A peer-reviewed version of this preprint was published in Peerj on 17 November 2017.

View the peer-reviewed version (peerj.com/articles/4076), which is the preferred citable publication unless you specifically need to cite this preprint.

Kean CO, Brown RJ, Chapman J. (2017) The role of biomaterials in the treatment of meniscal tears. Peerj 5:e4076 https://doi.org/10.7717/peerj.4076
The role of biomaterials in the treatment of meniscal tears

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Extensive investigations over the recent decades have established the anatomical, biomechanical and functional importance of the meniscus in the knee joint. As a functioning part of the joint, it serves to prevent the deterioration of articular cartilage and subsequent osteoarthritis. To this end, meniscus repair and regeneration is of particular interest from the biomaterial, bioengineering and orthopaedic research community. Even though meniscal research is previously of a considerable volume, the research community with evolving material science, biology and medical advances are all pushing toward emerging novel solutions and approaches to the successful treatment of meniscal difficulties.
The Role of Biomaterials in the Treatment of Meniscal Tears

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Survey Methodology Plan:

Our paper has been compiled using a methodical approach for a regular literature review. We have searched directly on the following terms:

- Biomaterials,
- Meniscal tears,
- Knee Arthroplasty

By establishing the problem “meniscal tears,” we were able to develop an unbiased search of literature – foundation papers, but also recent and emerging using biomaterials centred on the knee arthroplasty procedure.

We have encompassed a niche topic with a broad cross-disciplinary interest. There is currently no review that brings together the use of new biomaterials for meniscal tears representing our rationale to develop the paper.

Our search plan centred on the types of articles we required to formulate the article; for example, recent types of literature included: books, articles, conference proceedings, reviews.

The search plan was executed using the following search engines: Scopus and Google Scholar where higher citing and therefore better impact work was selected.
Abstract

Abstract: Extensive investigations over the recent decades have established the anatomical, biomechanical and functional importance of the meniscus in the knee joint. As a functioning part of the joint, it serves to prevent the deterioration of articular cartilage and subsequent osteoarthritis. To this end, meniscus repair and regeneration is of particular interest from the biomaterial, bioengineering and orthopaedic research community. Even though meniscal research is previously of a considerable volume, the research community with evolving material science, biology and medical advances are all pushing toward emerging novel solutions and approaches to the successful treatment of meniscal difficulties.

Keywords: Knee meniscus; biomaterials, tissue engineering, scaffolds, materials science
1.0 Introduction

The knee is considered a hinge joint; however, because it also features characteristics of an arthrodial joint, it is a more complex joint than other hinge joints such as the elbow and ankle. The knee consists of two articulations which form the tibiofemoral joint (further separated into the medial and lateral tibiofemoral joints) and the patellofemoral joint. The articulations are not entirely congruent and this arrangement allows for the combination of gliding and rolling motions which is constrained mainly by the ligaments of the knee. The menisci are fibrocartilage structures that sit on top of tibia to deepen the plateaus with the primary functions transmitting load through the joint and also serve to increase joint stability and lubrication of the articular cartilage [1-3].

The menisci are commonly injured due to traumatic events and/or degenerative stresses. In the United States alone, it was estimated that approximately 6.6 million patient visits to the emergency department between 1999 and 2008 were due to knee injuries equating to 2.29 knee injuries per 1000 people [4]. A large portion of knee injuries in the general population are meniscal related and meniscal injuries are even more common in a physically active population [5, 6]. Given the role meniscal tears, and subsequent partial or full removal of the meniscus, play in development of osteoarthritis [7, 8] there is an increased interest in preservation of these structures following injury. For this reason, there is also an increased interest the role biomaterials play in meniscal repair, regeneration and replacement options.

Advances in materials technology have brought about an increased usage of biomaterials and medical devices in the body [9]. A biomaterial is a material that interacts with surrounding
human tissue and body fluids to improve or replace the anatomical defect. Some examples of the recent advances for biomaterial use in medicine include knee and hip replacement [10], ocular implants [11], heart valves [12], bone implants [13], dental implants [14], biosensors [15], orthopaedic screws and sutures [16] and tissue allografts [17]. The achievements, in terms of biocompatibility, to lower risk of failure and improved surgical outcomes have contributed to the expanding use of biomaterials. For these reasons advancements in biomaterial development is a growing area of research.

This review article will focus on providing a brief general review of the menisci and meniscal injuries, biomaterials and the subsequent role biomaterials play in the surgical treatment options for meniscal repair, regeneration and replacement as well as future directions.

2.0 Meniscus

As previously mentioned, the menisci are fibrocartilage structures, composed mainly of type 1 collagen, that sit on top of tibia. The lateral meniscus is a C-shaped structure that covers approximately 80% of the lateral tibial plateau whereas the medial meniscus is a U-shaped structure and covers only 60% of the medial tibial plateau. The menisci are relatively avascular with only 10-30% of the peripheral region of the medial meniscus and 10-25% of the lateral meniscus being vascular [18]. Based on its vascularisation, the menisci can be divided into three zones: the red-red vascular zone (outer peripheral region), the white-white avascular zone (inner region) and the red-white zone which lies between of the two other zones and has characteristics of other two zones. The red vascular region is thick and convex and attaches to the capsule of the
joint whereas the white-white inner region is thin, concave and is a free edge unattached to the joint.

The menisci effectively deepen the tibial plateau and allow smooth articulation between the tibial and femoral condyles and the transmission of loads across the tibiofemoral joint. In full knee extension, the medial meniscus transmits approximately 50% of the load on the medial compartment, while lateral meniscus transmits approximately 70% of the load in the lateral compartment [2]. As knee flexion increases the amount of load transmitted to the lateral meniscus increases such that when the knee is flexed beyond 75° the entire load that passes through the lateral compartment, is transmitted by the lateral meniscus [2]. For the medial meniscus the increase in load transmission as the knee flexes is less apparent [2]. When the meniscus is intact, the load is well distributed across the tibiofemoral compartment; however when part or the entire meniscus is removed there is considerable alterations to load distribution such that there is a decrease in the contact area and increases in peak contact forces [19-21].

2.1 Meniscal tears

Meniscal tears are one of the most common intra-articular knee injuries [22, 23] and is typically the result of an axial loading and rotational forces which result in a shear load on the meniscus [24]. This may be a result of a traumatic event or cumulative stress leading to degenerative tears. The medial meniscus is more often injured than the lateral [23]; however, lateral meniscal tears are more often associated with acute ACL tear [25]. Although there is no uniformly accepted classification of meniscal tears, the classifications typically involve a description of the tear pattern and location. Common tear patterns that typically originate from traumatic events include
longitudinal, bucket-handle, and radial tears [26]. Whereas horizontal, flap and complex tears are typically seen in older adults and due to cumulative stress resulting in degeneration [26]. The location of the tears may be classified based on the zone classification system purposed by Cooper et al [27] in which the menisci are divided into 3 radial zones (anterior, medial and posterior) and 4 circumferential zones (meniscosynovial junction or periphery, outer third, middle third and inner third of the menisci), Figure 1.

Figure 1: Schematic diagram highlighting the various types of meniscal tears

In a similar fashion to the zone classifications, tears may be graded as partial or full-thickness tears or using a grading scheme 0-III in which 0 indicates a normal intact menisci and III a full-thickness tear [27].

Meniscal tears can result in significant pain and disability and for this reason account of a significant portion of surgical procedures performed by orthopaedic surgeons [28]. The surgical procedures involved in the treatment of a meniscal tear may include a partial or full menisectomy or a meniscal repair. The menisectomy procedures involves either part or all of the damaged
meniscus being removed which in turn leads to higher rates of osteoarthritis in subsequent years [7, 8, 29]. This is mainly due to changes in load distribution across the articular cartilage as studies have shown that following total meniscectomy peak contact pressures increase by 253% and 165% following partial meniscectomy [20, 30]. Following meniscectomy, there is also evidence of reduced muscle strength, altered gait patterns and clinical outcomes [31-37]. For these reasons there is increasing interest in performing meniscal repair; however not all meniscal tears are suitable for repair and thus other treatment options such as meniscal replacement and regeneration are of considerable interest when a surgical intervention is necessary to improve pain and symptoms.

3.0 Biomaterials

Of late, tissue-engineering and cellular biomaterial interactive concepts have been introduced to develop cellular-based reparation for cartilage regeneration [38]. The type of cell used to engineer cartilage is critical as a future goal of biomaterial development. Various cell populations that have been investigated for these roles include chondrocytes [39], mesenchymal stem cells, bone marrow stromal cells and perichondrocytes [40]. The choice of biomaterial is also critical to the success of tissue engineering approaches for cartilage repair.

The concept of ‘tissue engineering’ was first introduced and postulated by Green in 1977 [41] where chondrocytes grown ex vivo could be transplanted into a region of tissue defect. Recently, tissue and biomaterial engineering concepts have been initiated to develop cellular based approaches for tissue repair [42]. Typically, the process for engineering tissue involves the isolation of chondrocytes which are then seeded into a biocompatible matrix or scaffold and
finally cultivated for implantation into the defected region. A large variety of biomaterials, natural and synthetic, have been employed as potential cell-carriers for tissue regeneration. The most common naturally occurring materials include type I and type II collagen-based biomaterials. Furthermore, some of the contrasting synthetic approaches include: polyglycolic acid or poly-L-lactic acid or other various composite mixtures [39]. In essence, an ideal candidate biomaterial would be a cell-carrier substance which closely mimics the natural environment in the surrounding matrix – as given by the definition of a biomaterial.

Biomaterials are typically promoters of tissue repair through provision of scaffold layers for cellular attachment and growth and differentiation further acting as a vehicle for protein and gene transfer to regenerate functional tissue approaches.[43] Biomaterials in this area should have several properties to support viable repair. Typically, this is achieved through:

1) The material must act as a support structure for cell lines;
2) Possess sufficient mechanical strength to protect the surrounding cells;
3) Withstand in vivo forces during the joint movement operation;
4) Bioactivity should be provided to accommodate cellular attachment and cellular migration;
5) The biomaterial should have biodegradable properties and be able to remodel as the novel cartilage grows, embeds and replaces the original construct; therefore the matrix must be non-toxic, non-adhering and non-stimulating for inflammatory cells. Furthermore, they should be non-immunogenic as this is catastrophic for the biomaterial insertion.
One of the most important non-mechanical requirements of orthopaedic biomaterials is biocompatibility. Biocompatibility is the ability of a substrate to exist in contact with tissues of the human body without causing an unacceptable degree of harm in the body. The biomaterial domain has been aptly described by Mardis and Kroeger, “the utopian state where a biomaterial presents an interface with physiologic environment without the material adversely affecting the environment or environment adversely affecting the biomaterial” [44]. An understanding of biocompatibility requires an appreciation of tissue cell, bacterial cell and host defence response to the insertion of a biomaterial in particular for this review - for meniscal interventions. Once the biomaterial has been placed into the body, a conditioning film containing biomolecules such as; water, electrolytes, cholesterol, vitamins, lipids and proteins [45] (albumin, igG, fibronectin, fibrinogen, laminin, collagen and osteopontin) form on the surface long before cells are present and reach the state of equilibrium [46]. The conditioning layer represents a dynamic, ever-changing layer due to differential diffusion and mass transport of molecules in and out of the implant surface. Later stages of competitive binding then occur on the surface of the material owing to functional groups within the molecules. Cells therefore never see the ‘true’ surface of the biomaterial, but more correctly, respond and interact to a conditioned film that has consequently developed in-situ.

Following the conditioning sequence of the biomaterial, attachment cells secure themselves to the protein and protein matrices using integrin receptors. Thus, this conditioning layer is vital to the reaction of cells to the surface of the implanted biomaterial. This sequence is not always obvious as proteins have the ability to conform and expose epitopes that are not always identified as self-produced by the body’s immune system. Immune cells react as they detect what were
once normal proteins and recognise them as foreign bodies. This process can result in a cascade of blood coagulation and chronic inflammation that can lead to occlusion of nutrients, changes in oxygen and fibrous capsule formation – operating toward total rejection by the body of the implanted biomaterial [47]. The extent of the deformation process for proteins has been remedied based on the selection of material type. Surfaces are made more “passive” where chemical treatments are added to the manufacturing process. Passivation with acids such as nitric acid of stainless steel creates a less reactive oxide layer; this has been shown to improve the biocompatibility process. One added benefit to passivation is it serves as a means for removing foreign material from the surface, such as bacteria or biofilms [48].

3.1 Role of Biomaterials in Meniscal Repair

A recent article by Abrams et al. [49] has shown that while there was no increase in the overall number of meniscal procedures, over a seven year period there has been an 11.4% increase in isolated meniscal repairs and a 48.3% increase in meniscal repairs in combination with ACL reconstruction. This sharp increase in meniscal repair treatment is mainly due to the increased knowledge in the importance of the preservation of the meniscus to maintain normal knee function and prevent osteoarthritis. It has been shown that following meniscal repair, peak contact pressures are similar to that experienced with an intact meniscus [50]. Unfortunately, it is estimated that currently only 20% of all meniscal tears are repairable. Tears in the meniscal periphery (ie. the red-red vascular zone) are most likely to heal whereas those in the meniscal avascular zone (ie. the white-white zone) are unlikely to heal and those in the red-white zone have the potential to heal [51, 52]. Besides vascularisation, tear type and various patient characteristics can influence decision making on treatment options and success of a meniscal
Typically, tears that are less than 2 cm in length, longitudinal and acute are more amendable to repair than larger tears [53, 54]. Meniscal repairs are also not typically recommended for degenerative tears and thus repair success is typically superior in young patients (less than 50 years of age) [54]. When appropriately performed, meniscal repairs provide considerable improvements in terms of clinical outcome and osteoarthritis prevention compared to a partial meniscectomy [55]. Thus, finding ways to increase the number of meniscal tears that can be treated by meniscal reparation is of great importance.

Chitin sutures are an emerging material of choice for improvement of the mechanical properties of a knee healing process [56]. Owing to its favourable mechanical properties, chitin has been used for applications that require exceptional integrity and physical strength in surgical sutures, some new medical textiles and even as bone substitute materials. Electrospun scaffolds are also another emerging biomaterial that has begun to be used for cellular adhesion applications in regenerative medicine. Electrospinning involves the use of electrostatic forces to generate size tuneable fibres (nano to micron) that are seamlessly like collagen fibres found in orthopaedic soft tissue – including the knee meniscus [57]. The fibres have the ability to mimic both anisotropy of fibrous tissues and withstand high load forces that are imposed on the tissue during physiological motions [58]. Dependent on the material choice, cell interactions will occur, begin to proliferate and adhere and finally deposit matrix on to the fibre network - thereby improving the mechanical properties of the scaffold over time. Fibres can be collected on to rotating drums or flat collection plates, depending on the order, orientation and architectures that they are required. Cells typically are seeded on to these scaffolds and cultured over time in vitro. In a study by Passaretti et al. [59] tensile modulus was seen to improve on fibre aligned scaffolds some 7-fold.
higher than disorganised fibres approaching the value of a normal meniscus. Essentially, the
authors determined that cells prefer to align on ordered scaffold fibres rather than disorganised
arrangements. Further to these findings, internal organisation in the form of sheet fibres can also
be arranged for tissue-mimicking structures. Specifically, for meniscal tissue engineering, cells
can be isolated, expanded and manually seeded on to the surfaces of electrospun scaffolds prior
to an implantation operation, expediting the regenerative process. Cells along with host cells will
migrate on to the newly implanted scaffold and deposit proteoglycan and collagen. Some
implantation methods require surgery prior to this implant step to isolate the cells prior to
seeding, maturation and implantation.

Vascularisation in the meniscus tissue is of high relevance to biomaterial design. From prenatal
development up until after birth, the meniscus is fully vascularised. Following this, from the age
of ten, vascularisation reduces to 30% of the meniscus and at maturity the meniscus only in the
peripheral region of approximately 10% of the tissue. Vascularisation represents another
challenge in meeting the requirements of success for biomaterial implantation as a meniscus
operation. Vascular endothelial growth factor enhances the blood vessel density in peri-implant
spaces. Biomaterial scaffolds of knee menisci exist in a highly challenging environment as little
vascular support is provided in this region of the body. Electrospinning of polymeric fibres can
be produced to support other engineering applications such as blood vessel, tendons, meniscus
and cartilage [60]. Some authors have even begun to incorporate growth factors to stimulate and
promote further vascularisation within the knee region [61]. This emerging technique represents
a powerful tool to control cell behaviour for tissue and biomaterial engineering.
3.2 Role of Biomaterials in Meniscal Replacement and Meniscal Regeneration

Owing to the limited percentage of meniscal tears that can be repaired and the poor clinical results with untreated symptomatic meniscal injuries and partial meniscectomy, biomaterial synthetic and allogenic biomaterials have been investigated to serve as a matrix to lead meniscal regeneration medicine, particularly as a cellular support.

Using a biomaterial that has the ability to seamlessly integrate in a water based matrix is another attractive property for regenerative medicine. Hydrogels are hydrated polymer networks capable of absorbing and retaining fluids. Hydrogels are determined by their monomeric composition, crosslinking density and polymerisation ability. Due to the crosslinking process the polymer remains insoluble in solution. The insolvency property, along with the high hydration thresholds, make them appealing to use for human tissue mimics [62]. Some authors have used a poly (vinyl alcohol) hydrogel with a water content of approximately 90% to produce knee implants for a rabbit model [63]. The implant replaced the whole lateral meniscus over two years. In a follow-up study the authors demonstrated that the implant was not able to prevent damage to articular cartilage but was able to reduce progression of meniscal decay. Some of the new and emerging biomaterial approaches have been shown in Table 1.

Table 1 Summary of studies of biomaterial used in meniscus research

| Biomaterial Used  | Author             | Engineering Region | Success(es)                                                   | Species Model |
|-------------------|--------------------|--------------------|---------------------------------------------------------------|---------------|
| Synthetic polymers|                    |                    |                                                              |               |
| Hydrogels         | Kim and Healy [64] | Meniscus tissue engineering | Maintained 90% water content that are not degraded by proteases | Mammalian     |
| Polygolic acid    | Buma et al.        | Meniscus           | Optimal pore                                                 | Canine        |
As a new and emerging prominent tool in regenerative medicine, tissue engineering has been an active field of research for the past 35 years. Clinical applications of tissue engineering technologies are still relatively restricted owing in part to the limited number of biomaterials that are approved for human use. While many biomaterials have been developed, their translation into practice has been extremely slow. Consequently, many researchers are still using biodegradable choices that were approved some 30 years ago. Most degradable biomaterials used to date comprise of synthetic polyesters:

- Poly(L-lactic acid) PLLA;
Poly(L—glyolic acid) PLGA; and

Biological polymers such as: alginate or chitosan, collagen or fibrin [70].

Many fabrication techniques have been devised and used and afford differences in size, shapes, porosities and architecture. Composites of these synthetic and natural polymers alone or with bioactive ceramics such as hydroxyapatite can be designed to produce materials with wide ranging strengths and porosities particularly focusing on the engineering of hard tissues.

3.4 Discovery of new biomaterials – beyond state of the art

The next phase in developing knee meniscal biomaterials for replacement and or regeneration applications extends to the design, discovery and evaluation of bioactive materials. Initially, this is a relatively straightforward process whereby advanced synthesis of new materials can be performed. The difficulty lies with producing the novel activity and evaluation of the behaviour of the material in the biological system. Adapting the surface properties through the addition of synthetic peptides and or molecular drugs can yield thousands of candidate materials for testing. This approach has already been realised in the form of library derived screening techniques using commercially available methacrylate monomers – influencing attachment, growth, proliferation and differentiation of human embryonic stem cells [71].

Further developments in biomaterials will continue to expand at the interface of nanotechnology. Understanding the tribological interaction with the surrounding interface of the human body is an approach that is being realised using the “bottom-up” approach [72]. The bottom up approach will develop novel, self-assembling and environment reactive biomaterials. In particular, self-assembling peptides offer a new approach owing to the large variety of sequences that can be
produced by chemical synthesis. These advances include the design of short peptides that have
the ability to resemble nanofilaments which are compatible in vitro, without rejection. The use of
peptides in polymeric materials allows for resistance in concentration, pH or level of divalent
cation variability [73]

One final, prominent field emerging in material science lies with biomimetic biomaterial
approaches [74]. Biomimetic materials are materials that have been directly replicated from
nature to produce a solution to a specific problem. Some synthetic polymers may be able to
provide a more biomimetic environment than the previously discussed hydrogel approach. The
chemical functionalization of hydrogels is one strategy that needs future pursuit to create a more
native microenvironment for cells in a particular area of the body – i.e. the knee.

4.0 Conclusions

Evidently, the diversity of biomaterials for meniscal applications is immense. Many approaches
to mimicking the structure and function of the ECM have been conceived. It is crucial that these
advances continue to be investigated for their ability to interact within a biological system. The
importance of the meniscus in protecting joint function is gaining considerable interest.
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