and aid natural healing, remodeling and regeneration or it must be of a chemically inert artificial design with extended longevity. Tissue engineering and additive manufacturing approaches for fabrication of meniscal replacements have promising potential to deliver a new therapy. However, the body of research is at times disparate in that some approaches use synthetic polymers, some use ECM and hydrogels, others use combinations. And still other approaches use autologous and allogeneic cells [240] occasionally supplemented with growth factors. In some cases, these meniscal devices are subjected to application of force or tension in bioreactors. A common goal is the desire to produce an appropriately sized human meniscal substitute having mechanical properties and functionality closely resemble those typically found in humans. These efforts may lead to production of unique patient-specific meniscal replacements or a more generalized off-the-shelf implant that can be shaped during the repair surgery to conform to the defect and restore patient's knee mechanics. Each of these approaches require detailed preclinical study and then eventually human clinical trials. To this end, the time needed to create the device, the choice of materials, the adaptability of the procedures used in the lab as they are moved to a scaled-up GMP manufacturing environment and, ultimately, the cost required to produce a functional meniscal substitute will all need to be carefully considered. In addition, the end product will need to have minimal variability from manufacturing run to run in order to help achieve FDA clearance of such devices. The use of cell-containing meniscus substitutes, like all cellular therapeutics, may be a source of difficulty for regulatory approval. Use of allogeneic MSCs, which may be non-immunogenic [240-243], could make the process less difficult as MSCs are the subject of many ongoing clinical trials for various applications [244]. It is also possible to utilize the cell component only as a tool to help reorganize and structure the implant during the manufacturing process after which cells would be removed to generate an acellular scaffold for implantation. It is likely the balance between manufacturing complexity and reproducibility, biosafety and product efficacy may determine which approach to generate a novel meniscal substitute may lead to launch of a new medical device for treatment of damaged human menisci.

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Declaration of Competing Interest

None.

References

[1] Fox AJS, Wanivenhaus F, Burge AJ, Warren RF, Rodeo SA. The human meniscus: a review of anatomy, function, injury, and advances in treatment. Clin Anat 2015;28(2):269–87. doi:10.1002/ca.22456.
[2] LaPrade RF, Arendt EA, Getgood A, Faucett SC. The menisci: a comprehensive review of their anatomy, biomechanical function and surgical treatment, Berlin, Germany: Springer; 2017. 1 online resource.
[3] Makris EA, Hadidi P, Athanasiou KA. The knee meniscus: structure-function, pathophysiology, current repair techniques, and prospects for regeneration. Biomaterials 2011;32(30):7411–31. doi:10.1016/j.biomaterials.2011.06.037.
[4] Markes AR, Hodax JD, Ma CB. Meniscus form and function. Clin Sports Med 2020;39(1):1–12. doi:10.1016/j.csm.2019.08.007.
[5] Baratz ME, Fu FH, Mengato R. Meniscal tears: the effect of meniscectomy and of repair on intraarticular contact areas and stress in the human knee. A preliminary report. Am J Sports Med 1986;14(4):270–5. doi:10.1177/036354658601400405.
[6] Bernstein J. brief: meniscal tears. Clin Orthop Relat Res 2010;468(4):1190–2. doi:10.1007/s11999-010-1253-4.
[7] Doral MN, Bilge O, Huri G, Turhan E, Verdonk R. Modern treatment of meniscal tears. EFORT Open Rev 2018;3(5):260–8. doi:10.1302/2058-5241.3.170067.
[8] Maffulli N, Longo UG, Campi S, Denaro V. Meniscal tears. Open Access J Sports Med 2010;1:45–54. doi:10.2147/oajsm.s7753.
[9] Chen S, Fu P, Wu H, Pei M. Meniscus, articular cartilage and nucleus pulposus: a comparative review of cartilage-like tissues in anatomy, development and function. Cell Tissue Res. 2017;370(1):53–70. doi:10.1007/s00441-017-2613-0.
[10] Pinsard M, Laverty S, Richard H, Dubuc J, Schanne-Klein M-C, Légaré F. Maturation of the meniscal collagen structure revealed by polarization-resolved and directional second harmonic generation microscopy. Sci Rep 2019;9(1) 18448 10.1038/s41598-019-54942-0.
[11] Natsu-ume T, Majima T, Reno C, Shrive NG, Frank CB, Hart DA. Menisci of the rabbit knee require mechanical loading to maintain homeostasis: cyclic hydrostatic compression in vitro prevents derepression of catabolic genes. J Orthop Sci 2005;10(4):396–405. doi:10.1007/s00776-005-0912-x.
[12] Nowlan NC. Biomechanics of foetal movement. Eur Cell Mater 2015;29:1–21 discussion 21 10.22203/ecm.v029a01.
[13] Verbruggen SW, Kainz B, Shelmerdine SC, Hajnal JV, Rutherford MA, Arthurs OJ, et al. Stresses and strains on the human fetal skeleton during development. J Roy Soc Interface 2018;15(138):20170593. doi:10.1098/rsif.2017.0593.
[14] Mikic B, Johnson TL, Chhabra AB, Schalet BJ, Wong M, Hunziker EB. Differential effects of embryonic immobilization on the development of fibrocartilaginous skeletal elements. J Rehabil Res Dev 2000;37(2):127–33.
[15] Clark CR, Ogden JA. Development of the menisci of the human knee joint. Morphological changes and their potential role in childhood meniscal injury. JBJS 1983;65(4):538–47.
[16] Athanasiou KA, Sanchez-Adams J. Engineering the knee meniscus, morgan and claypool. CA: San Rafael; 2009.
[17] Abdelgaied A, Stanley M, Galfe M, Berry H, Ingham E, Fisher J. Comparison of the biomechanical tensile and compressive properties of decellularised and natural porcine meniscus. J Biomech 2015;48(8):1389–96. doi:10.1016/j.jbiomech.2015.02.044.
[18] Bloecker K, Wirth W, Hudelmaier M, Burgkart R, Frobell R, Eckstein F. Morphometric Differences between the Medial and Lateral Meniscus in Healthy Men – A Three-Dimensional Analysis Using Magnetic Resonance Imaging. Cells Tissues Organs 2012;195(4):353–64. doi:10.1159/000327012.
[19] Aman ZS, DePhillipo NN, Storaci HW, Moatshe G, Chahla J, Engebretsen L, LaPrade RF. Quantitative and qualitative assessment of posterolateral meniscal anatomy: defining the popliteal hiatus, popliteomeniscal fascicles, and the lateral meniscotibial ligament. Am J Sports Med 2019;47(8):1797–803. doi:10.1177/0363546519849933.
[20] DePhillipo NN, Moatshe G, Chahla J, Aman ZS, Storaci HW, Morris ER, Robbins CM, Engebretsen L, LaPrade RF. Quantitative and qualitative assessment of the posterior medial meniscus anatomy: defining meniscal ramp lesions. Am J Sports Med 2019;47(2):372–8. doi:10.1177/0363546518814258.
[21] Flandry F, Hommel G. Normal anatomy and biomechanics of the knee. Sports Med Arthrosc Rev 2011;19(2):82–92. doi:10.1097/JSA.0b013e318210c0aa.
[22] Śmigielski R, Becker R, Zdanowicz U, Ciszek B. Medial meniscus anatomy-from basic science to treatment. Knee Surg Sports Traumatol Arthrosc 2015;23(1):8–14. doi:10.1007/s00167-014-3476-5.
[23] Abraham AC, Donahue TLH. From meniscus to bone: a quantitative evaluation of structure and function of the human meniscal attachments. Acta Biomater 2013;9(5):6322–9. doi:10.1016/j.actbio.2013.01.031.
[24] Berlet GC, Fowler PJ. The anterior horn of the medical meniscus. An anatomic study of its insertion. Am J Sports Med 1998;26(4):540–3. doi:10.1177/03635465980260041201.
[25] Jacquet C, Magosch A, Mouton C, Seil R. The aspiration test: an arthroscopic sign of lateral meniscus posterior horn instability. J Exp Orthop 2021;8(1):17 10.1186/s40634-021-00327-0.
[26] Arno S, Hadley S, Campbell KA, Bell CP, Hall M, Beltran LS, Recht MP, Sherman OH, Walker PS. The effect of arthroscopic partial medial meniscectomy on tibiofemoral stability. Am J Sports Med 2013;41(1):73–9. doi:10.1177/0363546512464482.

[27] Shoemaker SC, Markolf KL. The role of the meniscus in the anterior-posterior stability of the loaded anterior cruciate-deficient knee. Effects of partial versus total excision. J Bone Joint Surg Am 1986;68(1):71–9.

[28] Novaretti JV, Lian J, Sheean AJ, Chan CK, Wang JH, Cohen M, Debski RE, Musahl V. Lateral meniscal allograft transplantation with bone block and suture-only techniques partially restores knee kinematics and forces. Am J Sports Med 2019;47(10):2427–36. doi:10.1177/0363546519858085.

[29] Devaraj AK, Acharya KK, Adhikari R. Comparison of biomechanical parameters between medial and lateral compartments of human knee joints. Open Biomed Eng J 2020;14(1):74–86. doi:10.2174/1874120702014010074.

[30] Johannsen AM, Civitarese DM, Padalecki JR, Goldsmith MT, Wijdicks CA, LaPrade RF. Qualitative and quantitative anatomic analysis of the posterior root attachments of the medial and lateral menisci. Am J Sports Med 2012;40(10):2342–7. doi:10.1177/0363546512457642.

[31] Keyhani S, Esmailiejah AA, Mirhoseini MS, Hosseininejad SM, Ghanbari N. The prevalence, zone, and type of the meniscus tear in patients with Anterior Cruciate Ligament (ACL) injury; does delayed ACL reconstruction affects the meniscal injury? Arch Bone Jt Surg 2020;8(3):432–8. doi:10.22038/abjs.2019.39084.2076.

[32] Paul JP. Force actions transmitted by joints in the human body. Proc R Soc Lond B Biol Sci 1976;192(1107):163–72. doi:10.1098/rspb.1976.0004.

[33] Walker PS, Erkiuan MJ. The role of the menisci in force transmission across the knee. Clin Orthop Relat Res® 1975;109:184–92.

[34] McDermott ID, Masouros SD, Amis AA. Biomechanics of the menisci of the knee. Curr Orthop 2008;22(3):193–201. doi:10.1016/j.cuor.2008.04.005.

[35] Herwig J, Egner E, Buddecke E. Chemical changes of human knee joint menisci in various stages of degeneration. Ann Rheum Dis 1984;43(4):635–40. doi:10.1136/ard.43.4.635.

[36] Pillai MM, Gopinathan J, Selvakumar R, Bhattacharyya A. Human knee meniscus regeneration strategies: a review on recent advances. Curr Osteoporos Rep 2018;16(3):224–35. doi:10.1007/s11914-018-0436-x.

[37] Petersen W, Tillmann B. Collagenous fibril texture of the human knee joint menisci. Anat Embryol (Berl) 1998;197(4):317–24. doi:10.1007/s004290050141.

[38] Drakos MC, Allen AA. Meniscal structure, function, repair, and replacement. In: Damron TA, editor. Oncology and basic science. Publisher: Lippincott Williams and Wilkins Philadelphia; 2008. p. 443–51. PA 19106.

[39] Skaggs DL, Warden WH, Mow VC. Radial tie fibers influence the tensile properties of the bovine medial meniscus. J Orthop Res 1994;12(2):176–85. doi:10.1002/jor.1100120205.

[40] Bursac P, Arnoczky S, York A. Dynamic compressive behavior of human meniscus correlates with its extra-cellular matrix composition. Biorheology 2009;46(3):227–37. doi:10.3233/bir-2009-0537.

[41] Scott PG, Nakano T, Dodd CM. Isolation and characterization of small proteoglycans from different zones of the porcine knee meniscus. Biochim Biophys Acta 1997;1336(2):254–62. doi:10.1016/s0304-4165(97)00040-8.

[42] Aspberg A. The different roles of aggrecan interaction domains. J Histochem Cytochem 2012;60(12):987–96. doi:10.1369/0022155412464376.

[43] Arnoczky SP, Warren RF. Microvasculature of the human meniscus. Am J Sports Med 1982;10(2):90–5. doi:10.1177/036354658201000205.

[44] Crawford MD, Hellwinkel JE, Aman Z, Akamefula R, Singleton JT, Bahney C, LaPrade RF. Microvascular Anatomy and Intrinsic Gene Expression of Menisci From Young Adults. Am J Sports Med 2020;48(13):3147–53. doi:10.1177/0363546520961555.

[45] Verdonk PC, Forsyth RG, Wang J, Almqvist KF, Verdonk R, Veys EM, Verbruggen G. Characterisation of human knee meniscus cell phenotype. Osteoarthritis Cartilage 2005;13(7):548–60. doi:10.1016/j.joca.2005.01.010.

[46] Furumatsu T, Kanazawa T, Yokoyama Y, Abe N, Ozaki T. Inner meniscus cells maintain higher chondrogenic phenotype compared with outer meniscus cells. Connect Tissue Res 2011;52(6):459–65. doi:10.3109/03008207.2011.562061.

[47] Declercq HA, Forsyth RG, Verbruggen A, Verdonk R, Cornelissen MJ, Verdonk PC. CD34 and SMA expression of superficial zone cells in the normal and pathological human meniscus. J Orthop Res 2012;30(5):800–8. doi:10.1002/jor.21582.

[48] Nielsen AB, Yde J. Epidemiology of acute knee injuries: a prospective hospital investigation. J Trauma 1991;31(12):1644–8. doi:10.1097/00005373-199112000-00014.

[49] Logerstedt DS, Snyder-Mackler L, Ritter RC, Axe MJ. A. orthopedic section of the American Physical Therapy, Knee pain and mobility impairments: meniscal and articular cartilage lesions. J Orthop Sports Phys Ther 2010;40(6):A1–A35. doi:10.2519/jospt.2010.0304.

[50] Donohue MA, Zhou L, Haley CA. Meniscus injuries in the military athlete. J Knee Surg 2019;32(2):123–6. doi:10.1055/s-0038-1676959.

[51] Jones JC, Burks R, Owens BD, Sturdivant RX, Svoboda SJ, Cameron KL. Incidence and risk factors associated with meniscal injuries among active-duty US military service members. J Athl Train 2012;47(1):67–73. doi:10.4085/1062-6050-47.1.67.

[52] Englund M, Guermazi A, Gale D, Hunter DJ, Aliabadi P, Clancy M, Felson DT. Incidental meniscal findings on knee MRI in middle-aged and elderly persons. N Engl J Med 2008;359(11):1108–15. doi:10.1056/NEJMoa0800777.

[53] Berthiaume MJ, Raynauld JP, Martel-Pelletier J, Labonte F, Beaudoin G, Bloch DA, Choquette D, Haraoui B, Altman RD, Hochberg M, Meyer JM, Cline GA, Pelletier JP. Meniscal tear and extrusion are strongly associated with progression of symptomatic knee osteoarthritis as assessed by quantitative magnetic resonance imaging. Ann Rheum Dis 2005;64(4):556–63. doi:10.1136/ard.2004.023796.

[54] Lefevre N, Naouri JF, Herman S, Gerometta A, Klouche S, Bohu Y. A Current Review of the Meniscus Imaging: proposition of a Useful Tool for Its Radiologic Analysis. Radiol Res Pract 2016;2016:8329296. doi:10.1155/2016/8329296.

[55] De Smet AA. How I diagnose meniscal tears on knee MRI. AJR Am J Roentgenol 2012;199(3):481–99. doi:10.2214/AJR.12.8663.

[56] Antinolfi P, Crisitiani R, Manfreda F, Bruè S, Sarakatsianos V, Placella G, Bartoli M, Caraffa A. Relationship between Clinical, MRI, and arthroscopic findings: a guide to correct diagnosis of meniscal tears. Joints 2017;5(3):164–7. doi:10.1055/s-0037-1605583.

[57] Smillie IS. The current pattern of internal derangements of the knee joint relative to the menisci. Clin Orthop Relat Res 1967;51:117–22.

[58] Beaufils P, Becker R, Kopf S, Englund M, Verdonk R, Ollivier M, et al. Surgical management of degenerative meniscus lesions: the 2016 ESSKA meniscus consensus. Knee Surg Sport Traumatol Arthrosc 2017;25(2):335–46. doi:10.1007/s00167-016-4407-4.

[59] Kopf S, Beaufils P, Hirschmann MT, Rotigliano N, Ollivier M, Pereira H, et al. Management of traumatic meniscus tears: the 2019 ESSKA meniscus consensus. Knee Surg Sport Traumatol Arthrosc 2020;28(4):1177–94. doi:10.1007/s00167-020-05847-3.

[60] Anderson AF, Irrgang JJ, Dunn W, Beaufils P, Cohen M, Cole BJ, Coolican M, Ferretti M, Glenn RE, Johnson R, Neyret P, Ochi M, Panarella L, Siebold R, Spindler KP, Ait Si Selmi T, Verdonk P, Verdonk R, Yasuda K, Kowalchuk DA. Interobserver Reliability of the International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (ISAKOS) classification of meniscal tears. Am J Sports Med 2011;39(5):926–32. doi:10.1177/0363546511400533.

[61] Mordecai SC, Al-Hadithy N, Ware HE, Gupte CM. Treatment of meniscal tears: an evidence based approach. World J Orthop 2014;5(3):233–41. doi:10.5312/wjo.v5.i3.233.

[62] Shakespeare DT, Rigby HS. The bucket-handle tear of the meniscus. A clinical and arthrographic study. J Bone Joint Surg Br 1983;65(4):383–7. doi:10.1302/0301-620x.65b4.6874707.

[63] Noble J. Lesions of the menisci. Autopsy incidence in adults less than fifty-five years old. J Bone Joint Surg Am 1977;59(4):480–3.

[64] Shanmugaraj A, Tejpal T, Ekhtiari S, Gohal C, Horner N, Hanson B, et al. The repair of horizontal cleavage tears yields higher complication rates compared to meniscectomy: a systematic review. Knee Surg Sport Traumatol Arthrosc 2020;28(3):915–25. doi:10.1007/s00167-019-05557-5.

[65] Harper KW, Helms CA, Lambert HS 3rd, Higgins LD. Radial meniscal tears: significance, incidence, and MR appearance. AJR Am J Roentgenol 2005;185(6):1429–34. doi:10.2214/AJR.04.1024.

[66] Bin SI, Kim JM, Shin SJ. Radial tears of the posterior horn of the medial meniscus. Arthroscopy 2004;20(4):373–8. doi:10.1016/j.arthro.2004.01.004.

[67] LaPrade RF, LaPrade CM, James EW. Recent advances in posterior meniscal root repair techniques. J Am Acad Orthop Surg 2015;23(2):71–6 10.5435/jaaos-d-14-00003.

[68] Zhang K, Li L, Yang L, Shi J, Zhu L, Liang H, Wang X, Yang X, Jiang Q. The biomechanical changes of load distribution with longitudinal tears of meniscal horns on knee joint: a finite element analysis. J Orthop Surg Res 2019;14(1):237. doi:10.1186/s13018-019-1255-1.

[69] Krych AJ, Reardon PJ, Johnson NR, Mohan R, Peter L, Levy BA, et al. Non-operative management of medial meniscus posterior horn root tears is associated with worsening arthritis and poor clinical outcome at 5-year follow-up. Knee Surg Sport Traumatol Arthrosc 2017;25(2):383–9. doi:10.1007/s00167-016-4359-8.

[70] Woodmass JM, Mohan R, Stuart MJ, Krych AJ. Medial meniscus posterior root repair using a transtibial technique. Arthrosc Tech 2017;6(3):e511–16. doi:10.1016/j.eats.2016.11.006.

[71] Chahla J, Dean CS, Moatshe G, Mitchell JJ, Cram TR, Yacuzzi C, et al. Meniscal ramp lesions: anatomy, incidence, diagnosis, and treatment. Orthop J Sport Med 2016;4(7):2325967116657815. doi:10.1177/2325967116657815.

[72] Thaunat M, Fayard JM, Guimaraes TM, Jan N, Murphy CG, Sonnery-Cottet B. Classification and surgical repair of ramp lesions of the medial meniscus. Arthrosc Tech 2016;5(4):e871–5. doi:10.1016/j.eats.2016.04.009.

[73] Young R, Devitt BM, Whitehead T. Meniscal ramp lesions: diagnosis and treatment strategies. In: LaPrade RF, Arendt EA, Getgood A, Faucett SC, editors. The menisci: a comprehensive review of their anatomy, biomechanical function and surgical treatment. Berlin, Heidelberg: Springer Berlin Heidelberg; 2017. p. 63–75.

[74] Liu X, Feng H, Zhang H, Hong L, Wang XS, Zhang J. Arthroscopic prevalence of ramp lesion in 868 patients with anterior cruciate ligament injury. Am J Sports Med 2011;39(4):832–7. doi:10.1177/0363546510388933.

[75] Scotti C, Hirschmann MT, Antinolfi P, Martin I, Peretti GM. Meniscus repair and regeneration: review on current methods and research potential. Eur Cell Mater 2013;26:150–70. doi:10.22203/ecm.v026a11.

[76] Cook JL. The current status of treatment for large meniscal defects. Clin Orthop Relat Res 2005;435:88–95. doi:10.1097/00003086-200506000-00014.

[77] Matsukura Y, Muneta T, Tsuji K, Koga H, Sekiya I. Mesenchymal stem cells in synovial fluid increase after meniscus injury. Clin Orthop Relat Res 2014;472(5):1357–64. doi:10.1007/s11999-013-3418-4.

[78] Vaquero-Picado A, Rodriguez-Merchan EC. Arthroscopic repair of the meniscus: surgical management and clinical outcomes. EFORT Open Rev 2018;3(11):584–94. doi:10.1302/2058-5241.3.170059.

[79] Nelson CG, Bonner KF. Inside-out meniscus repair. Arthrosc Tech 2013;2(4):e453–60. doi:10.1016/j.eats.2013.07.006.

[80] Chahla J, Gannon J, Moatshe G, LaPrade RF. Outside-in meniscal repair: technique and outcomes. In: LaPrade RF, Arendt EA, Getgood A, Faucett SC, editors. The menisci: a comprehensive review of their anatomy, biomechanical function and surgical treatment. Berlin, Heidelberg: Springer Berlin Heidelberg; 2017. p. 129–35.

[81] Steiner SRH, Feeley SM, Ruland JR, Diduch DR. Outside-in repair technique for a complete radial tear of the lateral meniscus. Arthrosc Tech 2018;7(3) e285–e288. doi:10.1016/j.eats.2017.09.006.

[82] Lozano J, Ma CB, Cannon WD. All-inside meniscus repair: a systematic review. Clin Orthop Relat Res 2007;455:134–41. doi:10.1097/BLO.0b013e31802ff806.

[83] Chahla J, Moulton SG, LaPrade CM, Dean CS, LaPrade RF. Posterior meniscal root repair: the transtibial double tunnel pullout technique. Arthrosc Tech 2016;5(2):e291–6. doi:10.1016/j.eats.2016.01.006.
[84] Hantes ME, Zachos VC, Varitimidis SE, Dailiana ZH, Karachalios T, Malizos KN. Arthroscopic meniscal repair: a comparative study between three different surgical techniques. Knee Surg Sports Traumatol Arthrosc 2006;14(12):1232–7. doi:10.1007/s00167-006-0094-x.
[85] Fillingham YA, Riboh JC, Erickson BJ, Bach BR Jr, Yanke AB. Inside-out versus all-inside repair of isolated meniscal tears: an updated systematic review. Am J Sports Med 2017;45(1):234–42. doi:10.1177/0363546516632504.
[86] Balke M, Akoto R, Offerhaus C, Hoeher J. Suture anchor refixation of meniscal root tears without an additional portal. Arthrosc Tech 2018;7(5):e511–15. doi:10.1016/j.eats.2018.01.003.
[87] Krych AJ, McIntosh AL, Voll AE, Stuart MJ, Dahm DL. Arthroscopic repair of isolated meniscal tears in patients 18 years and younger. Am J Sports Med 2008;36(7):1283–9. doi:10.1177/0363546508314411.
[88] Krych AJ, Pitts RT, Dajani KA, Stuart MJ, Levy BA, Dahm DL. Surgical repair of meniscal tears with concomitant anterior cruciate ligament reconstruction in patients 18 years and younger. Am J Sports Med 2010;38(5):976–82. doi:10.1177/0363546509354055.
[89] Ghazi Zadeh L, Chevrier A, Farr J, Rodeo SA, Buschmann MD. Augmentation techniques for meniscus repair. J Knee Surg 2018;31(1):99–116. doi:10.1055/s-0037-1602247.
[90] Griffin JW, Hadeed MM, Werner BC, Diduch DR, Carson EW, Miller MD. Platelet-rich plasma in meniscal repair: does augmentation improve surgical outcomes? Clin Orthop Relat Res 2015;473(5):1665–72. doi:10.1007/s11999-015-4170-8.
[91] Nakayama H, Kanto R, Kambara S, Iseki T, Onishi S, Yoshiya S. Successful treatment of degenerative medial meniscal tears in well-aligned knees with fibrin clot implantation. Knee Surg Sport Traumatol Arthrosc 2020;28(11):3466–73. doi:10.1007/s00167-019-05758-y.
[92] Chahla J, Kennedy NI, Geeslin AG, Moatshe G, Cinque ME, DePhillipo NN, LaPrade RF. Meniscal repair with fibrin clot augmentation. Arthrosc Tech 2017;6(6):e2065–9. doi:10.1016/j.eats.2017.08.006.
[93] Arnoczky SP, Warren RF, Spivak JM. Meniscal repair using an exogenous fibrin clot. An experimental study in dogs. J Bone Joint Surg Am 1988;70(8):1209–17.
[94] van Trommel MF, Simonian PT, Potter HG, Wickiewicz TL. Arthroscopic meniscal repair with fibrin clot of complete radial tears of the lateral meniscus in the avascular zone. Arthroscopy 1998;14(4):360–5. doi:10.1016/s0749-8063(98)70002-7.
[95] Dai WL, Zhang H, Lin ZM, Shi ZJ, Wang J. Efficacy of platelet-rich plasma in arthroscopic repair for discoid lateral meniscus tears. BMC Musculoskelet Disord 2019;20(1):113. doi:10.1186/s12891-019-2500-9.
[96] Kaminski R, Kulinski K, Kozar-Kaminska K, Wielgus M, Langner M, Wasko MK, Kowalczewski J, Pomianowski S, Prospective A. Randomized, double-blind, parallel-group, placebo-controlled study evaluating meniscal healing, clinical outcomes, and safety in patients undergoing meniscal repair of unstable. Complete vertical meniscal tears (Bucket handle) augmented with platelet-rich plasma. Biomed Res Int 2018; 2018. doi:101155/2018/9315815.
[97] Paxton ES, Stock MV, Brophy RH. Meniscal repair versus partial meniscectomy: a systematic review comparing reoperation rates and clinical outcomes. Arthroscopy 2011;27(9):1275–88. doi:10.1016/j.arthro.2011.03.088.
[98] Englund M, Lohmander LS. Risk factors for symptomatic knee osteoarthritis fifteen to twenty-two years after meniscectomy. Arthritis Rheum 2004;50(9):2811–19. doi:10.1002/art.20489.
[99] De Bruycker M, Verdonk PCM, Verdonk RC. Meniscal allograft transplantation: a meta-analysis. Sicot J 2017;3:33. doi:10.1051/sicotj/2017016.
[100] Rosso F, Bisicchia S, Bonasia DE, Amendola A. Meniscal allograft transplantation: a systematic review. Am J Sports Med 2015;43(4):998–1007. doi:10.1177/0363546514536021.
[101] Pereira H, Fatih Cengiz I, Gomes S, Espregueira-Mendes J, Ripoll PL, Monllau JC, Reis RL, Oliveira JM. Meniscal allograft transplants and new scaffolding techniques. EFORT Open Rev 2019;4(6):279–95. doi:10.1302/2058-5241.4.180103.
[102] Noyes FR, Heckmann TP, Barber-Westin SD. Meniscus repair and transplantation: a comprehensive update. J Orthop Sports Phys Ther 2012;42(3):274–90. doi:10.2519/jospt.2012.3588.
[103] Frank RM, Cole BJ. Meniscus transplantation. Curr Rev Musculoskelet Med 2015;8(4):443–50. doi:10.1007/s12178-015-9309-4.
[104] Lee SR, Kim JG, Nam SW. The tips and pitfalls of meniscus allograft transplantation. Knee Surg Relat Res 2012;24(3):137–45. doi:10.5792/ksrr.2012.24.3.137.
[105] Jacquet C, Erivan R, Sharma A, Pithioux M, Parratte S, Argenson JN, Ollivier M. Preservation methods influence the biomechanical properties of human lateral menisci: an ex vivo comparative study of 3 methods. Orthop J Sports Med 2019;7(4):2325967119841622. doi:10.1177/2325967119841622.
[106] Dienst M, Greis PE, Ellis BJ, Bachus KN, Burks RT. Effect of lateral meniscal allograft sizing on contact mechanics of the lateral tibial plateau: an experimental study in human cadaveric knee joints. Am J Sports Med 2007;35(1):34–42. doi:10.1177/0363546506291404.
[107] Alhalki MM, Howell SM, Hull ML. How three methods for fixing a medial meniscal autograft affect tibial contact mechanics. Am J Sports Med 1999;27(3):320–8. doi:10.1177/03635465990270030901.
[108] Chen MI, Branch TP, Hutton WC. Is it important to secure the horns during lateral meniscal transplantation? A cadaveric study. Arthroscopy 1996;12(2):174–81. doi:10.1016/s0749-8063(96)90007-9.
[109] Chahla J, Olivetto J, Dean CS, Serra Cruz R, LaPrade RF. Lateral meniscal allograft transplantation: the bone trough technique. Arthrosc Tech 2016;5(2):e371–7. doi:10.1016/j.eats.2016.01.014.
[110] Woodmass JM, Johnson NR, Levy BA, Stuart MJ, Krych AJ. Lateral meniscus allograft transplantation: the bone plug technique. Arthrosc Tech 2017;6(4):e1215–20. doi:10.1016/j.eats.2017.04.016.
[111] Dean CS, Olivetto J, Chahla J, Serra Cruz R, LaPrade RF. Medial meniscal allograft transplantation: the bone plug technique. Arthrosc Tech 2016;5(2):e329–35. doi:10.1016/j.eats.2016.01.004.
[112] Ambra LF, Mestriner AB, Ackermann J, Phan AT, Farr J, Gomoll AH. Bone-plug versus soft tissue fixation of medial meniscal allograft transplants: a biomechanical study. Am J Sports Med 2019;47(12):2960–5. doi:10.1177/0363546519870179.
[113] Ren S, Zhang X, You T, Jiang X, Jin D, Zhang W. Clinical and radiologic outcomes after a modified bone plug technique with anatomical meniscal root reinsertion for meniscal allograft transplantation and a minimum 18-month follow-up. J Orthop Surg Res 2018;13(1):97. doi:10.1186/s13018-018-0776-3.
[114] Abraham AC, Moyer JT, Villegas DF, Odegard GM, Haut Donahue TL. Hyperelastic properties of human meniscal attachments. J Biomech 2011;44(3):413–18. doi:10.1016/j.jbiomech.2010.10.001.
[115] Abraham AC, Villegas DF, Kaufman KR, Haut Donahue TL. Internal pressure of human meniscal root attachments during loading. J Orthop Res 2013;31(10):1507–13. doi:10.1002/jor.22408.
[116] Crook TB, Ardolino A, Williams LA, Barlow IW. Meniscal allograft transplantation: a review of the current literature. Ann R Coll Surg Engl 2009;91(5):361–5. doi:10.1308/003588409X428559.
[117] Stone KR, Steadman JR, Rodkey WG, Li ST. Regeneration of meniscal cartilage with use of a collagen scaffold. Analysis of preliminary data, J Bone Joint Surg Am 1997;79(12):1770–7. doi:10.2106/00004623-199712000-00002.
[118] Rodkey WG, Steadman JR, Li ST. A clinical study of collagen meniscus implants to restore the injured meniscus. Clin Orthop Relat Res 1999;367:S281–92 Suppl. doi:10.1097/00003086-199910001-00027.
[119] Buma P, van Tienen T, Veth R. The collagen meniscus implant. Expert Rev Med Devices 2007;4(4):507–16. doi:10.1586/17434440.4.4.507.
[120] Reguzzoni M, Manelli A, Ronga M, Raspanti M, Grassi FA. Histology and ultrastructure of a tissue-engineered collagen meniscus before and after implantation. J Biomed Mater Res B Appl Biomater 2005;74(2):808–16. doi:10.1002/jbm.b.30314.
[121] Martinek V, Ueblacker P, Bräun K, Nitschke S, Mannhardt R, Specht K, Gansbacher B, Imhoff AB. Second generation of meniscus transplantation: in-vivo study with tissue engineered meniscus replacement. Arch Orthop Trauma Surg 2006;126(4):228–34. doi:10.1007/s00402-005-0025-1.
[122] Bulgheroni E, Grassi A, Bulgheroni P, Marcheggiani Muccioli GM, Zaffagnini S, Marcacci M. Long-term outcomes of medial CMI implant versus partial medial meniscectomy in patients with concomitant ACL reconstruction. Knee Surg Sport Traumatol Arthrosc 2015;23(11):3221–7. doi:10.1007/s00167-014-3136-9.
[123] Monllau JC, Gelber PE, Abat F, Pelfort X, Abad R, Hinarejos P, Tey M. Outcome after partial medial meniscus substitution with the collagen meniscal implant at a minimum of 10 years' follow-up. Arthroscopy 2011;27(7):933–43. doi:10.1016/j.arthro.2011.02.018.
[124] Zaffagnini S, Marcheggiani Muccioli GM, Lopomo N, Bruni D, Giordano G, Ravazzolo G, Molinari M, Marcacci M. Prospective long-term outcomes of the medial collagen meniscus implant versus partial medial meniscectomy: a minimum 10-year follow-up study. Am J Sports Med 2011;39(5):977–85. doi:10.1177/0363546510391179.
[125] Schenk L, Bethge L, Hirschmann A, Berbig R, Lüthi U, Arnold MP, Hirschmann MT. Ongoing MRI remodeling 3-7 years after collagen meniscus implantation in stable knees. Knee Surg Sports Traumatol Arthrosc 2020;28(4):1099–104. doi:10.1007/s00167-019-05714-w.
[126] Zaffagnini S, Grassi A, Marcheggiani Muccioli GM, Bonanzinga T, Nitri M, Raggi F, et al. MRI evaluation of a collagen meniscus implant: a systematic review. Knee Surg Sport Traumatol Arthrosc 2015;23(11):3228–37. doi:10.1007/s00167-014-3155-6.
[127] Lucidi GA, Grassi A, Al-zu'bi BBH, Macchiarola L, Agostinone P, Marcacci M, et al. Satisfactory clinical results and low failure rate of medial collagen meniscus implant (CMI) at a minimum 20 years of follow-up. Knee Surg Sport Traumatol Arthrosc 2021. doi:10.1007/s00167-021-06556-1.
[128] Elsner JJ, Portnoy S, Zur G, Guilak F, Shterling A, Linder-Ganz E. Design of a free-floating polycarbonate-urethane meniscal implant using finite element modeling and experimental validation. J Biomech Eng 2010;132(9):095001. doi:10.1115/1.4001892.
[129] Verhaeghe L, Boeren K. A rare complication after synthetic meniscus replacement. J Belg Soc Radiol 2018;102(1):63. doi:10.5334/jbsr.1601.
[130] Shemesh M, Asher R, Zylberberg E, Guilak F, Linder-Ganz E, Elsner JJ. Viscoelastic properties of a synthetic meniscus implant. J Mech Behav Biomed Mater 2014;29:42–55. doi:10.1016/j.jmbbm.2013.08.021.
[131] Elsner JJ, Shemesh M, Shefy-Peleg A, Gabet Y, Zylberberg E, Linder-Ganz E. Quantification of in vitro wear of a synthetic meniscus implant using gravimetric and micro-CT measurements. J Mech Behav Biomed Mater 2015;49:310–20. doi:10.1016/j.jmbbm.2015.05.017.
[132] Shemesh M, Shefy-Peleg A, Levy A, Shabshin N, Condello V, Arbel R, Gefen A. Effects of a novel medial meniscus implant on the knee compartments: imaging and biomechanical aspects. Biomech Model Mechanobiol 2020. doi:10.1007/s10237-020-01323-6.
[133] Efe T, Getgood A, Schofer MD, Fuchs-Winkelmann S, Mann D, Paletta JRJ, et al. The safety and short-term efficacy of a novel polyurethane meniscal scaffold for the treatment of segmental medial meniscus deficiency. Knee Surg Sport Traumatol Arthrosc 2012;20(9):1822–30. doi:10.1007/s00167-011-1779-3.
[134] Houck DA, Kraeutler MJ, Belk JW, McCarty EC, Bravman JT. Similar clinical outcomes following collagen or polyurethane meniscal scaffold implantation: a

systematic review. Knee Surg Sports Traumatol Arthrosc 2018;26(8):2259–69. doi:10.1007/s00167-018-4838-1.
[135] Schüttler KF, Haberhauer F, Gesslein M, Heyse TJ, Figiel J, Lorbach O, et al. Midterm follow-up after implantation of a polyurethane meniscal scaffold for segmental medial meniscus loss: maintenance of good clinical and MRI outcome. Knee Surg Sport Traumatol Arthrosc 2016;24(5):1478–84. doi:10.1007/s00167-015-3759-5.
[136] Verdonk R, Verdonk P, Huysse W, Forsyth R, Heinrichs EL. Tissue ingrowth after implantation of a novel, biodegradable polyurethane scaffold for treatment of partial meniscal lesions. Am J Sports Med 2011;39(4):774–82. doi:10.1177/0363546511398040.
[137] Toanen C, Dhollander A, Bulgheroni P, Filardo G, Zaffagnini S, Spalding T, Monllau JC, Gelber P, Verdonk R, Beaufils P, Bulgheroni E, Asplin L, Pujol N, Verdonk P. Polyurethane meniscal scaffold for the treatment of partial meniscal deficiency: 5-year follow-up outcomes: a European Multicentric Study. Am J Sports Med 2020;48(6):1347–55. doi:10.1177/0363546520913528.
[138] Jang T-S, Jung H-D, Pan HM, Han WT, Chen S, Song J. 3D printing of hydrogel composite systems. Recent Adv Technol Tissue Eng 2018;4(1) 2018. doi:10.18063/ijb.v4i1.126.
[139] Irvine SA, Venkatraman SS. Bioprinting and differentiation of stem cells. Molecules 2016;21(9). doi:10.3390/molecules21091188.
[140] Rey-Rico A, Cucchiarini M, Madry H. Hydrogels for precision meniscus tissue engineering: a comprehensive review. Connect Tissue Res 2017;58(3–4):317–28. doi:10.1080/03008207.2016.1276576.
[141] Shimomura K, Hamamoto S, Hart DA, Yoshikawa H, Nakamura N. Meniscal repair and regeneration: current strategies and future perspectives. J Clin Orthop Trauma 2018;9(3):247–53. doi:10.1016/j.jcot.2018.07.008.
[142] in: Melrose J. Novel approaches in meniscal repair utilizing mesenchymal stem cells, new generation bioscaffolds and biological adhesives as cell delivery vehicles. Meniscus of the knee - function, pathology and management. Almqvist TAaK, editor. (Ed.) IntechOpen; 2018.
[143] Sun J, Vijayavenkataraman S, Liu H. An overview of scaffold design and fabrication technology for engineered knee meniscus. Materials (Basel) 2017;10(1). doi:10.3390/ma10010029.
[144] De Mori A, Peña Fernández M, Blunn G, Tozzi G, Roldo M. 3D printing and electrospinning of composite hydrogels for cartilage and bone tissue engineering. Polymers (Basel) 2018;10(3). doi:10.3390/polym10030285.
[145] DePhillipo NN, LaPrade RF, Zaffagnini S, Mouton C, Seil R, Beaufils P. The future of meniscus science: international expert consensus. J Exp Orthop 2021;8(1):24. doi:10.1186/s40634-021-00345-y.
[146] Fan D, Staufer U, Accardo A. Engineered 3D polymer and hydrogel microenvironments for cell culture applications. Bioengineering (Basel) 2019;6(4). doi:10.3390/bioengineering6040113.
[147] Her GJ, Wu HC, Chen MH, Chen MY, Chang SC, Wang TW. Control of three-dimensional substrate stiffness to manipulate mesenchymal stem cell fate toward neuronal or glial lineages. Acta Biomater 2013;9(2):5170–80. doi:10.1016/j.actbio.2012.10.012.
[148] Shav D, Einav S. The effect of mechanical loads in the differentiation of precursor cells into mature cells. Ann N Y Acad Sci 2010;1188:25–31. doi:10.1111/j.1749-6632.2009.05079.x.
[149] Zhang W, Chu G, Wang H, Chen S, Li B, Han F. Effects of matrix stiffness on the differentiation of multipotent stem cells. Curr Stem Cell Res Ther 2020. doi:10.2174/1574888X15666200408114632.
[150] Engler AJ, Sen S, Sweeney HL, Discher DE. Matrix elasticity directs stem cell lineage specification. Cell 2006;126(4):677–89. doi:10.1016/j.cell.2006.06.044.
[151] Li YY, Choy TH, Ho FC, Chan PB. Scaffold composition affects cytoskeleton organization, cell-matrix interaction and the cellular fate of human mesenchymal stem cells upon chondrogenic differentiation. Biomaterials 2015;52:208–20. doi:10.1016/j.biomaterials.2015.02.037.
[152] Murphy CM, Matsiko A, Haugh MG, Gleeson JP, O'Brien FJ. Mesenchymal stem cell fate is regulated by the composition and mechanical properties of collagen-glycosaminoglycan scaffolds. J Mech Behav Biomed Mater 2012;11:53–62. doi:10.1016/j.jmbbm.2011.11.009.
[153] Machado CB, Ventura JMG, Lemos AF, Ferreira JMF, Leite MF, Goes AM. 3D chitosan–gelatin–chondroitin porous scaffold improves osteogenic differentiation of mesenchymal stem cells. Biomed Mater 2007;2(2):124–31. doi:10.1088/1748-6041/2/2/010.
[154] Freeman FE, Kelly DJ. Tuning alginate bioink stiffness and composition for controlled growth factor delivery and to spatially direct MSC fate within bioprinted tissues. Sci Rep 2017;7(1):17042. doi:10.1038/s41598-017-17286-1.
[155] Gentile F, Tirinato L, Battista E, Causa F, Liberale C, di Fabrizio EM, Decuzzi P. Cells preferentially grow on rough substrates. Biomaterials 2010;31(28):7205–12. doi:10.1016/j.biomaterials.2010.06.016.
[156] McNamara LE, Sjostrom T, Seunarine K, Meek RD, Su B, Dalby MJ. Investigation of the limits of nanoscale filopodial interactions. J Tissue Eng 2014;5:2041731414536177. doi:10.1177/2041731414536177.
[157] Zhang ZZ, Jiang D, Ding JX, Wang SJ, Zhang L, Zhang JY, Qi YS, Chen XS, Yu JK. Role of scaffold mean pore size in meniscus regeneration. Acta Biomater 2016;43:314–26. doi:10.1016/j.actbio.2016.07.050.
[158] Loh QL, Choong C. Three-dimensional scaffolds for tissue engineering applications: role of porosity and pore size. Tissue Eng Part B Rev 2013;19(6):485–502. doi:10.1089/ten.TEB.2012.0437.
[159] Klompmaker J, Jansen HW, Veth RP, Nielsen HK, de Groot JH, Pennings AJ. Porous implants for knee joint meniscus reconstruction: a preliminary study on the role of pore sizes in ingrowth and differentiation of fibrocartilage. Clin Mater 1993;14(1):1–11. doi:10.1016/0267-6605(93)90041-5.
[160] Xie J, Bao M, Bruekers SMC, Huck WTS. Collagen gels with different fibrillar microarchitectures elicit different cellular responses. ACS Appl Mater Interface 2017;9(23):19630–7. doi:10.1021/acsami.7b03883.
[161] Hospodiuk M, Dey M, Sosnoski D, Ozbolat IT. The bioink: a comprehensive review on bioprintable materials. Biotechnol Adv 2017;35(2):217–39. doi:10.1016/j.biotechadv.2016.12.006.
[162] Keane TJ, Badylak SF. Biomaterials for tissue engineering applications. Semin Pediatr Surg 2014;23(3):112–18. doi:10.1053/j.sempedsurg.2014.06.010.
[163] Szojka A, Lalh K, Andrews S, Jomha N, Osswald M, Adesida A. Biomimetic 3D printed scaffolds for meniscus tissue engineering. Bioprinting 2017;8:1–7. doi:10.1016/j.bprint.2017.08.001.
[164] P D, C F, P AM, C E. Polymeric materials for bone and cartilage repair. Prog in Polymer Sci 2010;35(4):403–40. doi:10.1016/j.progpolymsci.2010.01.006.
[165] Woodruff MA, Hutmacher DW. The return of a forgotten polymer—Polycaprolactone in the 21st century. Prog Polym Sci 2010;35(10):1217–56. doi:10.1016/j.progpolymsci.2010.04.002.
[166] Kang HW, Yoo JJ, Atala A. Bioprinted scaffolds for cartilage tissue engineering. Methods Mol Biol 2015;1340:161–9. doi:10.1007/978-1-4939-2938-2_11.
[167] Huey DJ, Athanasiou KA. Maturational growth of self-assembled, functional menisci as a result of TGF-beta1 and enzymatic chondroitinase-ABC stimulation. Biomaterials 2011;32(8):2052–8. doi:10.1016/j.biomaterials.2010.11.041.
[168] Lyons LP, Hidalgo Perea S, Weinberg JB, Wittstein JR, McNulty AL. Meniscus-derived matrix bioscaffolds: effects of concentration and cross-linking on meniscus cellular responses and tissue repair. Int J Mol Sci 2019;21(1). doi:10.3390/ijms21010044.
[169] Toh WS, Loh XJ. Advances in hydrogel delivery systems for tissue regeneration. Mater Sci Eng C Mater Biol Appl 2014;45:690–7. doi:10.1016/j.msec.2014.04.026.
[170] Ramiah P, du Toit LC, Choonara YE, Kondiah PPD, Pillay V. Hydrogel-based bioinks for 3D bioprinting in tissue regeneration. Front Mater 2020;7(76). doi:10.3389/fmats.2020.00076.
[171] Kopecek J. Hydrogel biomaterials: a smart future? Biomaterials 2007;28(34):5185–92. doi:10.1016/j.biomaterials.2007.07.044.
[172] Gilpin A, Yang Y. Decellularization strategies for regenerative medicine: from processing techniques to applications. BioMed Res Int 2017:9831534 2017. doi:10.1155/2017/9831534.
[173] Dzobo K, Motaung K, Adesida A. Recent trends in decellularized extracellular matrix bioinks for 3D printing: an updated review. Int J Mol Sci 2019;20(18). doi:10.3390/ijms20184628.
[174] Garreta E, Oria R, Tarantino C, Pla-Roca M, Prado P, Fernandez-Aviles F, et al. Tissue engineering by decellularization and 3D bioprinting. Mater Today 2017;20(4):166–78. doi:10.1016/j.mattod.2016.12.005.
[175] Badylak SF, Taylor D, Uygun K. Whole-organ tissue engineering: decellularization and recellularization of three-dimensional matrix scaffolds. Annu Rev Biomed Eng 2011;13:27–53. doi:10.1146/annurev-bioeng-071910-124743.
[176] Rothrauff BB, Shimomura K, Gottardi R, Alexander PG, Tuan RS. Anatomical region-dependent enhancement of 3-dimensional chondrogenic differentiation of human mesenchymal stem cells by soluble meniscus extracellular matrix. Acta Biomater 2017;49:140–51. doi:10.1016/j.actbio.2016.11.046.
[177] Stapleton TW, Ingram J, Fisher J, Ingham E. Investigation of the regenerative capacity of an acellular porcine medial meniscus for tissue engineering applications. Tissue Eng Part A 2011;17(1–2):231–42. doi:10.1089/ten.TEA.2009.0807.
[178] Ruprecht JC, Waanders TD, Rowland CR, Nishimuta JF, Glass KA, Stencel J, DeFrate LE, Guilak F, Weinberg JB, McNulty AL. Meniscus-derived matrix scaffolds promote the integrative repair of meniscal defects. Sci Rep 2019;9(1):8719. doi:10.1038/s41598-019-44855-3.
[179] Chen M, Feng Z, Guo W, Yang D, Gao S, Li Y, et al. PCL-MECM-based hydrogel hybrid scaffolds and meniscal fibrochondrocytes promote whole meniscus regeneration in a rabbit meniscectomy model. ACS Appl Mater Interface 2019;11(44):41626–39. doi:10.1021/acsami.9b13611.
[180] Shimomura K, Rothrauff BB, Tuan RS. Region-specific effect of the decellularized meniscus extracellular matrix on mesenchymal stem cell-based meniscus tissue engineering. Am J Sports Med 2017;45(3):604–11. doi:10.1177/0363546516674184.
[181] Stapleton TW, Ingram J, Katta J, Knight R, Korossis S, Fisher J, Ingham E. Development and characterization of an acellular porcine medial meniscus for use in tissue engineering. Tissue Eng Part A 2008;14(4):505–18. doi:10.1089/tea.2007.0233.
[182] Maier D, Braeun K, Steinhauser E, Ueblacker P, Oberst M, Kreuz PC, Roos N, Martinek V, Imhoff AB. In vitro analysis of an allogenic scaffold for tissue-engineered meniscus replacement. J Orthop Res 2007;25(12):1598–608. doi:10.1002/jor.20405.
[183] Sandmann GH, Eichhorn S, Vogt S, Adamczyk C, Aryee S, Hoberg M, et al. Generation and characterization of a human acellular meniscus scaffold for tissue engineering. J Biomed Mater Res Part A 2009;91A(2):567–74. doi:10.1002/jbm.a.32269.
[184] Lutolf MP, Hubbell JA. Synthetic biomaterials as instructive extracellular microenvironments for morphogenesis in tissue engineering. Nat Biotechnol 2005;23(1):47–55. doi:10.1038/nbt1055.
[185] He Y, Chen Y, Wan X, Zhao C, Qiu P, Lin X, Zhang J, Huang Y. Preparation and characterization of an optimized meniscal extracellular matrix scaffold for meniscus transplantation. Front Bioeng Biotechnol 2020;8:779. doi:10.3389/fbioe.2020.00779.
[186] Yusof F, Sha'ban M, Azhim A. Development of decellularized meniscus using closed sonication treatment system: potential scaffolds for orthopedics tissue engineering applications. Int J Nanomed 2019;14:5491–502. doi:10.2147/ijn.S207270.
[187] Heo S-J, Song KH, Thakur S, Miller LM, Cao X, Peredo AP, Seiber BN, Qu F, Driscoll TP, Shenoy VB, Lakadamyali M, Burdick JA, Mauck RL. Nuclear soften-

ing expedites interstitial cell migration in fibrous networks and dense connective tissues. Sci Adv 2020;6(25):eaax5083. doi:10.1126/sciadv.aax5083.
[188] Qu F, Li Q, Wang X, Cao X, Zgonis MH, Esterhai JL, Shenoy VB, Han L, Mauck RL. Maturation state and matrix microstructure regulate interstitial cell migration in dense connective tissues. Sci Rep 2018;8(1):3295. doi:10.1038/s41598-018-21212-4.
[189] Qu F, Holloway JL, Esterhai JL, Burdick JA, Mauck RL. Programmed biomolecule delivery to enable and direct cell migration for connective tissue repair. Nat Commun 2017;8(1):1780. doi:10.1038/s41467-017-01955-w.
[190] Qu F, Pintauro MP, Haughan JE, Henning EA, Esterhai JL, Schaer TP, Mauck RL, Fisher MB. Repair of dense connective tissues via biomaterial-mediated matrix reprogramming of the wound interface. Biomaterials 2015;39:85–94. doi:10.1016/j.biomaterials.2014.10.067.
[191] Gao S, Guo W, Chen M, Yuan Z, Wang M, Zhang Y, et al. Fabrication and characterization of electrospun nanofibers composed of decellularized meniscus extracellular matrix and polycaprolactone for meniscus tissue engineering. J Mater Chem B 2017;5(12):2273–85. doi:10.1039/C6TB03299K.
[192] Zhang ZZ, Wang SJ, Zhang JY, Jiang WB, Huang AB, Qi YS, Ding JX, Chen XS, Jiang D, Yu JK. 3D-printed poly(epsilon-caprolactone) scaffold augmented with mesenchymal stem cells for total meniscal substitution: a 12- and 24-week animal study in a rabbit model. Am J Sports Med 2017;45(7):1497–511. doi:10.1177/0363546517691513.
[193] Gunja NJ, Athanasiou KA. Additive and synergistic effects of bFGF and hypoxia on leporine meniscus cell-seeded PLLA scaffolds. J Tissue Eng Regen Med 2010;4(2):115–22. doi:10.1002/term.221.
[194] Liang Y, Idrees E, Szojka ARA, Andrews SHJ, Kunze M, Mulet-Sierra A, Jomha NM, Adesida AB. Chondrogenic differentiation of synovial fluid mesenchymal stem cells on human meniscus-derived decellularized matrix requires exogenous growth factors. Acta Biomater 2018;80:131–43. doi:10.1016/j.actbio.2018.09.038.
[195] Tarafder S, Gulko J, Kim D, Sim KH, Gutman S, Yang J, Cook JL, Lee CH. Effect of dose and release rate of CTGF and TGFbeta3 on avascular meniscus healing. J Orthop Res 2019;37(7):1555–62. doi:10.1002/jor.24287.
[196] Tarafder S, Gulko J, Sim KH, Yang J, Cook JL, Lee CH. Engineered healing of avascular meniscus tears by stem cell recruitment. Sci Rep 2018;8(1):8150. doi:10.1038/s41598-018-26545-8.
[197] Sasaki H, Rothrauff BB, Alexander PG, Lin H, Gottardi R, Fu FH, Tuan RS. In vitro repair of meniscal radial tear with hydrogels seeded with adipose stem cells and TGF-beta3. Am J Sports Med 2018;46(10):2402–13. doi:10.1177/0363546518782973.
[198] Nakagawa Y, Fortier LA, Mao JJ, Lee CH, Goodale MB, Koff MF, Uppstrom TJ, Croen B, Wada S, Carballo CB, Potter HG, Rodeo SA. Long-term evaluation of meniscal tissue formation in 3-dimensional-printed scaffolds with sequential release of connective tissue growth factor and TGF-beta3 in an ovine model. Am J Sports Med 2019;47(11):2596–607. doi:10.1177/0363546519865513.
[199] Romanazzo S, Vedicherla S, Moran C, Kelly DJ. Meniscus ECM-functionalised hydrogels containing infrapatellar fat pad-derived stem cells for bioprinting of regionally defined meniscal tissue. J Tissue Eng Regen Med 2018;12(3):e1826–35. doi:10.1002/term.2602.
[200] Lee CH, Rodeo SA, Fortier LA, Lu C, Erisken C, Mao JJ. Protein-releasing polymeric scaffolds induce fibrochondrocytic differentiation of endogenous cells for knee meniscus regeneration in sheep. Sci Transl Med 2014;6(266):266ra171. doi:10.1126/scitranslmed.3009696.
[201] Zhang ZZ, Chen YR, Wang SJ, Zhao F, Wang XG, Yang F, Shi JJ, Ge ZG, Ding WY, Yang YC, Zou TQ, Zhang JY, Yu JK, Jiang D. Orchestrated biomechanical, structural, and biochemical stimuli for engineering anisotropic meniscus. Sci Transl Med 2019;11(487). doi:10.1126/scitranslmed.aao0750.
[202] Johns DE, Athanasiou KA. Growth factor effects on costal chondrocytes for tissue engineering fibrocartilage. Cell Tissue Res 2008;333(3):439–47. doi:10.1007/s00441-008-0652-2.
[203] Mohanraj B, Duan G, Peredo A, Kim M, Tu F, Lee D, Dodge GR, Mauck RL. Mechanically-activated microcapsules for 'on-demand' drug delivery in dynamically loaded musculoskeletal tissues. Adv Funct Mater 2019;29(15). doi:10.1002/adfm.201807909.
[204] Ionescu LC, Lee GC, Huang KL, Mauck RL. Growth factor supplementation improves native and engineered meniscus repair in vitro. Acta Biomater 2012;8(10):3687–94. doi:10.1016/j.actbio.2012.06.005.
[205] Eltom A, Zhong G, Muhammad A. Scaffold techniques and designs in tissue engineering functions and purposes: a review. Adv Mater Sci Eng 2019;2019:3429527. doi:10.1155/2019/3429527.
[206] Kim HJ, Lee JH, Im GI. Chondrogenesis using mesenchymal stem cells and PCL scaffolds. J Biomed Mater Res A 2010;92(2):659–66. doi:10.1002/jbm.a.32414.
[207] Kang SW, Son SM, Lee JS, Lee ES, Lee KY, Park SG, Park JH, Kim BS. Regeneration of whole meniscus using meniscal cells and polymer scaffolds in a rabbit total meniscectomy model. J Biomed Mater Res A 2006;78(3):659–71. doi:10.1002/jbm.a.30904.
[208] Puetzer JL, Bonassar LJ. High density type I collagen gels for tissue engineering of whole menisci. Acta Biomater 2013;9(8):7787–95. doi:10.1016/j.actbio.2013.05.002.
[209] Halili AN, Karahan S, Kurum B, Hasirci V. Collagen based multilayer scaffolds for meniscus tissue engineering: in vivo test results. Biomater Med App 2018;2(1). doi:10.4172/2577-0268.1000112.
[210] Halili AN, Hasirci N, Hasirci V. A multilayer tissue engineered meniscus substitute. J Mater Sci Mater Med 2014;25(4):1195–209. doi:10.1007/s10856-014-5145-0.
[211] Lee JM, Yeong WY. Design and printing strategies in 3D Bioprinting of cell-hydrogels: a review. Adv Healthc Mater 2016;5(22):2856–65. doi:10.1002/adhm.201600435.
[212] Yan Q, Dong H, Su J, Han J, Song B, Wei Q, Shi Y. A review of 3D printing technology for medical applications. Engineering 2018;4(5):729–42. doi:10.1016/j.eng.2018.07.021.
[213] Cengiz IF, Pitikakis M, Cesario L, Parascandolo P, Vosilla L, Viano G, Oliveira JM, Reis RL. Building the basis for patient-specific meniscal scaffolds: from human knee MRI to fabrication of 3D printed scaffolds. Bioprinting 2016;1-2:1–10. doi:10.1016/j.bprint.2016.05.001.
[214] Filardo G, Petretta M, Cavallo C, Roseti L, Durante S, Albisinni U, Grigolo B. Patient-specific meniscus prototype based on 3D bioprinting of human cell-laden scaffold. Bone Joint Res 2019;8(2):101–6. doi:10.1302/2046-3758.82.BJR-2018-0134.R1.
[215] Senior JJ, Cooke ME, Grover LM, Smith AM. Fabrication of complex hydrogel structures using Suspended Layer Additive Manufacturing (SLAM). Adv Functional Mater 2019;29(49) doi.org/10.1002/adfm.201904845.
[216] Moxon SR, Cooke ME, Cox SC, Snow M, Jeys L, Jones SW, Smith AM, Grover LM. Suspended manufacture of biological structures. Adv Mater 2017;29(13). doi:10.1002/adma.201605594.
[217] Hinton TJ, Jallerat Q, Palchesko RN, Park JH, Grodzicki MS, Shue HJ, Ramadan MH, Hudson AR, Feinberg AW. Three-dimensional printing of complex biological structures by freeform reversible embedding of suspended hydrogels. Sci Adv 2015;1(9):e1500758. doi:10.1126/sciadv.1500758.
[218] Lee A, Hudson AR, Shiwarski DJ, Tashman JW, Hinton TJ, Yerneni S, Bliley JM, Campbell PG, Feinberg AW. 3D bioprinting of collagen to rebuild components of the human heart. Science 2019;365(6452):482–7. doi:10.1126/science.aav9051.
[219] Ning L, Yang B, Mohabatpour F, Betancourt N, Sarker MD, Papagerakis P, Chen X. Process-induced cell damage: pneumatic versus screw-driven bioprinting. Biofabrication 2020;12(2):025011. doi:10.1088/1758-5090/ab5f53.
[220] Yourek G, McCormick SM, Mao JJ, Reilly GC. Shear stress induces osteogenic differentiation of human mesenchymal stem cells. Regen Med 2010;5(5):713–24. doi:10.2217/rme.10.60.
[221] Dado D, Sagi M, Levenberg S, Zemel A. Mechanical control of stem cell differentiation. Regen Med 2012;7(1):101–16. doi:10.2217/rme.11.99.
[222] Blaeser A, Duarte Campos DF, Puster U, Richtering W, Stevens MM, Fischer H. Controlling shear stress in 3D bioprinting is a key factor to balance printing resolution and stem cell integrity. Adv Healthc Mater 2016;5(3):326–33. doi:10.1002/adhm.201500677.
[223] Lee C, O'Connell CD, Onofrillo C, Choong PFM, Di Bella C, Duchi S. Human articular cartilage repair: sources and detection of cytotoxicity and genotoxicity in photo-crosslinkable hydrogel bioscaffolds. Stem Cells Transl Med 2020;9(3):302–15. doi:10.1002/sctm.19-0192.
[224] Bahcecioglu G, Hasirci N, Bilgen B, Hasirci V. A 3D printed PCL/hydrogel construct with zone-specific biochemical composition mimicking that of the meniscus. Biofabrication 2019;11(2):025002. doi:10.1088/1758-5090/aaf707.
[225] Narayanan LK, Huebner P, Fisher MB, Spang JT, Starly B, Shirwaiker RA. 3D-bioprinting of Polylactic Acid (PLA) nanofiber–alginate hydrogel bioink containing human adipose-derived stem cells. ACS Biomater Sci Eng 2016;2(10):1732–42. doi:10.1021/acsbiomaterials.6b00196.
[226] Bahcecioglu G, Bilgen B, Hasirci N, Hasirci V. Anatomical meniscus construct with zone specific biochemical composition and structural organization. Biomaterials 2019;218:119361. doi:10.1016/j.biomaterials.2019.119361.
[227] Bandyopadhyay A, Mandal BB. A three-dimensional printed silk-based biomimetic tri-layered meniscus for potential patient-specific implantation. Biofabrication 2019;12(1):015003. doi:10.1088/1758-5090/ab40fa.
[228] Ghodbane SA, Patel JM, Brzezinski A, Lu TM, Gatt CJ, Dunn MG. Biomechanical characterization of a novel collagen-hyaluronan infused 3D-printed polymeric device for partial meniscus replacement. J Biomed Mater Res B Appl Biomater 2019;107(8):2457–65. 10.1002/jbm.b.34336.
[229] Ghodbane SA, Brzezinski A, Patel JM, Plaff WH, Marzano KN, Gatt CJ, Dunn MG. Partial meniscus replacement with a collagen-hyaluronan infused three-dimensional printed polymeric scaffold. Tissue Eng Part A 2019;25(5–6):379–89. doi:10.1089/ten.TEA.2018.0160.
[230] Fiordeliso J, Bron S, Kohn J. Design, synthesis, and preliminary characterization of tyrosine-containing polyarylates: new biomaterials for medical applications. J Biomater Sci Polym Ed 1994;5(6):497–510.
[231] Ertel SI, Kohn J. Evaluation of a series of tyrosine-derived polycarbonates as degradable biomaterials. J Biomed Mater Res 1994;28(8):919–30. doi:10.1002/jbm.820280811.
[232] Petri M, Ufer K, Toma I, Becher C, Liodakis E, Brand S, et al. Effects of perfusion and cyclic compression on in vitro tissue engineered meniscus implants. Knee Surg Sport Traumatol Arthrosc 2012;20(2):223–31. doi:10.1007/s00167-011-1600-3.
[233] Puetzer JL, Koo E, Bonassar LJ. Induction of fiber alignment and mechanical anisotropy in tissue engineered menisci with mechanical anchoring. J Biomech 2015;48(8):1436–43. doi:10.1016/j.jbiomech.2015.02.033.
[234] Puetzer JL, Bonassar LJ. Physiologically distributed loading patterns drive the formation of zonally organized collagen structures in tissue-engineered meniscus. Tissue Eng Part A 2016;22(13–14):907–16. doi:10.1089/ten.TEA.2015.0519.
[235] McHenry JA, Zielinska B, Donahue TL. Proteoglycan breakdown of meniscal explants following dynamic compression using a novel bioreactor. Ann Biomed Eng 2006;34(11):1758–66. doi:10.1007/s10439-006-9178-5.
[236] Huey DJ, Athanasiou KA. Tension-compression loading with chemical stimulation results in additive increases to functional properties of anatomic meniscal constructs. PLoS ONE 2011;6(11):e27857. doi:10.1371/journal.pone.0027857.
[237] Meinert C, Schrobback K, Hutmacher DW, Klein TJ. A novel bioreactor system for biaxial mechanical loading enhances the properties of tissue-engineered human cartilage. Sci Rep 2017;7(1):16997. doi:10.1038/s41598-017-16523-x.
[238] Chen M, Guo W, Gao S, Hao C, Shen S, Zhang Z, Wang Z, Li X, Jing X, Zhang X, Yuan Z, Wang M, Zhang Y, Peng J, Wang A, Wang Y, Sui X, Liu S, Guo Q. Biome-

chanical stimulus based strategies for meniscus tissue engineering and regeneration. Tissue Eng Part B Rev 2018;24(5):392–402. doi:10.1089/ten.TEB.2017.0508.
[239] McCorry MC, Bonassar LJ. Fiber development and matrix production in tissue-engineered menisci using bovine mesenchymal stem cells and fibrochondrocytes. Connect Tissue Res 2017;58(3–4):329–41. doi:10.1080/03008207.2016.1267152.
[240] Jacob G, Shimomura K, Krych AJ, Nakamura N. The meniscus tear: a review of stem cell therapies. Cells 2019;9(1):92. doi:10.3390/cells9010092.
[241] Schu S, Nosov M, O'Flynn L, Shaw G, Treacy O, Barry F, Murphy M, O'Brien T, Ritter T. Immunogenicity of allogeneic mesenchymal stem cells. J Cell Mol Med 2012;16(9):2094–103. doi:10.1111/j.1582-4934.2011.01509.x.
[242] Gu LH, Zhang TT, Li Y, Yan HJ, Qi H, Li FR. Immunogenicity of allogeneic mesenchymal stem cells transplanted via different routes in diabetic rats. Cell Mol Immunol 2015;12(4):444–55. doi:10.1038/cmi.2014.70.
[243] Uccelli A, Moretta L, Pistoia V. Immunoregulatory function of mesenchymal stem cells. Eur J Immunol 2006;36(10):2566–73. doi:10.1002/eji.200636416.
[244] Saeedi P, Halabian R, Imani Fooladi AA. A revealing review of mesenchymal stem cells therapy, clinical perspectives and Modification strategies. Stem Cell Investig 2019;6:34. doi:10.21037/sci.2019.08.11.
[245] McCorry MC, Mansfield MM, Sha X, Coppola DJ, Lee JW, Bonassar LJ. A model system for developing a tissue engineered meniscal enthesis. Acta Biomater 2017;56:110–17. doi:10.1016/j.actbio.2016.10.040.
[246] Perea SH, Lyons LP, Nishimuta JF, Weinberg JB, McNulty AL. Evaluation of culture conditions for in vitro meniscus repair model systems using bone marrow-derived mesenchymal stem cells. Connect Tissue Res 2020;61(3–4):322–37. doi:10.1080/03008207.2019.1680656.
[247] Gopinathan J, Pillai MM, Shanthakumari S, Gnanapoongothai S, Dinakar Rai BK, Santosh Sahanand K, Selvakumar R, Bhattacharyya A. Carbon nanofiber amalgamated 3D poly-ε-caprolactone scaffold functionalized porous-nanoarchitectures for human meniscal tissue engineering: in vitro and in vivo biocompatibility studies. Nanomedicine 2018;14(7):2247–58. doi:10.1016/j.nano.2018.07.012.
[248] Alexander FA Jr, Johnson L, Williams K, Packer K. A Parameter study for 3D-printing organized nanofibrous collagen scaffolds using direct-write electrospinning. Materials (Basel) 2019;12(24). doi:10.3390/ma12244131.
[249] López-Calzada G, Hernandez-Martínez AR, Cruz-Soto M, Ramírez-Cardona M, Rangel D, Molina GA, Luna-Barcenas G, Estevez M. Development of meniscus substitutes using a mixture of biocompatible polymers and extra cellular matrix components by electrospinning. Mater Sci Eng C Mater Biol Appl 2016;61:893–905. doi:10.1016/j.msec.2016.01.018.
[250] Yang X, Lu Z, Wu H, Li W, Zheng L, Zhao J. Collagen-alginate as bioink for three-dimensional (3D) cell printing based cartilage tissue engineering. Mater Sci Eng C Mater Biol Appl 2018;83:195–201. doi:10.1016/j.msec.2017.09.002.
[251] Merriam AR, Patel JM, Culp BM, Gatt CJ Jr, Dunn MG. Successful total meniscus reconstruction using a novel fiber-reinforced scaffold: a 16- and 32-week study in an Ovine model. Am J Sports Med 2015;43(10):2528–37. doi:10.1177/0363546515595065.
[252] Bahcecioglu G, Hasirci N, Bilgen B, Hasirci V. Hydrogels of agarose, and methacrylated gelatin and hyaluronic acid are more supportive for in vitro meniscus regeneration than three dimensional printed polycaprolactone scaffolds. Int J Biol Macromol 2019;122:1152–62. doi:10.1016/j.ijbiomac.2018.09.065.
[253] Zhang Z, Liu R, Zepeda H, Zeng L, Qiu J, Wang S. 3D printing super strong hydrogel for artificial meniscus. ACS Appl Polym Mater 2019;1(8):2023–32. doi:10.1021/acsapm.9b00304.