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Meniscal repair and regeneration: Current strategies and future perspectives

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ABSTRACT

The management of meniscal injuries remains difficult and challenging. Although several clinical options exist for the treatment of such injuries, complete regeneration of the damaged meniscus has proved difficult due to the limited healing capacity of the tissue. With the advancements in tissue engineering and cell-based technologies, new therapeutic options for patients with currently incurable meniscal lesions now potentially exist. This review will discuss basic anatomy, current repair techniques and treatment options for loss of meniscal integrity. Specifically, we focus on the possibility and feasibility of the latest tissue engineering approaches, including 3D printing technologies. Therefore, this discussion will facilitate a better understanding of the latest trends in meniscal repair and regeneration, and contribute to the future application of such clinical therapies for patients with meniscal injuries.

1. Introduction

The meniscus is a crescent-shaped fibrocartilaginous tissue, comprised of both a medial and a lateral component positioned between the corresponding femoral condyle and tibial plateau, and plays important roles in the knee joint, including force transmission, shock absorption, joint lubrication, and the provision of joint stability.[1–3] For many in the young and active population who injure their knee, this commonly involves injury to the menisci.[4,5] The previously reported mean annual incidence of meniscal lesions per 10,000 populations was 9.0 for males and 4.2 for females.[6] However, it has been widely accepted that a meniscus tear does not heal spontaneously, owing to its hypovascularity and hypocellularity.[1,3,7] In the absence of effective long-term repair of these meniscal injuries, damage to the knee may compromise athletic careers and lead to development of osteoarthritis at an early age.[8,9] Therefore, the development of novel therapeutic methods for meniscal repair is both timely and necessary.

Historically, the menisci were considered to be a functionless vestigial structure, one that should be entirely removed once damaged.[10] Since King reported “the function of the semilunar cartilages” in 1936 [11], the importance of meniscal functions in the knee joint has been gradually recognized. In 1948, Fairbank reported joint degenerative changes were observed after meniscectomy, suggesting such changes were due to loss of the weight-bearing function of the meniscus.[12] In the 1980s, several biomechanical studies addressed the importance of the meniscus as a joint stabilizer and shock absorber in the knee joint,[13,14] and meniscal preservation has been recognized to be essential to retention of normal knee biomechanics. However, meniscectomy to remove the damaged, unstable portion of the meniscus has still been the gold standard of surgical treatment for meniscal tears, since there have not been effective therapeutic methods developed for such tears.

In this review, we focus on the current strategies and therapeutic methods for meniscal repair and regeneration following such previously incurable meniscal tears, and highlight recent advances in meniscal tissue engineering approaches. This will facilitate an understanding of the latest trends for meniscal repair and regeneration, and contribute to the future application of such

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clinical therapies in patients with meniscal injuries that previously were progressive and led to an increased risk for development of osteoarthritis.

2. Anatomy, biochemistry and biomechanics

The meniscus is a crescent-shaped highly complex structure with low cellularity and dense extracellular matrix (ECM), which is stabilized by the medial collateral ligament, the transverse ligament, the meniscofemoral ligaments, and attachments at the anterior and posterior horns.[1,15] Vascularization in the adult meniscus exists only in the peripheral 10–25% of the tissue, and the extent of the vascular zone has implications for the healing potential of meniscal tears.[7] Biochemically, normal menisci compose of 72% water, 22% collagen, 0.8% glycosaminoglycans and 0.12% DNA.[16] Collagen is the main ECM component of the meniscus, and different collagen types exist in each region of the tissue. In the red-red zone (vascular zone), collagen type I is predominant at approximately 80% composition by dry weight. In the white-white zone (avascular zone), 40% of the tissue by dry weight is collagen type I and 60% is collagen type II.[17] Regarding meniscal cells, cells in the red-red zone are more fibroblast-like in appearance and connected via cellular networks, while cells in the white-red zone and white-white zone are more chondrocyte-like and exist as single cells.[1,18] Cells of the menisci require loading to maintain the integrity of the menisci, as loss of loading can lead to derepression of catabolic genes and potential induction of tissue atrophy.[19] Loss of appropriate loading after an injury could thus contribute to the progressive deterioration of the injured tissue. Collagen fiber arrangement is highly specialized, with the majority being circumferentially aligned.[20,21] This circumferential orientation creates biomechanically optimal resistance to hoop stresses, resulting from displacement of the meniscus from the tibial plateau during normal weight-bearing.[3] The organization of the collagen fibers, as well as the proteoglycan in the meniscus is quite complex, with different organization near the surface, the periphery, and in the central, more cartilaginous zones.[22,23]

3. Current surgical repair techniques

Based on meniscal anatomy and vascularity, the meniscus has limited healing capacities especially in central two-thirds avascular zone, while meniscal tears in peripheral vascular zone should be reparable.[24] To preserve important meniscal functions, surgeons should always consider repairing the meniscal injury as extensively as possible. As many studies have addressed, meniscal tears in the vascular zone of peripheral area, such as vertical longitudinal tears, have good indications for effective meniscal repair.[25,26] As horizontal tears were previously considered to be rarely healed due to the involvement of inner avascular zone, either non-operative treatment or meniscectomy were chosen.[27] Recently, meniscal preservation techniques suturing the tear have been attempted to preserve meniscal function, and successful outcomes can be obtained especially in younger patients without degenerative meniscal changes.[28,29] On the other hand, meniscal tears that include lesions of the avascular zone, such as radial tears, are not expected to spontaneously heal, and thus such tears have been mostly treated by partial meniscectomy.[30] To overcome this problem following injuries to the avascular zone tissue, several suture techniques have been recently developed to enhance healing in this zone, and some case series reported the improvement of clinical outcomes in short-term results.[31–35] Regarding other types of meniscal tears, meniscal root tears[36,37] and discoid lateral meniscal tears[38–40] have been paid attention to as recent topics, and several suture and/or preservation techniques have been developed and tested in clinical practice. To further enhance the repair potential, some biologic augmentation have been attempted to promote the healing of torn meniscal sites in clinical practice, and these include mechanical stimulation of the adjacent synovium or the meniscus by rasping,[41] augmentation with fibrin clots[42] or platelet-rich plasma,[43] as well as introduction of stem cells from the bone marrow by a marrow venting technique,[44] which has been proven to improve the meniscal healing rate. In experimental studies using large preclinical porcine models, mesenchymal stem cell (MSC)-based therapies were demonstrated to be feasible for meniscal repair.[45,46] Also, biomaterial augmentation via wrapping the meniscal tear (e.g. collagen membrane or nanofibrous scaffold) has been investigated to enhance the healing of the torn meniscal sites in either experimental[47] or clinical studies,[48] and such a technique will be expected as a potential therapeutic method.

4. Current therapeutic options for meniscal deficiency

Once the injured part of the meniscus is excised, the natural healing response will not occur at the site of the injury due to its limited healing capacity, and thus the meniscal deficiency will remain. Several therapeutic options have been proposed to reconstruct the resected meniscus and/or substitute an autologous tissue, allograft or meniscal substitute in the case where the original meniscus has been removed.[49]

4.1. Autologous tissues

Autologous tissues such as fat pad,[50] tendon,[51–53] periosteum,[54] synovial flap[55] and perichondrium[56] have been used as an autograft in preclinical animal or clinical studies. However, satisfactory results were rarely obtained owing to compromised mechanical properties, inferior vascularization, and differences in the shape and internal structure of the repair tissue.[49] Therefore, it can be concluded that these tissues are not a good option for effective replacement of the meniscus.

4.2. Allografts

Meniscal allograft transplantations have been widely performed for meniscal deficiency after total or nearly total meniscectomy. The meniscal transplantation emerges as a good indication for patients with a stable joint, appropriate alignment, and with early osteoarthritis of the knee, while these procedures are contraindicated for patients with severe osteoarthritis.[57] A recent systematic review concluded that meniscal allograft transplantation appears to provide good clinical results over short-term and midterm follow-up, with improvement in knee function.[58] In a long-term follow-up study (mean follow-up time of 152 months), meniscal transplantation resulted in significant improvements in pain and functional outcomes over the study period, despite an increase in joint space narrowing.[59] Also, this study reported 34.7% of the patients underwent some type of revision surgery including total knee arthroplasty at the final follow-up. On the other hand, some drawbacks of allografts were reported to include immunological reaction to the implanted tissue, potential disease transmission, and limited donor availability.[58,60] Also, graft size matching, appropriate preservation techniques, and surgical transplantation technique are important issues for the success of such transplantation procedures. Future studies will be necessary to optimize these parameters to improve surgical outcomes.[49]

4.3. Meniscal substitutes

Several materials have been developed and assessed for efficacy

in addressing meniscal deficiency, either in vitro or in vivo. There have been two implants that have been made available for clinical practice, one is a collagen meniscus implant (CMI®) and the other, a polyurethane polymeric implant (Actifit®).[1,61] These two implants can be offered to patients with an intact peripheral meniscal rim and limited damaged cartilage after meniscectomy. Recent long-term follow-up studies have reported that CMI® provided significant pain relief and functional improvement with safety and a low rate of implant failure.[62,63] Additionally, some studies reported that CMI® showed better clinical outcomes than did partial meniscectomy, but with limited evidence provided,[64,65] and thus further studies are necessary to allow drawing stronger conclusions regarding this approach. Similarly, Actifit® showed safety and effectiveness with improved clinical outcomes with short- and middle-term follow-up.[66–69] On the other hand, several studies reported negative outcomes based on MRI results with these two implants, despite the general observation of improved clinical scores.[66,67,70] These implants were partially or total resorbed during follow-up. Also, the implants mostly showed hyperintensity and/or extrusion, accompanied by subchondral bone edema. Thus, there is likely still room for improvement, regarding the development of such implants serving as meniscal substitutes.

Surgeons agree that meniscal allograft transplantation is currently the best treatment for symptomatic meniscectomied patients, but a number of issue still remain such as graft availability, size matching, high costs, possible disease transmission, and limited widespread practice of this procedure, as mentioned above.[61] As an alternative to this procedure, total meniscus replacement using a synthetic meniscus has been assessed for such patients, although the shape of implant is anatomically different. Recently, a synthetic polyethylene reinforced polycarbonate urethane (PCU) meniscus implant (NUsurface®) has been developed to the stage of clinical trials.[61,71] Some preliminary data based on MRI results showed restoration of the joint space and maintenance of the cartilage signal intensity at 12 months post-surgery.[61]

5. New trends for meniscal regeneration – possibilities and feasibilities

Although several clinical options exist for addressing an incurable meniscal deficiency as discussed above, effective long-term repair methods are not available for these injuries. Therefore, the development of novel therapeutic methods for meniscus repair is both timely and necessary. Recently, tissue engineering approaches that involve the use of cells and biomaterial scaffolds have gained increasing attention as potential regenerative therapies in the field of musculoskeletal medicine.[1,72,73] These approaches are still primarily in the preclinical phases of development, but likely will progress to the clinical application stage in near future. Thus, the likelihood and feasibility of tissue engineering approaches to become effective interventions will be discussed in the following section.

5.1. Tissue engineering approaches

Tissue engineering is defined as the application of the principles of biology and engineering to the development of functional substitutes for damaged tissue, and usually utilize a combination of cells, scaffolds, and growth factors.[74] Regarding the selection of cell sources, meniscal cells,[75] chondrocytes,[76] and mesenchymal stem cells (MSCs) derived from bone marrow,[77] fat tissue[78] or synovium[45] have been used. However, there is still no consensus regarding the best cell resource for meniscal regeneration due to the lack of comparative studies being performed. Scaffolds for tissue engineering the meniscus may be categorized into four broad classes: synthetic polymers (e.g. polyurethane (PU), polycaprolactone (PCL), polylactic acid (PLA), polyglycolic acid (PGA), polylactic co-glycolic acid (PLGA)), hydrogels, natural matrix (e.g. collagen, hyaluronan), or tissue-derived materials (e.g. decellularized ECM).[1] For the ideal selection of a scaffold for meniscal regeneration, it is important to know the material properties of each of the potential scaffolds in order to pick the most appropriate for the environment for which they will be used. In general, synthetic polymers are easy to handle and have high mechanical properties, while natural materials retain higher bioactivity, which might be advantageous for tissue healing and remodeling.[1] Similar to cell sources, there is still no consensus regarding the ideal materials for a scaffold to be used for meniscal regeneration.

As listed in Table 1, we have outlined the recent pre-clinical animal studies of cell-based meniscal tissue engineering. There have been some promising studies reported, and thus, some of these approaches may be expected to lead to the initiation of clinical trials in the near future.

5.2. Anatomy-based meniscal regeneration

While a number of meniscal biomaterial scaffolds and tissue engineering approaches have been developed and show promise, complete meniscus regeneration remains challenging because of the difficulty in reproducing the complex meniscal collagen fiber arrangements and the anatomically complex meniscus structure composed of a region-specific matrix organization and biochemical composition, as potential limitations of previous studies and currently available treatments.[22,23] Specifically, many biomaterials resemble the shape of native meniscus, but with a porous structure inside,[1,61] although the meniscus has unique collagen fiber arrangements.[20–23,] Recently, a fiber-reinforced scaffold, composed of a type I collagen and hyaluronic acid sponge reinforced with a unique pattern of continuous tyrosine-derived biodegradable polymer fiber, has been developed and tested in large animal studies.[79,80] The fiber-reinforced scaffolds were implanted into sheep knee joints after a total meniscectomy, and it exhibited formation of a functional neo-meniscus tissue, with the potential to prevent joint degeneration at one year postoperatively. Thus, such fiber-reinforced scaffolds might provide the appropriate structural properties to take over the load-bearing role that is required of the meniscus, and provide long-term chondro-protective effects. As another anatomy-based meniscal tissue engineering approach, the applicability of decellularized meniscal ECM (dmECM) has been investigated by specifically comparing region-dependent effects of the dmECMs on 3-dimensional constructs seeded with human bone marrow MSCs in an experimental study.[81,82] Such studies have shown that the inner dmECM (avascular zone) enhances the fibrocartilaginous differentiation of MSCs, while the outer dmECM (vascular zone) promotes a more fibroblastic phenotype, supporting the feasibility to engineer a meniscus-like tissue that mimics the anatomy and biochemistry of the native meniscus by using region-specific dmECM preparations.

5.3. 3D bioprinting meniscal regeneration

Since 3D printing was first conceptualized and invented by Charles Hull in the early 1980s, these technologies have garnered attention in the field of regenerative medicine, especially in the last decade.[83,84] The recent advancements in medical imaging such as CT and MRI can provide the exact 3D reconstructed images for creating 3D objects via printing. Going forward, 3D printed objects will contribute significantly to the visualization of complex pathologies, surgical planning, manufacture of patient-specific instruments and implants, as well as making patient-specific

Table 1
Summary of cell-based meniscal tissue engineering in preclinical large animal study.

Authors	Reference	Animal	Experimental model	Cell source	Scaffold	Follow-up period	Outcome measure	Outcomes
Weinand C et al.	Am J Sports Med 2006	Pig	1 cm buckethandle lesion	Chondrocyte	Woven Vicryl mesh	12 weeks	Gross, histology	Macroscopic & histological healing
Weinand C et al.	Arch Orthop Trauma Surg 2006	Pig	1 cm buckethandle lesion in avascular zone	Chondrocyte	Woven Vicryl mesh PLGA	12 weeks	Gross, histology, gross mechanical test	Bonding lesion, healing by new tissue
Martinek V et al.	Arch Orthop Trauma Surg 2006	Sheep	Subtotal meniscectomy	Meniscal fibrochondrocyte	CMI	3 months	Gross, histology	Enhanced vascularization & re-modelling, higher content of ECM
Kon E et al.	Tissue Eng Part A 2008	Sheep	Total meniscectomy	Chondrocyte	Hyaluronic acid/ polycaprolactone	4 months	Gross, histology	Better implant appearance & integrity, lower joint degeneration, cellular infiltration & vascularization
Zhang H et al.	Clin Orthop Relat Res 2009	Goat	φ3 mm defect	Bone marrow MSC transfected w/hIGF-1	Calcium alginate gel	16 weeks	Histology, electron microscopy, proteoglycan determination, MRI	Fibrocartilaginous repair, higher proteoglycan content
Kon E et al.	Tissue Eng Part A 2012	Sheep	Total meniscectomy	Chondrocyte	Hyaluronic acid/ polycaprolactone	12 months	Gross, histology	No extrusion, fibrocartilaginous repair
Gu Y et al.	Exp Ther Med 2012	Dog	2.5 mm width defect	Myoblast	PLGA	12 weeks	Gross, histology, immunohistochemistry	Good defect filling & integration, fibrocartilaginous repair
Moriguchi Y et al.	Biomaterials 2013	Pig	φ4 mm defect	Synovial MSC	Scaffold-free	6 months	Gross, histology	Fibrocartilaginous repair, chondroprotective effect
Zhu WH et al.	Mol Med Rep 2014	Dog	2 mm width defect	Myoblast transfected w/ hCDMP-2	PLA/PGA	12 weeks	Gross, histology, immunohistochemistry, collagen I & II, GAG quantification	Fibrocartilage-like tissue regeneration

CMI: collagen meniscal implant, ECM: extracellular matrix, hIGF-1: human insulin-like growth factor-1, PLGA: poly(lactic-co-glycolide acid), MSC: mesenchymal stem cell, hCDMP-2: human cartilage-derived morphogenetic protein-2, PLA: polylactic acid, PGA: polyglycolic acid, GAG: glycosaminoglycan.

scaffolds for tissue engineering approaches for meniscal repair.[85]

As the meniscus has highly complex shape and structure, the application of 3D printing technology will be very appropriate for meniscal tissue engineering. As listed in Table 2, there have been several studies recently reported regarding 3D printed menisci, but the long-term evidence for their effectiveness in meniscal repair is still limited. Mostly, these studies trend to reproduce the meniscal fiber arrangement using a 3D printer,[86–88] and such design of the scaffold should potentially improve the clinical outcomes. For that approach to be accepted, further comparative studies with the more conventional methods discussed earlier will be necessary.

3D printing is an innovative and promising technique for regenerative medicine, and it will enable provision of "made-to-order" medicine according to the needs of the individual condition by the fabrication of size-matching implant (Fig. 1). However, the approach currently still has some limitations. First, 3D printing costs are currently high because such technologies require hardware, software, manpower for maintenance and the cost of printing materials.[85] Secondly, the safety of 3D printing technology is another concern, and potential risks have not been fully elucidated as this technology continues to integrate and gain popularity into medical practice.[85] Thirdly, the accuracy of 3D printer may be considered as another limitation. The higher resolution of initial 3D imaging and more accurate printing techniques will be needed to make for more reliable procedures.[83] However, in the future when many of the current obstacles are overcome, 3D printing of stem cell-biological ECM composites may lead to engineered meniscal constructs that can then be exposed to biomechanical loading during development to make them more functional prior to implantation,[89] and enhance the chances for success after

Table 2
Summary of 3D printed meniscus.

Authors	Reference	Experimental model	Cell source	Scaffold	Growth factor	Shape	internal structure	Outcome measure
Ballyns JJ et al.	Tissue Eng Part C Methods 2010	in vitro	–	Alginate hydrogel	–	Meniscus	unknown	Geometric analysis
Grogan SP et al.	Acta Biomater 2013	in vitro	Meniscal cell	Methacrylated gelatin	–	Parallelepiped	Fiber	Cell viablity, histology, immunohistochemistry, PCR, SEM, mechanical testing
Lee CH et al.	Sci Transl Med. 2014	Sheep	–	PCL	CTGF & TGFβ3	Meniscus	Fiber	Gross, histology, mechanical testing
van Bochove B et al.	Macromol Biosci 2016	in vitro	–	PTMC	–	Meniscus	pore	micro CT, mechanical testing
Warren PB et al.	Connect Tissue Res 2017	Rat	–	PCL	–	Cylinder	Strand-pore	Histology, immunohistochemistry
Zhang ZZ et al.	Am J Sports Med 2017	Rabbit	Bone marrow MSC	PCL	–	Meniscus	Fiber	Gross, histology, SEM, mechanical testing

PCR: polymerase chain reaction, SEM: Scanning electron microscopy, PCL: poly-ε-caprolactone, CTGF: connective tissue growth factor, TGFβ3: transforming growth factor−β3, PTMC: poly(trimethylene carbonate), MSC: mesenchymal stem cell.

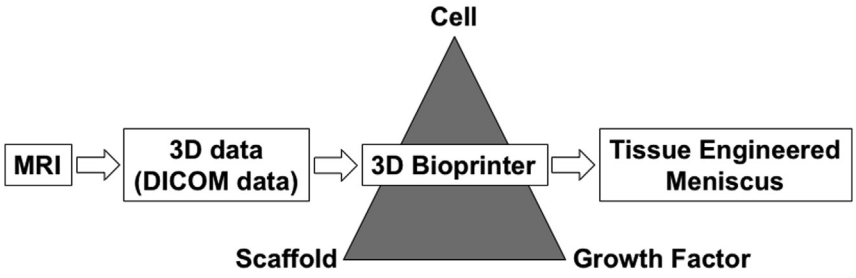

Fig. 1. Schematic representation of the fabrication of an order-made bioactive meniscal implant in 3D bioprinter.

implantation to repair meniscal defects.

6. Conclusions and future perspectives

With recent advancements in surgical techniques, biomaterials and cell-based technologies in tissue engineering, we may have new therapeutic options on the horizon for addressing meniscal injuries in clinical practice. On the other hand, there are still several potential problems to be solved, considering complete meniscus regeneration remains challenging for managing meniscal deficiencies with currently available techniques. First, the selection and design of biomaterials with sufficient mechanical strength and long-term durability for the optimal repair and remodeling of menisci have not been fully elucidated. Additionally, such biomaterials are essential to also prevent the progression of cartilage degeneration in a long-term. Due to the lack of evidences regarding these issues, further studies (e.g. high quality comparative studies) will be needed and should be conducted in a methodologically rigorous fashion. Secondly, current approaches indicate that meniscal function could not be fully restored effectively, based on observing meniscal extrusion and the progression of joint space narrowing after biomaterial implantation in many cases.[66,67,70] It is likely that newly developed technologies such as 3D printing may be a key technology to assist in solving several of these problems, getting closer to the native meniscus regarding anatomical and biomechanical aspects. Also, surgical techniques will need to be refined, especially in the prevention of meniscal extrusion and the restoration of meniscal functions. Furthermore, surgeons should consider the cost-effectiveness to apply these new techniques into clinical practice. A last consideration is that an ideal cell-seeded, size-matching meniscal implant mimicking the native meniscus may not be absolutely needed to satisfy the needs of all patients (i.e. precision medicine). Therefore, further studies (e.g. cellular versus acellular scaffolds) are needed to determine whether the increased intervention costs can be balanced with the observable advantages of these new technologies (cost/benefit analysis). However, as the technologies become perfected and implemented, the costs will likely come down, making the optimal choices for individual patients more feasible.

Disclosure statement

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