Tampereen yliopisto

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TISSUE ENGINEERING OF HUMAN KNEE MENISCUS

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ABSTRACT

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The knee menisci are c-shaped fibrocartilaginous structures in the knee joint that have a crucial function in stabilization, shock absorption and load transmission. A knee has two menisci, medial on the inside and lateral on the outside. Meniscus lesions are common knee injuries that typically occur in the form of tears. Current clinical practice is based on removing either the whole meniscus or only a part of it, repairing the meniscus with the help of sutures, arrows, and screws, or utilizing meniscus reconstruction methods to replace the native meniscus. Due to the high incidence in the knee injuries and resulting expenses, tissue-engineered meniscus repair has become a widely investigated option.

Traditional meniscus tissue engineering is based on combining three-dimensional support structures called scaffolds, cells, and biochemical and mechanical stimulation to develop an ideal, biocompatible meniscus replacement. Besides scaffold-based approaches, scaffold-free tissue engineering, which does not utilize cell seeding or attachment within an exogenous material, has also gained interest lately.

The aim of this literature review is to get acquainted with the different tissue engineering applications related to meniscus. The current commercial applications and the possible applications for the human knee meniscus in the future are described. The contemporary scientific situation of the applications is also discovered, as well as the challenges and advantages related to the tissue engineering applications. This thesis demonstrates that promising meniscus-preserving and -replacing treatment options have been developed. However, additional research is still essential before the solutions can be commercialized.

Keywords: meniscus, knee, tissue engineering, meniscectomy, meniscal repair, meniscal reconstruction

TIIVISTELMÄ

Matilda Luojus: Nivelkierukkaan liittyvä kudosteknologia
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Polven nivelkierukat ovat polvinivelessä olevia c:n muotoisia kuitumaisia rustorakenteita, joilla on keskeinen rooli stabiloinnissa, iskunvaimennuksessa ja kuormituksen siirtämisessä. Jokaisessa polvessa on kaksi nivelkierukkaa, sisäpuolella mediaalinen ja ulkopuolella lateraalinen. Nivelkierukan vauriot ovat yleisiä polvivammoja, jotka ilmenevät tyypillisesti repeäminä. Nykyinen kliininen käytäntö perustuu joko kokonaiseen tai osittaiseen nivelkierukan poistamiseen, nivelkierukan korjaamiseen ompeleiden, nuolien ja ruuvien avulla tai rekonstruktiomenetelmien hyödyntämiseen alkuperäisen nivelkierukan korvaamisessa. Polvivammojen yleisyyden ja kustannusten vuoksi kudosteknisestä nivelkierukan korjauksesta on tullut laajasti tutkittu vaihtoehto.

Perinteinen nivelkierukkaan liittyvä kudosteknologia perustuu kolmiulotteisten tukirakenteiden eli skaffoldien, solujen sekä biokemiallisen ja mekaanisen stimulaation yhdistämiseen ideaalisen, bioyhteensopivan keinonivelkierukan kehittämiseksi. Skaffoldeja hyödyntävän lähestymistavan lisäksi myös skaffoldittomat ratkaisut, jotka eivät vaadi soluviljelyä tai solujen kiinnittämistä eksogeeniseen materiaaliin, ovat herättäneet kiinnostusta.

Tämän kirjallisuuskatsauksen tavoitteena on kuvata erilaisia nivelkierukkaan liittyviä kudosteknologisia sovelluksia. Tutkielmassa esitellään nykyiset kaupalliset ja mahdolliset tulevaisuuden menetelmät nivelkierukan korjauksessa. Lisäksi kuvataan menetelmien tämänhetkinen tieteellinen tilanne sekä kudosteknologisiin ratkaisuihin liittyvät haasteet ja edut. Tämä opinnäytetyö osoittaa, että nivelkierukan korjaukseen on kehitetty lupaavia säilyttäviä ja korvaavia hoitovaihtoehtoja. Lisätutkimus on kuitenkin edelleen välttämätöntä ennen kuin ratkaisut voidaan kaupallistaa.

Avainsanat: nivelkierukka, polvi, kudosteknologia, nivelkierukan poisto, nivelkierukan korjaus, nivelkierukan korvaus

CONTENTS

LIST OF SYMBOLS AND ABBREVIATIONS

ACL	Anterior cruciate ligament
µm	Micrometer (10^{-6} m)
bFGF	Basic fibroblast growth factor
BM-MSCs	Bone marrow–derived mesenchymal stem cells
BMP-2	Bone morphogenetic protein 2
BMP-7	Bone morphogenetic protein 7
CE mark	The Conformité Européenne mark
CMI	Collagen Meniscus Implant
CTGF	Connective tissue growth factor
DNA	Deoxyribonucleic acid
ECM	Extracellular matrix
FDA	U.S. Food and Drug Administration
FGF-2	Fibroblast growth factor-2
f-PGA	Film-coated PGA lamination
GAGs	Glycosaminoglycans
hESCs	Human embryonic stem cells
IGFs	Insulin-like growth factors
MAT	Meniscal allograft transplantation
MFCs	Meniscus fibrochondrocytes
MRI	Magnetic resonance imaging
OA	Osteoarthritis
PCL	Posterior anterior cruciate ligament
PDGF	Platelet-derived growth factor
PGA	Polyglycolic acid
PLGA	Polylactic co-glycolic acid
PLLA	Poly(L-lactide)
PU	Polyurethane
SF	Silk fibroin
SIS	Small intestine submucosa
SMSCs	Synovium-derived MSCs
TGF-β	Transforming growth factor-beta
TGF-β1	Transforming growth factor-beta 1
TGF-β3	Transforming growth factor-beta 3
VEGF	Vascular endothelial growth factor

1. INTRODUCTION

Tissue engineering is a biomedical engineering discipline that combines biology and engineering to create functional constructs that heal, sustain, or enhance damaged tissues or body parts. Tissue engineering procedures utilize cells within a human body, which requires appropriate biochemical and biomechanical factors, and biomaterials. Meniscus lesions are common knee injuries in all age groups, and over 1.5 million menisci are surgically operated yearly in the United States and Europe (Z.-Z. Zhang et al., 2019). Meniscal operations cause significant socioeconomic costs for healthcare systems globally. Because of the injury frequency and limited regeneration capacity of the meniscus, tissue engineering has the potential to offer superior treatment methods compared to traditional solutions.

The aim of this literature review is to present the current commercial applications and the possible future tissue engineering applications for the human knee meniscus. The current clinical practice in meniscus repair is also described. In addition, the challenges and advantages of the tissue engineering applications are discussed.

At first, the structure and function of the meniscus are described in chapter 2. Chapter 3 then contains meniscus lesions and degeneration. Chapter 4 includes current clinical practice in meniscus tissue engineering, which can be divided into arthroscopic total/partial meniscectomy, meniscal repair, and meniscal reconstruction. Chapter 5 consists of tissue engineering applications for the human knee meniscus. The typical scaffold for meniscus tissue engineering, different scaffold types, possible practical cells for tissue engineering of the meniscus, biochemical and biomechanical stimuli, and scaffold-free approaches are discussed. Finally, chapter 6 summarizes the findings of this thesis.

2. STRUCTURE AND FUNCTION OF THE KNEE MENISCUS

The knee menisci, medial and lateral meniscus, are semi-circular, wedge-shaped fibrocartilaginous structures in the knee joint. The term fibrocartilaginous refers to both fibrous and cartilaginous tissues. The menisci are located between the femoral condyles and the tibial plateau within the medial and lateral compartments of the knee. (Amendola & Bonasia, 2012, p. 5; Sanchez-Adams & Athanasiou, 2009, p. 332) In this chapter, meniscus anatomy, biochemical content, cells, and both biomechanical and functional properties are discussed.

2.1 Meniscus anatomy, biochemical content, and cells

There are two menisci found in the knee joint. The medial meniscus is located on the inner side of the knee joint whereas the lateral meniscus is on the outside of the knee joint (Amendola & Bonasia, 2012, pp. 25–26). The medial and lateral meniscus look very similar, but one main difference is that the horn attachments of the lateral meniscus are closer together compared to the medial meniscus (Sanchez-Adams & Athanasiou, 2009, p. 332). The lateral meniscus also has greater range of variation when it comes to size, shape and thickness compared to the medial meniscus (McDermott et al., 2004). In addition, the lateral meniscus is not capable of withstanding external compressive forces very site-specifically, contrary to the medial meniscus. Overall, the lateral meniscus is proved to be more mobile compared to the medial (Beaufils & Verdonk, 2010, pp. 28–29).

A network of ligaments holds the medial and lateral menisci in place (Sanchez-Adams & Athanasiou, 2009, p. 332). Crucial ligaments for menisci stabilization are the horn attachments, medial collateral ligament, Humphrey and Wrisberg ligaments, coronary ligament, transverse ligament, and the anterior and posterior cruciate ligaments (ACL and PCL) (Amendola & Bonasia, 2012, pp. 25–26). Horn attachments are ligamentous attachments that connect the menisci to the midline of the tibial plateau. They hold the menisci still while bearing joint loads. Medial collateral ligament joins the medial sides of the femoral condyle and tibial plateau. The posterior horn of the lateral meniscus and the lateral side of the medial femoral condyle are connected with Humphrey and Wrisberg ligaments. (Sanchez-Adams & Athanasiou, 2009, p. 332) The capsular attachment be-

tween the menisci and the joint capsule is called the coronary ligament (Beaufils & Verdonk, 2010, p. 23). The transverse ligament connects the anterior horns of the medial and lateral meniscus. Finally, the ACL and PCL prevent meniscal injuries by connecting the tibia to the femur. Because of all the mentioned ligaments, menisci act as a cushion between the femur and tibia (Sanchez-Adams & Athanasiou, 2009, p. 332). Meniscus anatomy is illustrated in figure 1.

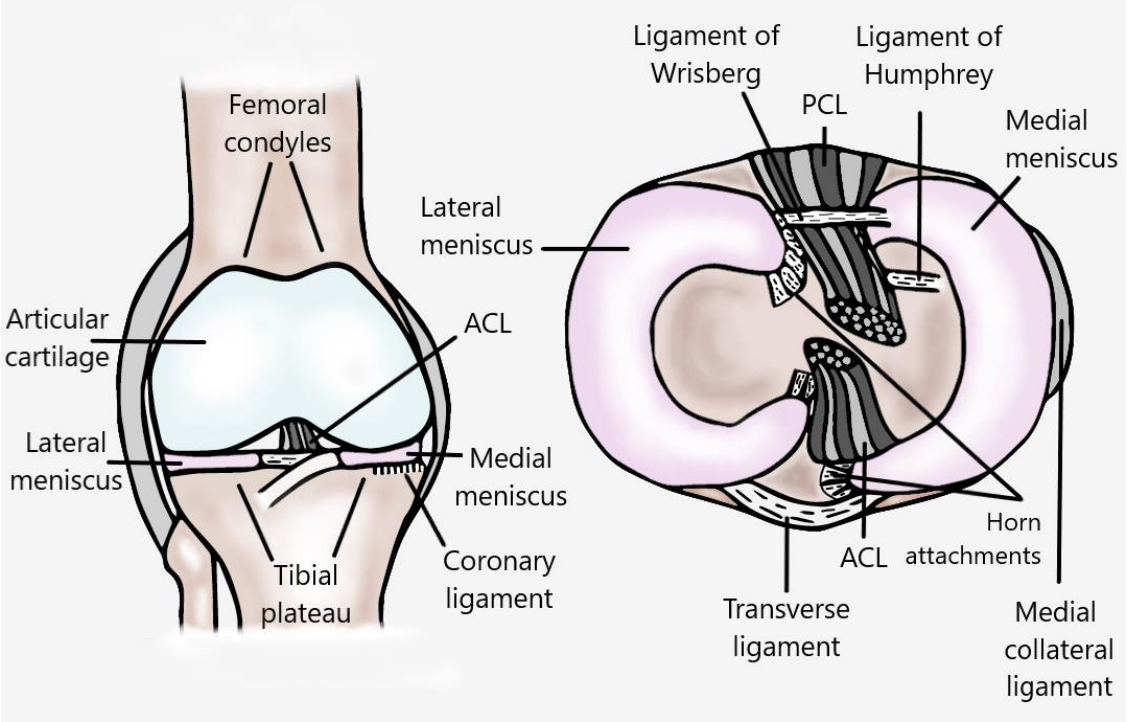

Figure 1. *Anterior view of the meniscus within the knee joint and top view of the right knee. Adapted from the publications by Makris et al. (2011) and Nukavarapu et al. (2015, p. 220).*

Normal human adult menisci consist of water (72 %) and organic matter (28%), which is mostly extracellular matrix (ECM) and DNA. The ECM consists of collagen and glycosaminoglycans. (Herwig et al., 1984, p. 635) Most of the collagen in meniscus is type I, while the remaining part consists of types II, III, and IV (Eyre & Wu, 1983, p. 269–270). Collagen enhances the tensile strength of the meniscal tissue and glycosaminoglycans provide compressive strength. Meniscus must be able to endure these forces while undergoing compression in the knee joint. (Pangborn & Athanasiou, 2005)

At the early stages of the embryo, the meniscus cells have a resemblance in size and shape. Due to tissue maturation, the cells start to differ. (Sanchez-Adams & Athanasiou, 2009, p. 334) Cells in the outer layer are more flattened in shape whereas cells found in the outer periphery are typically more oval, fusiform shaped thus they are similar to fibroblast morphology. The outer portion of the meniscus consists mainly of type I colla-

gen, which also explains the fibroblast-like cells as they help to maintain the fibrocartilaginous matrix there. In addition, outer portion cells are proved to contain gap junctions that allow more effective chemical signal exchange. When moving towards the inner zone of the meniscus, cell processes decrease and there is no gap junctions present. In the inner zone of the meniscus cells are small and round, more chondrocyte-like. The inner portion of the meniscus consists predominantly of type II collagen with only a little amount of type I collagen and thus is more hyaline-like in nature. (Sanchez-Adams & Athanasiou, 2009, p. 334–335)

2.3 Biomechanical and functional properties

The meniscus has a significant responsibility in load transmission, load bearing, shock absorption, and stabilizing the knee. It must be able to withstand various forces such as compression, tension, and shear. It is also responsible for the nutrition and lubrication of articular cartilage. The ultrastructure, composition, and geometry of the meniscus enable it to tolerate the forces exerted on the tissue. (Nukavarapu et al., 2015, p. 222) The meniscus has the ability to transfer load between the inner hyaline-like zone and the outer more fibrous-like zones. The shape of the meniscus together with the horn attachments can convert the vertical forces to lateral hoop stresses. (Baker et al., 2009)

In Walker et al. (2015) study, load distribution between different compartments of the meniscus was examined by exposing the knee to only compression force, compression and anterior shear forces, and compression and posterior shear forces. It was noted that the amount of load carried by the meniscus stays comparatively unchanged throughout flexion. However, load distributions vary between the anterior and posterior horns, the central body of the meniscus, and the uncovered cartilage in the centre of the meniscus. The total load transmitted through the meniscus differs from 40% to 80%. The posterior horn was stated to carry most of the shear load, particularly after 30 degrees flexion on the knee when applying posterior shear force. When the anterior shear force was applied to the femur and the knee was in early flexion, the anterior horn was exposed to its maximum loads. The central body of the meniscus offers support and increases stability, therefore, protecting the knee from luxations and lesions. (Walker et al., 2015)

The compressive properties of the meniscus can be explained mostly by its high-water content and low permeability. When the compressive load is applied, hydrostatic pressure occurs and spreads to the tissue distributing the load evenly. As the pressure increases, interstitial fluid moves out of the meniscus allowing tissue deformation. Due to this deformation, the contact area between the articular surfaces and the meniscus increases, which decreases the peak stress. After removing the load, Donnan osmotic

pressure gradient causes the fluid to be drawn back to the meniscus thus returning its size and shape. (Nukavarapu et al., 2015, p. 222)

Meniscus tensile properties are a result of the content, type, and organization of the collagen fibres. When the collagen fibres are stretched and aligned, stiffness stays relatively low and strain small. As higher loads are applied, the tissue deforms. The meniscus is generally stiffer and stronger in the circumferential direction compared to radial due to the orientation of type I collagen bundles. Besides tensile properties, collagen fibre ultrastructure affects the meniscus shear properties as well. The meniscus has been stated to be about 30% stiffer in planes perpendicular to the large type I collagen bundles. (Nukavarapu et al., 2015, pp. 222–223)

3. MENISCUS LESION AND DEGENERATION

Meniscus lesions have a high incidence in knee injury, and they occur in the form of tears. Tears will further progress meniscus degeneration and the development of knee osteoarthritis. This chapter talks about meniscus lesions and degeneration.

Meniscus lesions can be classified into vertical-longitudinal, radial, oblique, horizontal, and complex tears. Vertical-longitudinal, radial, and oblique tears are more common in younger patients whereas horizontal and complex tears occur more frequently in older people. (Mulry & McIntyre, 2018; Nukavarapu et al., 2015, p. 223) For this reason, horizontal and complex tears can also be referred to as degenerative tears. The classification of the meniscus lesions varies slightly depending on the source. For example, according to Nukavarapu et al. (2015, p. 224), meniscal tears can be classified based on their tear pattern as longitudinal, radial, bucket, horizontal and oblique. Meniscal injuries can also be classified based on their location, resulting stability, vascularity, and size (Lawton et al., 2019).

Vertical-longitudinal meniscus tears typically occur after a considerable traumatic event. They appear between the circumferential collagen fibres, are perpendicularly positioned towards the tibial plateau, and parallel to the long axis of the meniscus. They divide the meniscus into central and peripheral portions. Vertical longitudinal tears can be either complete or incomplete. Incomplete tears originate in the posterior horn, and they can occur in the superior and inferior surfaces of the menisci. Incomplete tears can often be asymptomatic. Complete tears also originate in the posterior horn, but they usually cause mechanical symptoms. They are larger compared to incomplete tears and can involve up to 65% of the meniscus. Complete tears can also be called bucket handle tears. The name bucket handle describes how the torn, flipped-over meniscus resembles a handle of a bucket. (Maffulli et al., 2010)

Besides vertical tears, radial tears also often result as a traumatic event and occur in younger patients. They are directed perpendicular to the tibial plateau and the long axis of the meniscus. Radial tears are usually severe and hard to repair because they make it more difficult for collagen fibres to transmit hoop stresses. The last tear type occurring more frequently in younger patients is an oblique tear. Oblique tears, including parrot beak and flap tears, are also often traumatic in origin and can cause mechanical symptoms. They share a resemblance with radial tears but are formed obliquely relative to the circumferential meniscus fibres. (Mulry & McIntyre, 2018; Noyes & Barber-Westin, 2010)

The tear types occurring more often in older patients are horizontal and complex tears. Horizontal tears divide the meniscus into superior and inferior leaflets as they are parallel to the tibial plateau. Complex tears refer to various tears in the meniscus that usually have components in multiple directions. Complex tears are more general in people over 40 years and are often associated with degenerative changes occurring in the articular cartilage. These degenerative changes have certain features including cavitation, fibrillation, or softening of the meniscal tissue. (Noyes & Barber-Westin, 2010) Meniscus tear types are presented in figure 2.

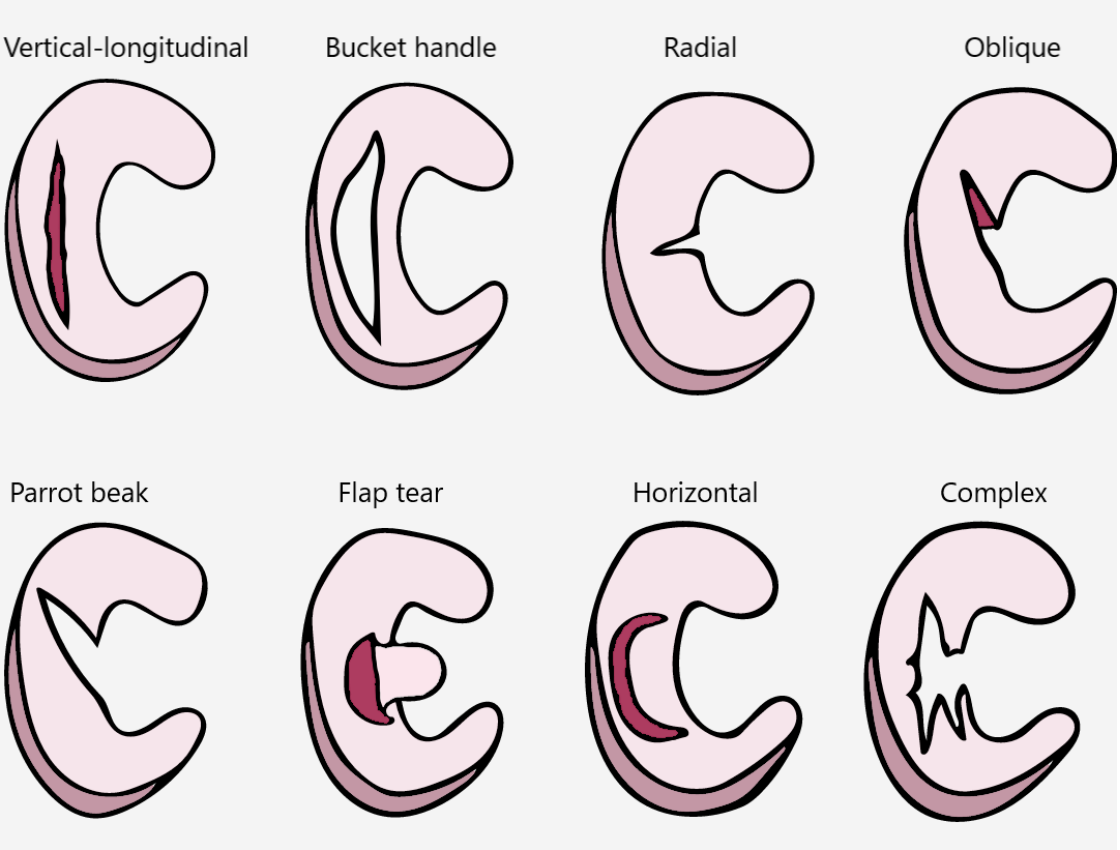

Figure 2. *Meniscus tear types. Adapted from the publication by Almqvist et al. (2010, p. 211).*

As a dense connective tissue, the meniscus has an insufficient self-healing capacity. Vascularization is associated with healing processes and the whole meniscus is mostly avascular in adults. Severe meniscus tears appearing in the avascular zone generally heal poorly. (Baker et al., 2009; Maffulli et al., 2010) Only 10–30% of the outer meniscus is vascularized. The outer part is referred to as the red zone and the inner part as the white zone since there is no blood supply. Nutrients are transferred to the white zone with the help of diffusion. Because of the limited blood supply, cellularity is also decreased in the white zone. (Nukavarapu et al., 2015, p. 221)

Collagen type I is the most prevalent protein of the meniscal ECM, and it is arranged into three different layers on the meniscus. The superficial layer consists of a thin layer of fine fibrils. The middle layer consists of circumferential collagen fibres that are anchored by a few radially oriented fibres. The deep layer is smaller compared to the middle layer and it consists of irregularly aligned collagen bundles. (Prokopi et al., 2021) Meniscus degeneration includes shredding of the type I collagen fibres, ECM degradation, mucinous degeneration, and loss of proteoglycans and chondrocytes. (Prokopi et al., 2021) It has also been discovered that the wet weight of degenerative meniscus is larger compared to intact meniscus due to increased water content and decreased amount of collagen and glycosaminoglycans (López-Franco & Gómez-Barrena, 2018).

According to Wesdorp et al. (2020), degeneration is proceeded more in traumatically torn meniscus compared to the undamaged, healthy meniscus. Trauma directed to the meniscus increases the contact pressure and leads to cartilage degeneration and loss. It has been proved that partial meniscectomy where only 15–34% of the meniscus is removed will increase the contact pressure over 350%. (Prokopi et al., 2021) Besides meniscal traumas and meniscectomy, meniscal degeneration also furthers the development and progression of knee osteoarthritis (OA). OA is a progressively disabling disease that occurs as a result of a pathological imbalance of degenerative and reparative processes in the knee joint. It is typical for degeneration that the meniscal cell population decreases and disturbs the normal meniscal functions. The cell clusters have also been discovered already in the early stages of OA. In addition, disturbances in collagen and non-collagen protein expression have been discovered. Degeneration of the knee meniscus causes both cellular and molecular changes in menisci and advances the progression of OA. (López-Franco & Gómez-Barrena, 2018)

4. CURRENT CLINICAL PRACTICE IN MENISCUS REPAIR

Current clinical practice in meniscus repair is based on both non-operative and operative management. Non-operative management can be an initial treatment of meniscal injuries, but if it is not effective enough or the lesion is severe, operative management comes into account. Non-operative management that has been shown to reduce pain and improve knee function includes anti-inflammatory and analgetic drugs, rest, physiotherapy, strengthening exercises of the quads, intra-articular injections, and modifications to day-to-day activities. (Vasiliadis et al., 2021) Orthotic auxiliaries can also be effective in some cases of medial and lateral meniscal lesions. However, often the non-operative treatment is effective only for a brief period and operative management is required to accomplish long-term results. The location and type of meniscal tear, patient's age, lifestyle, health condition, level of activity, degenerative changes of the articular cartilage, and request to undergo major surgery determine the treatment method for meniscus repair (Doral et al., 2010). This chapter discusses operative management methods, which include arthroscopic total/partial meniscectomy, meniscal repair, and meniscal reconstruction. Current clinical practice methods, meniscal repair, and meniscal reconstruction, already utilize tissue engineering.

4.1 Arthroscopic total/partial meniscectomy

Arthroscopic meniscectomy refers to the surgical removal of the whole meniscus wall or part of the meniscus with the help of an arthroscope (Bonnin et al., 2012, p.112). The arthroscope is a telescope inserted into the body during surgery. It contains lenses and a camera, and it generates a magnified image for the surgeon to see the joint interior. (A. Martin & A. McFerran., 2017) Besides the arthroscopic technique, an open approach is also possible. It refers to a technique where meniscectomy is performed as an open procedure. (Beaufils & Verdonk, 2010, p. 327) Arthroscopic meniscectomy can be either total or partial. Total meniscectomy means the removal of all the meniscal tissue and in consequence of removal, the femoral condyle rests directly on the tibial plateau. In partial meniscectomy, only a part of the meniscus is removed. (Nukavarapu et al., 2015, p. 224)

Current clinical practices aim to conserve as much of the meniscus as possible to prevent meniscus degeneration and the development of osteoarthritis. The short-term results of partial and total meniscectomy are decent, but medial meniscectomy has been thought

to accomplish better results compared to lateral meniscectomy (Jeong et al., 2012). The contact pressure of the knee always increases after meniscectomy and causes an overload of the articular cartilage. The increased contact pressure also gives rise to proteoglycan disaggregation and loss, raises hydration levels, and can affect to patient's activity level. Knowing the possible complications related to meniscectomy, it is stated in the Abram et al. (2018) study that the procedure should carefully be pre-considered. Instead of meniscectomy, the meniscal repair is recommended whenever it is possible because it has reported to have a more successful long-term outcome. However, in some cases, meniscectomy is an inevitable option. To be able to avoid and restrain the degeneration in the knee joint, arthroscopic partial meniscectomy is advisable compared to total meniscectomy as it provides quicker recovery time and lowers morbidity compared to total meniscectomy (Doral et al., 2010; Jeong et al., 2012).

4.2 Meniscal repair

Meniscal repair refers to a surgical procedure that aims to repair and preserve the meniscus and its biomechanical functions. Repair is always recommended unless the meniscus is irreparably torn because the contact pressure after the repair returns almost to the intact level. Additionally, the tear type determines whether the meniscal repair is possible or not. For example, radial and horizontal tear types are hard to repair whereas vertical tears of the posterior horns and bucket-handle tears can often be repaired. (Beaufils & Verdonk, 2010, p. 107; Yoon & Park, 2014)

Arthroscopic techniques are a common method for meniscal repair, and they can be divided into inside-out, outside-in, and all-inside repairs (McClain et al., 2021). All repair techniques are based on suturing the torn meniscus back together. The terms inside-out and outside-in refer to the passing directions of the sutures. In the inside-out technique, the sutures are passed from the inside to the outside of the meniscus, whereas the outside-in technique is based on inserting the sutures from the outside to the inside of the meniscus. One of the main problems in inside-out and outside-in techniques is the risk of neurovascular complications. The all-inside technique has increased its popularity because it eliminates this risk and enables to place sutures and tie the knots intraarticularly. (Beaufils & Verdonk, 2010, p. 119, 121–122).

The all-inside technique is based on suture-based devices which can repair the meniscus arthroscopically thus eliminating the need to penetrate the skin with sutures or needles. There are multiple all-inside devices available, such as Meniscal Cinch, RapidLoc, FasT-Fix, and CrossFix System. These current therapies utilize braided nonabsorbable sutures, and the used needles are especially invented for an inside-out or an all-inside

repair. (Ramappa et al., 2014) Venjakob et al. (2019) studied the possible harmful effects of the suture materials for cartilage in animal models. Study results stated that the braided nonabsorbable suture materials can cause damage to cartilage during long-lasting cyclic loading in vitro. However, in total the different arthroscopic repair techniques and their combinations have shown to be successful in meniscal repair for both lateral and medial menisci (Ahn et al., 2013; Jung et al., 2012). Besides sutures, bioabsorbable meniscal screws and bioabsorbable meniscus arrows can also be utilized in all-inside meniscal repair (Järvelä et al., 2010).

4.3 Meniscal reconstruction

Meniscal reconstruction refers to the replacement of meniscal tissue and it can be either total or partial. Meniscal allograft transplantation (MAT) is currently used to manage the symptoms caused by partial or total meniscus resection. Practically, MAT is performed by replacing the patient's own meniscus with a new meniscus taken from a cadaver. (J.-M. Kim et al., 2012) Besides allogenic substitutes, autologous transplants have also been studied for possible meniscal substitution (Johnson & Feagin, 2000). However, no clinical routine has been able to establish, which is why autologous transplants will not be discussed more in this literature review. In addition to MAT, there are two scaffold-based artificial substitutes used for partial meniscal tissue replacement (Richard, 1997; R. Verdonk et al., 2011). The most recently approved clinical method for meniscal reconstruction is the meniscus prosthesis. (De Coninck et al., 2014; Vrancken et al., 2017)

MAT procedure begins with the removal of the torn meniscus. After the removal and debridement of the damaged compartment is completed, a meniscal allograft is implanted into the knee. MAT has stated to be a successful procedure for the treatment of symptomatic post-meniscectomized knee. It has shown to decrease pain and improve the functionality of the knee in the short-, medium- and long-term follow-ups. (Vundelinckx et al., 2014) In a recent study, a minimum of 10-year outcomes after MAT were studied. The survival rate of allografts was 91% after 5 years of implantation and 86% after 10 years. Lateral MAT was stated to have a lower survival rate (73%) compared to medial MAT (96%). (Grassi et al., 2020) One significant factor that has reported to decrease the survival rate of allografts in long-term follow-ups is meniscal extrusions (S.-M. Lee et al., 2020; Wang et al., 2022).

Besides MAT, it is possible to use artificial scaffold-based biocompatible substitutes for partial meniscal replacement. There are currently two different artificial meniscal substitutes commercialized for clinical practice. The first one is Collagen Meniscus Implant (CMI), which is made of type I collagen fibres purified from bovine Achilles' tendons

(Richard, 1997; Zaffagnini et al., 2011). The other artificial meniscal substitute is called Actifit. Actifit meniscal scaffold consists of polycaprolactone and urethane segments. (Leroy et al., 2017; Verdonk et al., 2011) Both CMI and Actifit have received the Conformité Européenne (CE) mark in Europe. CMI also has the approval of the U.S. Food and Drug Administration (FDA). Actifit has received FDA Breakthrough Designation, but it has not yet been given FDA approval. (Claudia Ghisa & Kenneth R. Zaslav, 2022) The implantation process of both scaffolds is initiated with the debridement of the residual meniscus. Only the peripheral rim of the meniscus is conserved. Then the exact dimensions of the scaffold are taken, and the implantation is conducted. Once the scaffold is in its place, it is attached to the surrounding tissue with meniscal sutures. (Leroy et al., 2017)

CMI has proved to support new tissue ingrowth and integrate well with the host meniscus rim. The new tissue was discovered to be stable and biomechanically competent, and the scaffold was assumed to be reabsorbed in 12-18 months (Lucidi et al., 2021; Rodkey et al., 2008; Zaffagnini et al., 2011). Rodkey et al. (2008) recognized that patients who had received a CMI after prior meniscal surgical procedures regained considerable amounts of their lost activity compared to the patients that had not received an implant. Lucidi et al. (2021) also stated that the clinical results are expected to be adequate up to at least 20 years after CMI implantation. However, moderate osteoarthritis progression has been detected and the implant failure, infections, reduced size of the scaffold, and additional surgeries in the long term are also reported to be possible.

Actifit is a synthetic, acellular scaffold made of slowly degrading polycaprolactone and urethane segments. The degrading process starts when ester bonds are hydrolysed in polycaprolactone segments. This takes about 5 years. The degradation of urethan is more time-consuming compared to polycaprolactone, but over the time urethane segments integrate into the surrounding tissue or are phagocytized by macrophages or giant cells. The Actifit scaffold has its own configuration for medial and lateral meniscus. It is a biocompatible, flexible, strong, and porous material. The porosity supports tissue ingrowth. (Dhollander et al., 2016) This aliphatic polyurethane scaffold was invented to treat irreparable partial meniscus lesions (Verdonk et al., 2011).

Actifit implant is a more recent device compared to CMI which means that the long-term effects have not been able to study yet. However, the short-term results seem to be promising as the implant has improved knee joint function and reduced pain (Dhollander et al., 2016; Leroy et al., 2017; Toanen et al., 2020). According to a recent study, 87.9% of the medial and 86.9% of the lateral scaffolds were still functioning after 5 years of implantation (Toanen et al., 2020).

Despite the promising short-term results, compared to the CMI the failure rate of Actifit has reported to be relatively high. One probable reason for it can be the worsening of the cartilage condition (Leroy et al., 2017). Magnetic resonance imaging (MRI) results have shown differences between the scaffold and normal meniscus at midterm clinical outcomes (Toanen et al., 2020). The scaffold differed from the original meniscal tissue, extrusion was detected, and the scaffold size was reduced. Because of the relatively high failure rate of Actifit implants, there is still a need for further information related to medium- and long-term outcomes (Leroy et al., 2017; Toanen et al., 2020).

The newest clinical method for medial meniscal reconstruction is an anatomic or non-anatomic artificial meniscal substitute, also called meniscus prosthesis (De Coninck et al., 2014; Vrancken et al., 2017). The prosthesis was developed for total replacement of the medial meniscus, and it is supposed to decrease pain, improve joint function, and restrain the degeneration in the knee joint that leads to osteoarthritis progression (Shemesh et al., 2020). Currently approved meniscus prosthesis is made from polycarbonate-urethane, and it is called NUsurface Meniscus Implant (Shemesh et al., 2020). NUsurface implant has been CE-approved for commercialization in Europe and Israel, and it is currently under review by FDA (“Active Implants’ NUsurface Meniscus Implant Provides Statistically Superior Pain Relief,” 2021).

The implantation of NUsurface meniscus implant is performed arthroscopically with a partial meniscectomy technique. Meniscus implant is free-floating and non-anchored, which means that it does not need any additional sutures or screws to stay in place after implantation. (De Coninck et al., 2014; Shemesh et al., 2020) The in vivo performance and chondroprotective effect of an anatomically shaped meniscal implant were examined in goat models in a 1-year-study. Study results demonstrate that the implant resisted wear and deformation well, but degenerative changes of cartilage were similar for the implant, MAT, and total meniscectomy. (Vrancken et al., 2017) Shemesh et al. (2020) study results indicated that the implantation of NUsurface enhances the load distribution on the medial side but does not remarkably affect the lateral side of the knee. The NUsurface meniscus implant still needs further investigations, but current study results suggest that meniscus prosthesis can restore the injured or degenerated medial meniscus back to nearly intact levels.

5. TISSUE ENGINEERING OF THE MENISCUS

Tissue engineering scaffolds are three-dimensional support structures designed to assist tissue integration and provide optimal conditions for new tissue formation and cellular proliferation. Desired cells for meniscus tissue engineering can be expanded in culture and then seeded on scaffolds. Scaffolds can be either resorbable or non-resorbable. Resorbable scaffolds will degrade over time as the new tissue grows, whereas non-resorbable scaffolds will permanently replace the meniscus. Scaffolds can also act as delivery systems for different biomolecules that control the growth and proliferation of the cells. In addition, they offer mechanical strength for surgical handling. (Chiari et al., 2008) Besides scaffold-based tissue engineering, scaffold-free approaches have also aroused interest in meniscus tissue engineering lately. This chapter talks about the typical scaffold for meniscus tissue engineering, different scaffold types, possible practical cells for tissue engineering of the meniscus, biochemical and mechanical stimuli, and scaffold-free approaches.

5.1 Typical scaffold for meniscus tissue engineering

A typical scaffold for meniscus tissue engineering should prevent the progression of degenerative changes in the knee joint and provide successful long-term outcomes for meniscal repair and replacement (Merriam et al., 2015). An ideal meniscus scaffold is biocompatible, biodegradable, mechanically stable, and has a suitable microarchitecture for tissue growth. It is crucial for the scaffold to perform an appropriate host response when implanted into the knee and not cause any immune responses. (Costa et al., 2019; Merriam et al., 2015) For example, meniscus allografts and scaffolds can be decellularized to remove the cells and DNA thus minimizing their immunogenicity. In addition to being non-toxic for the body, biodegradability is also often a sought-after property. The scaffold should degrade in phase with the new meniscal tissue regeneration. Degradation by-products should also be biocompatible to not cause any inflammatory responses in the body. (Qi et al., 2013)

The desired meniscus scaffold should have similar mechanical properties to the native meniscus, meaning that it should be strong and stable to be able to support tissue regeneration. It is essential for the scaffold to hold its shape to offer the required support for the knee (Gao et al., 2016). Additionally, the meniscus scaffold should be able to

convert axial compressive loads to circumferential tensile loads and thus protect the proliferating cells (Costa et al., 2019; Merriam et al., 2015). Scaffold microarchitecture also affects its mechanical properties. According to Ahmad et al. (2005) study, increased porosity leads to the weakening of the mechanical properties. On the other hand, increased porosity leads to improved interconnectivity and tissue ingrowth inside the scaffold. For this reason, it is crucial to design the scaffold in a way that it assists mechanical functions and the chondroprotective effect of the scaffold. (Costa et al., 2019)

Besides porosity, the pore size has also stated to influence cell behaviour, biomechanics, ECM production, and rehabilitation of the scaffold (Z. Z. Zhang et al., 2016). The pore size of native menisci is about 100–150 μm (Gao et al., 2016). To achieve a suitable cell infiltration rate, scaffold pore size should be close to that value. In addition to porosity and pore size, suitable surface properties are also crucial for functioning meniscal scaffolds. Scaffold surface should be hydrophilic because hydrophilicity has shown to increase the degradation rate and mechanical strength, whereas hydrophobicity has noted to disturb cellular behaviour on the scaffold (Zhou et al., 2020). To conclude, the design of the meniscal scaffold should be carefully considered to accomplish the desired clinical outcome.

5.2 Different scaffold types

Currently, there are various kinds of scaffold materials developed for tissue-engineered meniscus. It has been proved challenging to create a scaffold that would completely simulate the qualities and geometry of the native meniscus. Table 1 aggregates the main advantages and disadvantages related to different cell-free scaffold types, example scaffold materials and the current clinical state of each scaffold type.

Table 1. *A summary of main advantages and disadvantages related to different scaffold types, example scaffold materials and their current clinical state.*

Scaffold type	Advantages	Disadvantages	Example materials	Current clinical state
Tissue-derived	- Natural environment - Contain glycosaminoglycans and growth factors - Biocompatible and bioactive	- Complicated supply - Hard to achieve appropriate pore size - Decellularization can decrease mechanical integrity - Insufficient compression properties	- Small intestine submucosa (SIS) - Decellularized tissue/ECM - Periosteal tissue - Acellular porcine meniscal tissue	- No commercialized scaffolds in clinical use
ECM component	- Natural environment - Easy to process and fabricate - Biocompatible	- Can be ineffective in mimicking meniscus cell microenvironment - Cell proliferation rate can be inferior to synthetic polymers	- Collagen - Hyaluronic acid - Proteoglycans - Elastin molecules	- Collagen meniscus implant (CMI) is accepted for clinical use in Europe and U. S.
Synthetic polymers	- Diversity: The pore size, porosity, mechanical properties, geometry, and degradation rate easy to modify	- Immune responses - Foreign body inflammatory reactions - Toxic component release - Hydrophobic properties	- Polyurethane (PU) - Polycaprolactone (PCL) - Silk fibroin (SF) - Polyglycolic acid (PGA) - Poly(L-lactide) (PLLA) - Polylactic co-glycolic acid (PLGA)	- Actifit PU/PCL meniscus scaffold is accepted for clinical use in Europe, and it has accepted FDA Breakthrough Designation
Hydrogels	- The ability to fill meniscus lesions of various shapes - Resemblance to native meniscal tissue	- Insufficient mechanical properties	- Porcine meniscus - Various polymers	- No commercialized scaffolds in clinical use - Further examination required before initiating clinical trials in humans

Following subchapters provide a more detailed analysis of the scaffold types presented in the table above.

5.2.1 Tissue-derived scaffolds

Tissue-derived materials have been examined as potential meniscal scaffolds because they offer natural conditions for cell seeding and ECM deposition. They include processed whole tissues and components or by-products of living tissue, such as small intestine submucosa (SIS), decellularized tissue/ECM, periosteal tissue derived from the surface of bones, and acellular porcine meniscal tissue. (Batista et al., 2020; Gao et al., 2016; Mandal et al., 2011; Popowics et al., 2002; Tan et al., 2010) After the tissue-derived materials have been decellularized, they are mainly composed of collagen and elastin, the two main components of native meniscus ECM (Kremer et al., 2017). Tissue-derived materials have also been potential meniscal scaffolds because they contain glycosaminoglycans (GAGs) and growth factors and support cell growth, differentiation, and formation of host-derived neo matrix after the scaffold has degraded and new tissue has formed. Additionally, they demonstrate excellent biocompatibility and bioactivity. (Batista et al., 2020; Gao et al., 2016; Mandal et al., 2011; Popowics et al., 2002; Tan et al., 2010)

Despite the many advantages related to tissue-derived materials, several problems remain. The first problem is related to the supply of these materials. The supply is complicated because tissue-derived materials need to be segregated from natural tissue. (Batista et al., 2020) Another difficulty is related to the appropriate pore size with this type of scaffold. It has been proved challenging to create tissue-derived scaffolds with proper pore size for cells to infiltrate to the surface of the scaffold. For example, in the Gao et al. (2016) study, decellularized scaffold derived from porcine meniscus was investigated as a possible meniscus scaffold. The study results show that the pore size of the scaffold was too small compared to the native meniscus, which caused only an extremely small number of porcine chondrocytes to infiltrate to the scaffold. Too small pore size can also make the nutrient supply and metabolic waste removal more difficult.

Besides inadequate pore size, decellularization can harm the mechanical integrity of the scaffold. According to Abdelgaied et al. (2015) and Gao et al. (2016) studies, the decellularized porcine scaffold displayed decreased compression properties compared to the natural porcine meniscus. Losses of GAG content are also noted in multiple studies (Batista et al., 2020; Gao et al., 2016).

5.2.2 ECM component scaffolds

Besides tissue-derived materials, ECM components also provide a natural environment for seeded cells. ECM component scaffolds refer to materials that are naturally derived from the ECM, such as collagen, hyaluronic acid, proteoglycans, and elastin molecules (Freymann et al., 2012; Kremer et al., 2017). A collagen meniscus implant (CMI) is an ECM-component scaffold that is currently used for clinical practice (Lucidi et al., 2021). One major advantage related to ECM component scaffolds is that they can be processed and fabricated to mimic the native meniscus more accurately. For example, in the Baek et al. (2016) study, the repair of avascular tears with electrospun human cell-seeded collagen type I scaffolds was investigated ex vivo. Electrospun collagen was stated to resemble the native meniscal tissue quite precisely, which is beneficial as it further promotes new meniscus-like tissue growth. The processing also increases the strength of the ECM component scaffolds.

The desirable effects of ECM component scaffolds can be enhanced by combining multiple ECM components. In Ghodbane et al. (2019) study, collagen-hyaluronan polymeric scaffolds were investigated for partial meniscal replacement in sheep models. The scaffolds were divided into anatomic, partially displaced, and completely displaced after 24 weeks of follow-up. Anatomic scaffolds gave the best results with the most considerable fibrocartilage-like tissue ingrowth and the best biochemical composition.

Even though the ECM component scaffolds have many desirable properties, some drawbacks can still be perceived. Even if the ECM components are derived from the natural matrix, it is possible that they are not able to fully recapitulate the meniscus cell microenvironment. For instance, in the Hofmann et al. (2006) study, mesenchymal stem cells were shown to proliferate more robustly on the silk fibroin scaffolds compared to collagen matrices. It is also important to realize that not all ECM components are identically effective. This observation was detected already in an early study, which noted that GAG-collagen II matrices were able to improve meniscus cell proliferation and GAG deposition more compared to GAG-collagen I matrices (Mueller et al., 1999).

5.2.3 Synthetic polymers

Synthetic polymers are human-made polymers that have been examined as possible meniscus scaffolds. They include polymers like polyurethane (PU), polycaprolactone (PCL), silk fibroin (SF), polyglycolic acid (PGA), and copolymers like poly(L-lactide) (PLLA) and polylactic co-glycolic acid (PLGA). SF is a biomaterial generated by spiders and silkworms, but in this literature review, it is considered to be a synthetic polymer

scaffold, because SF-based scaffolds are often synthetically modified before utilizing them. Synthetic polymers have been intrigued by scientists due to their diversity. The pore size, porosity, mechanical properties, geometry, and degradation rate of scaffolds can easily be modified to meet the demands of functional meniscal scaffolds (Park et al., 2008). The key issues related to synthetic polymers are possible immune responses and foreign body inflammatory reactions, toxic component release during the degradation process, and hydrophobic properties (Esposito et al., 2013; Warnock et al., 2014; Welsing et al., 2008).

PU has received attention in the treatment of meniscal injuries due to its desired degradation rate, blood compatibility, and suitable mechanical properties for meniscus tissue engineering (Filardo et al., 2017; W. Li et al., 2021). Besides PU, PCL also has a slow degradation rate and suitable architecture for meniscal reconstruction. However, pure PCL scaffolds can further progress the degenerative changes of articular cartilage. (Z. Li et al., 2020) For this reason, PCL is usually combined with some other polymer, such as PU or SF. Actifit meniscal scaffold consists of PCL and PU and it is currently used in clinical practice (Leroy et al., 2017). PCL/SF scaffolds have also been investigated for meniscus regeneration because they have excellent biomechanical properties and biocompatibility. However, further studies are needed to ensure the safety of PCL/SF scaffolds. (Z. Li et al., 2020)

PGA and PLLA are currently utilized in clinical use for suture threads and bone fixation, and they have lately gained interest as possible meniscal scaffolds, too. Murakami et al. (2017) examined different PGA and PLLA scaffolds by implanting them into the rabbit menisci. The study stated that especially PLA film-coated PGA lamination (f-PGA) scaffolds could be used for meniscal repair due to their regeneration, chondroprotective effect, and greater strength compared to PLLA scaffolds. Additionally, PGA scaffolds did not cause any inflammatory reactions in 12 weeks follow-up, contrary to PLLA scaffolds. The main challenge of PGA scaffolds is related to their degradation rate. According to Warnock et al. (2014), PGA has stated to hydrolyse too quickly and therefore it may not be the best option for long-term meniscal reconstruction.

In addition to copolymer PLLA, PLGA has also been studied as a meniscal scaffold because its degradation rate matches the new meniscal formation rate (Gu et al., 2013; Kwak et al., 2014). One of the fundamental issues related to PLGA scaffolds is their hydrophobic nature. For this reason, the PLGA scaffold can be modified with some other polymer, such as SF. SF changes the scaffold hydrophobicity to more hydrophilic. SF has also stated to improve the mechanical properties of the PLGA scaffold. (Woo Ju et al., 2013)

5.2.4 Hydrogels

The last cell-free scaffold type is hydrogel scaffolds. A hydrogel refers to a three-dimensional network of hydrophilic polymers that are not water-soluble. Hydrogels can hold a large amount of water while maintaining their structures, and they are classified to either natural, synthetic, or a combination of both according to the polymers from which they are derived. Hydrogels that combine cells and growth factors have shown to be potential in regenerating meniscus lesions (C. Chen et al., 2020). The major advantages of hydrogel scaffolds include the ability to fill meniscus lesions of various shapes and their resemblance to native meniscal tissue due to high water content (Okuno et al., 2021). However, it has been reported in many studies that the mechanical properties of hydrogel scaffolds still need to be improved to meet the requirements of meniscal applications (C. Chen et al., 2020; Okuno et al., 2021).

Wu et al. (2015) studied a porcine meniscus that was processed into an injectable hydrogel. The properties of this hydrogel were examined both in vitro cell culture and in vivo mouse model to determine whether it is suitable for treating meniscus injuries and diseases. Study results stated good cellular compatibility, and toxicity was not detected. By altering the ECM concentration, it was also possible to change the mechanical properties of the injectable hydrogel. Despite that, the mechanical features of the hydrogel scaffold were noted to be much lower compared to the native meniscus. Due to this, the meniscus-derived hydrogel is not suitable for a whole meniscus replacement. However, it is stated to be suitable to repair a partially defective meniscus. Hydrogel scaffolds need further research to ensure their safety and efficacy before initiating clinical trials in humans. Notwithstanding, hydrogel scaffolds are a promising option for treating meniscus lesions. An example of all the different scaffold types is illustrated in Figure 3.

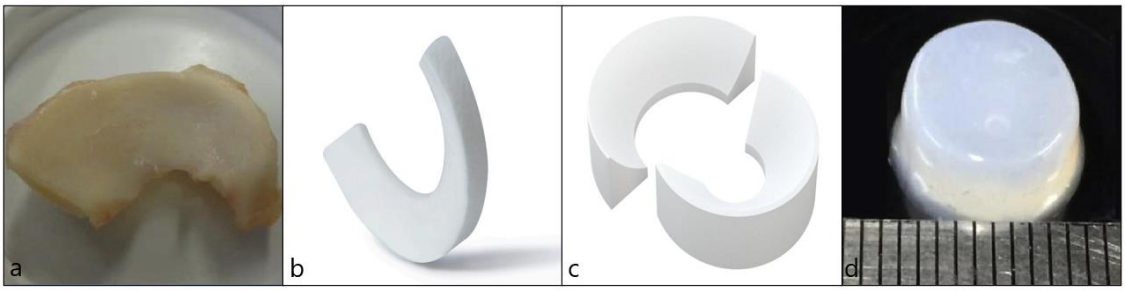

Figure 3. *An illustrative picture of all the scaffold types. a, A porcine meniscus is an example of a tissue-derived scaffold (Wu et al., 2015). b, CMI is an example of an ECM component scaffold (Stryker, referenced 5.5.2022). c, Actifit is an example of a synthetic scaffold (Orteq, referenced 5.5.2022). d, Hydrogel (Wu et al., 2015).*

5.3 Possible practical cells for tissue engineering of the meniscus

Cells are a crucial part of tissue engineering as cell proliferation, migration, and matrix synthesis have a considerable effect on tissue healing and host tissue response (Nukavarapu et al., 2015, p. 230). Cell-based meniscus tissue engineering has shown to accomplish better repair results compared to cell-free approaches. No mutual agreement has been able to reach concerning the best cell source for meniscal regeneration. This chapter discusses some common practical cells for meniscus tissue engineering: stem cells, fibrochondrocytes, and articular chondrocytes.

Stem cells have been examined as possible cell seeds for meniscus tissue engineering because they can be differentiated into fibrochondrogenic, meniscus-like cells. Bone marrow-derived mesenchymal stem cells (BM-MSCs), synovium-derived MSCs (SMSCs), and adipose tissue-derived MSCs are widely used cell types in meniscus regeneration (W. Kim et al., 2020). MSCs are popular in meniscus reconstruction since they can integrate with meniscus lesions to enhance repair. Additionally, they can be guided to deliver therapeutic agents to lesion areas thus intensifying cellular differentiation and tissue repair, as well as repressing the pro-inflammatory microenvironment following the trauma. (Hidalgo Perea et al., 2020) Besides MSCs, human embryonic stem cells (hESCs) have also been studied as a potential cell source for meniscal repair and reconstruction. For instance, Koay & Athanasiou (2008) studied the effects of low oxygen conditions on the chondrogenic differentiation of hESCs. Hypoxia was noted to improve the cartilage construct production.

Besides stem cells, meniscus cells are another commonly used cell for meniscus tissue engineering. At present, the majority of the studies focusing on meniscus cells involve fibrochondrocytes. Meniscus fibrochondrocytes (MFCs) are functional cells of the meniscus that can maintain and generate the ECM without any induced differentiation. This ability makes MFCs an interesting cell option for meniscus regeneration. (M. Chen et al., 2019; Liang et al., 2017, 2019) One major concern related to MFCs has been their habit to lose the ECM-forming phenotype during in vitro cell expansion, which leads to decreased expression of type II collagen and aggrecan (Liang et al., 2019). Aggrecan is a large proteoglycan found from articular cartilage. A possible solution for this problem is to expand the MFCs at the same time with certain growth factors, such as transforming growth factor-β1 (TGF-β1) and fibroblast growth factor-2 (FGF-2). This simultaneous expansion was reported to help the MFCs to re-express an inner-like meniscus ECM-form-

ing phenotype. (Liang et al., 2017, 2019) MFCs have shown promising results in promoting the regeneration of the meniscus in terms of histological structure, biochemical contents, and biomechanical performance when seeded into PCL-meniscus ECM –based hydrogel hybrid scaffolds and implanted into animal models (M. Chen et al., 2019).

Articular chondrocytes are a specialized cell type responsible for maintaining the cartilage. They have shown the capacity for repairing meniscus tissue when seeded onto the scaffold (Moradi et al., 2017). Chondrocytes derived from various sources, such as human, porcine, and bovine, have been investigated with good success (Gao et al., 2016; Kwak et al., 2014; Wu et al., 2015). For example, human articular chondrocytes seeded on platelet-rich plasma –pre-treated PLGA mesh scaffolds were able to intensify the healing capability of the meniscus and improve cell attachment in mice models (Kwak et al., 2014). In addition, porcine chondrocytes seeded on the surface of tissue-derived decellularized porcine scaffolds demonstrated an ability to proliferate on the scaffold surface, and a few cells were even able to infiltrate into the scaffold (Gao et al., 2016). Further investigation of articular chondrocytes is required, including a more thorough evaluation of the regenerative capabilities and functional properties of the cells.

A classic strategy for developing a tissue-engineered meniscus is to seed only a single type of cell onto the scaffold. It has been challenging to attempt mimicking the native meniscus structure using only one cell type. This has caused increased interest in cell co-culture. Culturing two cell types has stated to augment ECM formation and mechanical properties of scaffolds (Cui et al., 2012; McCorry et al., 2016). For instance, Cui et al. (2012) noted that the co-culture of mature meniscal cells and MSCs emphasized GAG and collagen type I production, decreased hypertrophy of the cells, and demonstrated optimal ECM production. Similar results were stated in a more recent study where McCorry et al. (2016) co-cultured BM-MSCs and MFCs. Co-culturing increased GAG preservation in the construct, decreased MSC hypertrophy, supported MSCs transformation into more rounded, meniscus-like cells, and improved mechanical properties of the collagen scaffold.

5.4 Biochemical and mechanical stimulation

The cells, scaffolds, and biochemical and mechanical stimulation are usually regarded as irreplaceable elements of tissue engineering. Biochemical and mechanical stimulation aim to combine the tissue-engineered structure and the functional tissue. Growth factors are a common biochemical stimulation method used in meniscus tissue engineering. They have a vital role in cell growth, proliferation, and differentiation and are a crucial

part of tissue maturation and remodelling. Additionally, mechanical stimulation is essential for the development and regeneration of the meniscus by imitating the native meniscus biomechanical environment. (Nukavarapu et al., 2015, pp. 10, 17, 77) The combination of growth factors and mechanical stimulation can yield great benefits in the field of meniscus tissue engineering in the future. This chapter discusses some common growth factors and mechanical stimuli utilized in meniscus tissue engineering.

The transforming growth factor β (TGF-β) superfamily is a polypeptide family considered one of the most important for cartilage tissue engineering (Batista et al., 2020; Chen et al., 2020). TGF-β family has the ability to enhance meniscus cell proliferation and differentiation. Only two growth factors, bone morphogenetic protein 2 (BMP-2) and bone morphogenetic protein 7 (BMP-7), have gained FDA approval and they both belong to the TGF-β superfamily (Schmal et al., 2012). Besides BMP-2 and BMP-7, TGF-β1 and TGF-β3 have also been studied widely in meniscus tissue engineering and they have shown promising results. TGF-β1 has noted to support matrix deposition of meniscus cells, articular chondrocytes, and fibroblasts (Batista et al., 2020). Chen et al. (2020) developed a thermosensitive, injectable, in situ crosslinked hydrogel seeded with BMSCs and studied how TGF-β1 influences the chondrogenic differentiation of MSCs. The results showed that hydrogels with TGF-β1 induced strong fibrochondrogenic differentiation. Besides TGF-β1, TGF-β3 has also been examined in meniscus tissue engineering. It has shown to improve the quantity and quality of the new extracellular matrix, stimulate GAG and collagen production and enhance cell attachment to repaired tissue (Chen et al., 2020; Nakagawa et al., 2019).

Basic fibroblast growth factor (bFGF) is a heparin-binding protein that stimulates the differentiation, proliferation, and migration of fibroblasts and fibrochondrocytes (Batista et al., 2020). The strong stimulating effects of bFGF have been demonstrated in multiple studies (Buckley & Kelly, 2012; Stewart et al., 2007). Ionescu et al. (2012) examined the effects of bFGF and TGF-β3 growth factors on natural and synthetic meniscus repair constructs. The influence of these growth factors was studied for 1- and 8-weeks periods, separately and combined. The most significant mechanical integration strength of the repair was detected by using short-term delivery of bFGF and continuous delivery of TGF-β3.

Insulin-like growth factors (IGFs) are peptide hormones investigated in meniscus tissue engineering for their growth-stimulating properties. Puetzer et al. (2013) demonstrated IGF-1 stimulation in tissue-engineered menisci. The study results stated that IGF-1 treatment improved mechanical properties and ECM production of the menisci and increased

GAG and collagen production. However, collagen production still needs to be intensified to reach the levels of the native meniscus.

The combinations of growth factors have also been studied to enhance meniscus repair. For example, a mixture of bFGF, TGF-β1, and IGF-1 has shown to increase expression levels of aggrecans and collagen type II in fibroblast-like cells in vitro (Fox et al., 2010). Besides the above-mentioned growth factors, other growth factors and biomolecules like vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), biotin, glucose, and chondroitinase-ABC, have also been examined due to their ability to enhance meniscal repair and regeneration (Batista et al., 2020; Chen et al., 2020).

Besides biochemical stimulation, the mechanical stimulus of the cells is also required to guarantee decent scaffold remodelling. Cells respond to changing environment by altering their chemical and physical interactions. Positive mechanical stimuli will enhance the ECM whereas negative stimuli will cause matrix degradation and inflammation. The mechanical attributes of the ECM can be improved through deposition, alignment, and compaction. There are multiple methods for stimulating meniscus tissue, such as tension, compression, shear, hydrostatic pressure, fluid flow, and ultrasound. To achieve the optimal cellular response, proper conditions and type, duration, and magnitude of stimulus must be thoroughly determined. (Nukavarapu et al., 2015, p. 231; Zhang et al., 2019)

The mechanical stimulus has shown to enhance the differentiation of various cell types, such as MSCs, to more meniscus-like cells. For instance, tensile loading has stated to induce fibrogenesis with better tensile strength and increase collagen type I synthesis, and compressive loading has resulted in more effective chondrogenesis with increased GAG content and collagen type II synthesis (Baker et al., 2011; O'Conor et al., 2013). However, it has proved challenging to mimic the native meniscus structure due to different cell types and mechanical properties in the outer and inner regions of the meniscus. This challenge could possibly be overcome by combining the cell co-culturing, biochemical stimulus, and multiple mechanical stimuli.

In a recent study, biochemical and mechanical stimuli were applied on a PCL scaffold seeded with BM-MSCs (Zhang et al., 2019). The scaffolds were inserted into rabbit models and the results were examined after 6, 12, and 24 weeks. The aim of the study was to create a region-specific meniscus structure that would provide long-term chondroprotection for the knee by preserving the chondrocytes. TGF-β3 growth factor was noted to enhance fibrochondrogenic and chondrogenic gene expression, whereas CTGF in-

creased fibrochondrogenic and fibrogenic gene expression when combined with a dynamic compression-tension stimulus. The double-stimuli group illustrated almost as high tensile and aggregate moduli and ultimate tensile strength values as the native meniscus. The chondroprotective effect was also spotted and no noteworthy cartilage degradation was detected. The limitations of the study include the use of rabbit models instead of larger animals, the inability to study the fate of the stem cells in the knee joint in vivo due to euthanasia of the models randomly after 6, 12, or 24 weeks, and challenges resulting from the small size of the meniscus scaffold. Despite the limitations, this study assists to develop a long-term chondroprotective, region-specific meniscus structure.

5.5 Scaffold-free approaches

The scaffold has traditionally considered to be a principal factor in meniscus tissue engineering, but scaffold-free approaches have gained attention in recent years. A platform that does not need cell seeding or attachment within an exogenous material is referred to as scaffold-free tissue engineering. (Athanasiou et al., 2013) It has several advantages compared to approaches including scaffolds, such as a biomimetic environment for cells to proliferate and enhance ECM production, no immunogenicity or toxicity reactions in consequence of scaffold degradation by-products, no need for scaffold degradation before initiating tissue synthesis, and no possible stress shielding problems that may occur in scaffold approaches (Gonzalez-Leon et al., 2020; Murata et al., 2018). Meniscus regeneration has also been insufficient in scaffold-based approaches and hence scaffold-free approach may offer a solution to that problem.

Scaffold-free approaches can be divided into self-organization and self-assembly processes. When it comes to the self-organization process, order occurs when some external energy or forces affect the system. On the other hand, the self-assembling process does not require external energy or forces, but the order just spontaneously occurs. Cell sheet engineering and aggregate engineering belong to the self-organization process. In cell sheet engineering, cell sheets are formed by expanding the cells in a monolayer for extended periods of time. Once the ECM-rich sheets have formed, the sheet is lifted and assembled to form desired-shaped tissues. Assembling can be done by for instance draping, layering, or rolling and it also requires external manipulation. (Athanasiou et al., 2013)

Cell sheet engineering has shown promising results in meniscus regeneration and OA prevention. Ql et al. (2016) prepared a BM-MSC cell sheet and transplanted it into a rat meniscal defect model. The results were studied 4 and 8 weeks after implantation. In the

BM-MSC sheet group, meniscus regeneration was noted, and neo-meniscus was integrated well into the native tissue. In cell sheet engineering, cell-to-cell, cell-to-matrix contacts, and ECM remodelling are typical. These above-mentioned contacts were detected 8 weeks after cell sheet implantation. However, slightly decreased GAG content was also observed. Takata et al. (2020) also studied the effects of the scaffold-free cell sheet approach by using adipose-derived MSCs. Study results stated that stem cell sheet may promote meniscus regeneration after meniscectomy as the sheet showed to improve the histological score of the neo-tissue. Longer follow-up periods are required to get more information about the degeneration of the neo-meniscus when exploiting scaffold-free cell sheet engineering.

In addition to cell sheet engineering, aggregate engineering is also a self-organization tissue engineering technique. Aggregates are made by mildly stirring or shaking the suspensions of non-adherent cells. The speed and duration of the shaking can be altered to enhance diffusion and nutrient exchange. Aggregates can then be implanted into meniscal defects, dissociated, or assembled into larger tissue constructs. (Athanasiou et al., 2013) Scaffold-free approaches do not have the exogenous material unlike scaffold-based approaches, so the neo-tissue development often requires external manipulation, like growth factors and mechanical stimulation, to enhance ECM formation. Szojka et al. (2019) examined inner meniscus ECM-formation by human MFC aggregates in vitro. Study results show that the synergistic insertion of hypoxia and TGF-β3 improved inner meniscus-like matrix formation.

The last scaffold-free approach is called the self-assembling process. It is based on separate phases that mimic the native meniscus development to form a meniscus-like structure. First, the high-density cell suspension is seeded into a non-adherent substance. Then cell coalescence appears due to spontaneous minimization of free energy. In the third phase, cells migrate, and meniscus-like ECM is produced. During the last phase, final matrix maturation occurs. (Athanasiou et al., 2013) With the help of biomolecules, meniscal constructs with biochemical and biomechanical properties comparable to native meniscus have been developed (Huey & Athanasiou, 2011). Although scaffold-free approaches have shown to be potential for meniscus tissue engineering, further investigation is required to overcome current limitations. These limitations include, for instance, the need for large cell numbers to form a meniscal construct and the difficulty of developing desired shaped and sized support structures due to diffusion limitations (Athanasiou et al., 2013).

6. CONCLUSIONS

As discussed in previous chapters, musculoskeletal cartilage, such as meniscus, is generally characterized by low cellularity and vascularity and it has a poor regeneration capacity. These above-mentioned characteristics make the meniscus an appealing target for tissue engineering. Clinical practice in meniscus repair has improved remarkably during the past decades, but no single functional and long-lasting approach has been discovered.

Meniscus lesions are a prevalent knee injury among people of all ages. The long-term outcome of the current clinical practice has turned out to be ineffective, as the activity level of the patients has not been able to be fully restored after meniscectomy, meniscal repair, or meniscal reconstruction. Solely meniscectomy should be avoided because it will further progress meniscus degeneration and development of the OA. When it comes to MAT, extrusions and inflammation reactions have been reported after implantation. Two different scaffolds, CMI and Actifit, and NUsurface meniscal prosthesis, have partially alleviated the symptomatic post-meniscectomy syndrome, but the failure rate of the current meniscus replacement options is still too high.

Further improvements regarding meniscus replacement include, for instance, a wider focus on creating functional replacements. More extensive, well-defined randomized controlled studies are also essential to support the process. Additionally, the studies could help to prove that the clinical outcome of the new products surpasses the results of current clinical practices available. This is extremely important because the meniscus replacement requires an expensive implant and an implantation surgery compared to meniscectomy only. Expenses are another remarkable factor when considering a new tissue engineering approach.

Meniscal scaffolds are widely investigated tissue engineering options for meniscus repair. As mentioned before, meniscal scaffolds can be divided into tissue-derived materials, ECM components, synthetic polymers, and hydrogels. Despite the promising early results, certain obstacles concerning each scaffold type firmly remain. Both tissue-derived materials and ECM component scaffolds have better biomimetic and bioactive properties than synthetic scaffolds. Some processing and decellularization methods decrease the mechanical integrity of tissue-derived materials, whereas ECM component scaffolds may offer more strength, but they cannot fully recapitulate the native meniscus. The last scaffold type, hydrogel scaffolds, can also quite accurately represent the native

meniscus structure, but progress in mechanical properties and bioactivity is required compared to other scaffold types.

No material can completely simulate the complex structure of the natural meniscus, and further research of scaffold materials is needed. The biocompatibility, vascularization, and regeneration rate of the tissue engineering approaches currently in development still need to be enhanced to be able to create an ideal treatment method for meniscal repair. As the idea of saving the meniscus instead of removing it is fairly new, it is possible that the most effective treatment method has not been discovered yet. However, scaffolds are an attractive option because they enable a personalized treatment due to their adaptability.

Future studies of meniscus replacement will be centred on generating a biocompatible material that will have a similar microstructure and biomechanical and functional properties to the native meniscus. One option to achieve this goal could be to combine various scaffold types. Besides scaffolds, suitable cell types to be seeded on the scaffolds must also be investigated more along with proper biomolecules and mechanical stimulation. Scaffold-free approaches should not be completely excluded either, because they mimic the elements of developmental processes underlying the meniscus tissue. In addition, studies need to focus on minimizing healthcare costs. To summarize, a significant amount of knowledge has been gained concerning the meniscus-preserving and -replacing treatment options, but further research is still needed.

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