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Review

Biomaterials in search of a meniscus substitute

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ABSTRACT

The menisci fulfill key biomechanical functions in the tibiofemoral (knee) joint. Unfortunately meniscal injuries are quite common and most often treated by (partial) meniscectomy. However, some patients experience enduring symptoms, and, more importantly, it leads to an increased risk for symptomatic osteoarthritis. Over the past decades, researchers have put effort in developing a meniscal substitute able to prevent osteoarthritis and treat enduring clinical symptoms. Grossly, two categories of substitutes are observed: First, a resorbable scaffold mimicking biomechanical function which slowly degrades while tissue regeneration and organization is promoted. Second, a non resorbable, permanent implant which mimics the biomechanical function of the native meniscus. Numerous biomaterials with different (material) properties have been used in order to provide such a substitute. Nevertheless, a clinically applicable cartilage protecting material is not yet emerged. In the current review we provide an overview, and discuss, these different materials and extract recommendations regarding material properties for future developmental research.

1. Introduction

The menisci, once merely regarded as a functionless development remnant, are two semilunar fibrocartilaginous disks fulfilling key biomechanical functions in the tibiofemoral (knee) joint. Unfortunately meniscal injuries are quite common. Acute tears are most frequent in younger patients and are caused by twisting injuries [1]. Chronic degenerative tears are more frequent in elderly patients either induced by minimal twisting or stress or by chronic degenerative processes [1]. Acute symptoms encompass joint line tenderness, impaired motion (e.g. locking), and joint effusions. Whereas first documented treatments embraced swift and total meniscectomy [2], later less rigorous interventions (e.g. partial meniscectomy) were adopted after appreciating its clinical significance [3–7]. Currently, the importance of the menisci has been widely adopted and, if possible, meniscus repairs are preferentially being performed over (partial) meniscectomies [8]. However, meniscus repair techniques are not suitable for all types of tears and some patients experience enduring symptoms post meniscectomy (e.g. persisting joint line tenderness and reduced functionality) [9]. Although the development of symptomatic osteoarthritis is a complex interplay of multiple factors, it is accepted that, (partial) meniscectomy increases the risk for osteoarthritis related changes in the knee joint [10–13]. The amount of meniscal tissue removed is the strongest predictor of these chances on long term [14]. Debate remains whether degenerative osteoarthritis is more likely to follow medial or lateral meniscectomy. Some authors have reported that patients who had a lateral meniscectomy fared worse than those who had a medial meniscectomy [15–17] whereas others did not find any difference [13,18–21]. A comprehensive review suggested that, concerning partial arthroscopic procedures, there was a lower incidence of osteoarthritis following medial than lateral meniscectomy [14]. In the end, knee osteoarthritis can become symptomatic, causing knee pain, swelling, increasing disability, and reducing quality of life. [22–24] In severe symptomatic osteoarthritis, after failing non-operative treatment, only partial or total knee arthroplasty will provide marked pain relief and functional improvement [25]. However, this is a major orthopedic operation with concomitant risks and costs. Therefore, there has been increasing scientific and clinical interest

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for a meniscal substitute aimed to minimize the risk for developing knee osteoarthritis but also to offer a solution for patients suffering from enduring symptoms post meniscectomy.

Since pioneers first started, numerous materials have been used in order to produce such a substitute, from autologous tissue to synthetic materials. It is the purpose of this article to provide an overview of the different materials, and find out what recommendations can be made for future developmental research.

2. Meniscus anatomy, biochemical content and cells

The menisci are paired (one laterally, one medially) crescent-shaped pads of fibrocartilage located between the femoral condyles and the tibial plateaus, and are firmly attached via the anterior and posterior horns onto the tibial plateau (Fig. 1). The medial and lateral menisci have their own distinct anatomy, meeting anatomic constraints of the femoral and tibial condyles. The medial meniscus is firmly attached to the joint capsule and medial collateral ligament, whereas the lateral meniscus is not as rigidly attached to its circumference, mostly due to the popliteal hiatus. Although subject to anatomic variation, the anterior horns of the medial and lateral menisci are connected via the anterior intermeniscal ligament, and two more meniscofemoral ligaments connect the posterior horn of the lateral meniscus to the lateral side of the medial femoral condyle (ligaments of Humphrey and Wrisberg) [26]. Blood flow, originating from branches of the geniculate arteries, is limited to the peripheral zone whereas the central zone of the menisci receives nutrition from synovial fluid by passive diffusion [27,28]. Critically, the healing capacity of meniscal tears is directly related to its blood supply, leaving the central zone susceptible to permanent post-traumatic and degenerative lesions [28,29].

By wet weight, the meniscus is highly hydrated (72% water), with the remaining (28%) comprised of organic matter, mostly cells and extracellular matrix. Collagens make up the majority (75%) of this extracellular matrix, followed by glycosaminoglycans (17%), adhesion glycoproteins (<1%), and elastin (<1%). Collagen is the main fibrillar component of the meniscus. Different collagen types exist in varying quantities in each region of the tissue, of which type I and II are most abundant. Collagen type I appears throughout most of the menisci whereas collagen type II is mostly detected within the central part of the meniscus [30,31]. Overlap in collagen type distributions is observed throughout juvenile meniscus tissue [32] However, discrete areas with a more pronounced separation of collagen types seems to appear with increasing age [33,34]. For general comparison, type I collagen is the primary collagen in tendon tissue, and type II is the principal collagen of articular cartilage. The spatial orientation of these collagen fibers are highly functionalized in order to provide the meniscus' unique mechanical properties [35–37] (Figs. 2 and 3).

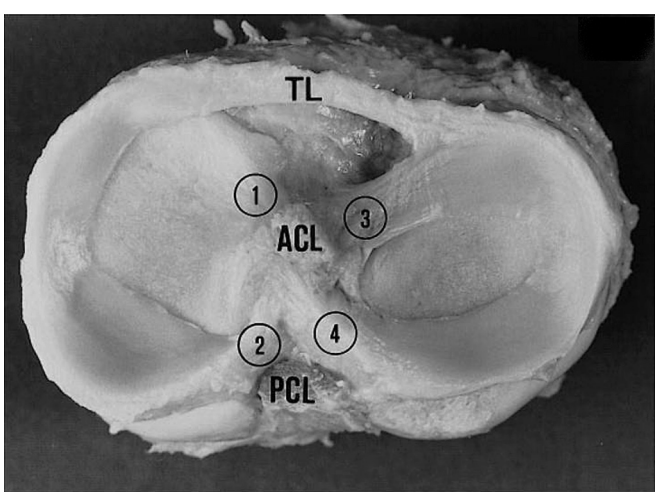

Fig. 1. Human anatomy. Right human knee joint viewed from above (the femur has been removed); the tibial tuberosity is on top. The medial (left hand side of figure) and lateral (right hand side of figure) menisci are connected by a transverse ligament. 1, anterior insertional ligament of the medial meniscus; 2, posterior insertional ligament of the medial meniscus; 3, anterior insertional ligament of the lateral meniscus; 4, posterior insertional ligament of the lateral meniscus; ACL, cross section of the anterior cruciate ligament; PCL, cross section of the posterior cruciate ligament. (reprinted from Ref. [136]).

The main function of the glycosaminoglycans is to enable the meniscus to absorb water, whose confinement supports specific mechanical characteristics discussed later. The adhesion glycoproteins serve as a link between components of the extracellular matrix and cells [28].

Several types of cells can be identified within different regions of the meniscus. Within the central zone small round chondrocytes like cells (fibrochondrocytes) are mainly observed, whereas in the peripheral zone elongated fibroblasts like cells are dominant [38]. Regarding these cells and their embedding extracellular matrix, the peripheral zone of the meniscus has similarities to fibrocartilage, while the central portion demonstrates resemblance to articular cartilage [28]. Another population of cells, also known as superficial zone meniscus cells, is observed within the meniscus surface layer. These cells are believed to synthesize and secrete surface zone proteins which act as lubricant and anti-adhesive [39].

3. Biomechanical functioning

The main function of the menisci is to transfer forces between the femoral and tibial joint surfaces, transmitting 50% through 90% of the load during weight-bearing [40,41]. Two mechanisms are mainly responsible for this load transfer [26,42]. First, the menisci transfer forces between the femoral and tibial joint surfaces by the development of hoop (circumferential) stresses within the meniscal tissue. These are tensile stresses transferred along the circumferential collagen fibers of the meniscus, counteracting the tendency of the menisci to be extruded peripherally during compressive loading. Second, as well as energy being absorbed into the collagen fibers, as the tissue is compressed energy is absorbed by the expulsion of the joint fluid out of the highly fluid absorbed menisci. An important feature of soft biological tissue is a so called stress stiffening or non linear elasticity, in which biological materials stiffen as they are strained, thereby preventing large deformations that could threaten tissue integrity [43]. This could be true also for meniscal tissue by its collagen fibers of which is mainly built up, evidenced by the different modulus at different strains in tension and compression showed in the next sections. Fiber recruitment and the braided structure of collagen fibers within the circumferential alignment may be responsible for this phenomenon.

The importance of an intact meniscus in load transfer is stressed by the increase of contact forces by 350% after meniscal loss of as little as 16–34% [44]. Even more so, radial meniscal tears extending to the periphery result in contact forces equivalent to a completely meniscectomized knee [45], which can be explained by the total disrupted hoop stress. Despite their firm attachments, menisci are dynamic structures. To effectively maintain their load-bearing function over moving, incongruent, joint surface, they have the limited ability to move as the knee flexes [46]. In Humans, following displacements in weight-bearing knees were observed (medial/lateral meniscus, mean ± SD): anterior-posterior displacement of the anterior horn 7.1 ± 2.5/9.5 ± 4.0 mm and

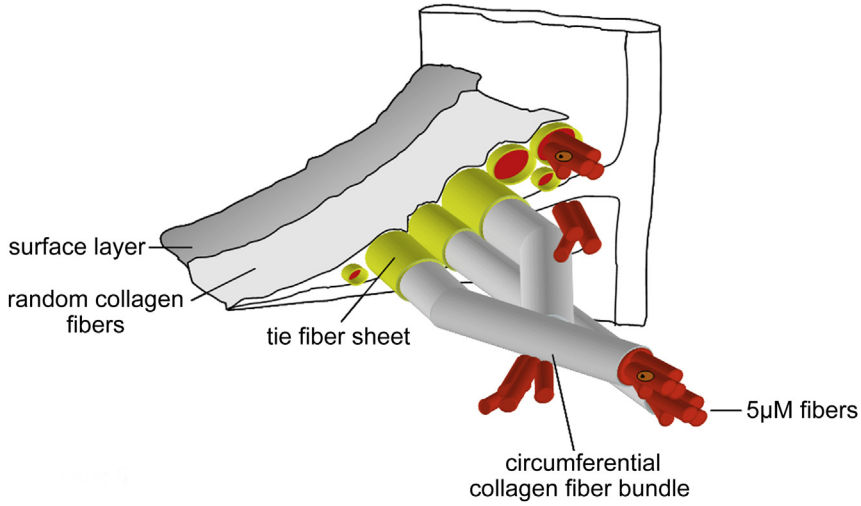

Fig. 2. Diagrammatic representation of the meniscus. Diagrammatic representation of the complex model of the meniscus. Underneath the surface layers of collagen fibrils and cells are circumferential collagen fibril arrays that are shown weaving through a honeycomb network of radial tie fibril sheets (yellow). Individual circumferential collagen fibril (exploded view not drawn to scale) arrays are composed of a series of 5 μm collagen fibril bundles. In the peripheral circumference loose connective tissue from the joint capsule penetrates radially between the circular bundles (reprinted from Ref. [36]). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

that of the posterior horn 3.9 ± 1.8/5.6 ± 2.8 mm and a radial displacement of 3.6 ± 2.3 mm/3.7 ± 1.7 mm [47]. This mobility in respect to the articular cartilage emphasizes the importance of optimal tribologic properties.

In the light of aforementioned, mechanical properties are of most importance for understanding meniscus functioning in situ. However, the inhomogeneous and anisotropic nature of the meniscal tissue causes regional variations in the material properties, complicating attempts to define them.

Several authors examined circumferential tensile modulus of the human meniscus, which varied depending on experimental set up, sample location, and thickness. With respect to the medial meniscus, Lechner observed modulus ranging from 43.4 through 141.2 MPa [48], Fithian observed modulus ranging from 93.2 through 159.6 MPa [49], and Tissakht and Ahmed observed modulus ranging from 58.0 through 106.2 MPa [50]. For general comparison, the tensile modulus for the anterior cruciate ligament is approximately 200–300 MPa, for the patellar tendon approximately 600–700 MPa and for high-density polyethylene approximately 1000 MPa [51,52].

Chia and Hull determined axial compressive aggregate modulus by unconfined compression testing at different strain levels [53]. The modulus ranged from: 11.5 through 52.4 kPa with a 6% strain; 36.5 through 72.9 kPa with a 9% strain; and 32.8 through 137.6 kPa with a 12% strain. Sweigart et al observed aggregate modulus ranging from 90 to 150 kPa with the strain applied to the tissue being under 10% [54]. Overall, the anterior portion of the meniscus seems to be stiffer than the central or posterior portions of the meniscus. For general comparison, the compression modulus is in the range of 1–7 MPa for articular cartilage from the femoral head [55], 500–1500 MPa for cortical femoral bone, and 250–750 MPa for cancellous femoral bone [56].

The complex nature of tribologic properties makes defining them challenging. McCann et al. determined friction coefficients of bovine menisci using a custom pendulum friction simulator with dynamic loading during a flexion-extension motion [57]. Values ranged between 0.06 and 0.09 at a peak load of 1000N with peak contact stresses of 4.9 Mpa; and between 0.01 and 0.03 at a peak load of 250N with peak contact stresses of 2.3 Mpa. Galley et al. using a custom linearly oscillating friction apparatus found that the equilibrium friction coefficient of ovine meniscus ranged from 0.1 to 0.4 when slid at speeds from 0.2 to 30 mm/s in a bath of phosphate buffered saline. [58] For general comparison, the friction coefficient of cartilage on cartilage is in the range of 0.001–0.05 [59,60], and in total knee arthroplasty, between the polyethylene and the femoral component, in the range of 0.03 and 0.10 [61].

The differences in all the above mentioned values stress out the need to compare mechanical properties of any material of interest against the native meniscus within the same experimental set up.

4. Meniscus implants and tissue engineering

In search of a clinical solution for meniscal lesions which are beyond repair and/or enduring symptoms after (partial) meniscectomy numerous materials have been investigated. Goal is to construct a permanent meniscal implant or a scaffold for meniscal tissue engineering. Aims of such a construct would be to relieve symptoms after (partial) meniscectomy, functional improvement, and in the long term to prevent the development of osteoarthritis. In the upcoming sections different materials will be discussed, focusing on materials used in order to replace the resected (section of the) meniscus, disregarding meniscal tear repair, cell seeding and tissue grafting techniques.

Polymers are macromolecules built up by the linkage of large numbers of much smaller monomers, and can be synthetically produced via polymerization techniques but can also found in nature. Their large molecular mass relative to small molecule building blocks and the ability to form mutual crosslinks provides them with unique physical properties. Crosslinking is a requirement to obtain the resilience associated with a rubber. The presence of a crosslinked network prevents polymer chains from irreversibly slipping past one another on deformation and allows for rapid and complete recovery from deformation. These unique properties make that polymers are widely used, from daily life (e.g. plastics) to scientific frontiers (e.g. tissue engineering). Due to the versatility in manufacturing possibilities specific properties can be tailored to meet demands in tissue engineering, such as biocompatibility, porosity, biodegradability, and mechanical characteristics [62]. Next, several natural occurring polymers are attractive for tissue engineering because they exhibit some outstanding characteristics

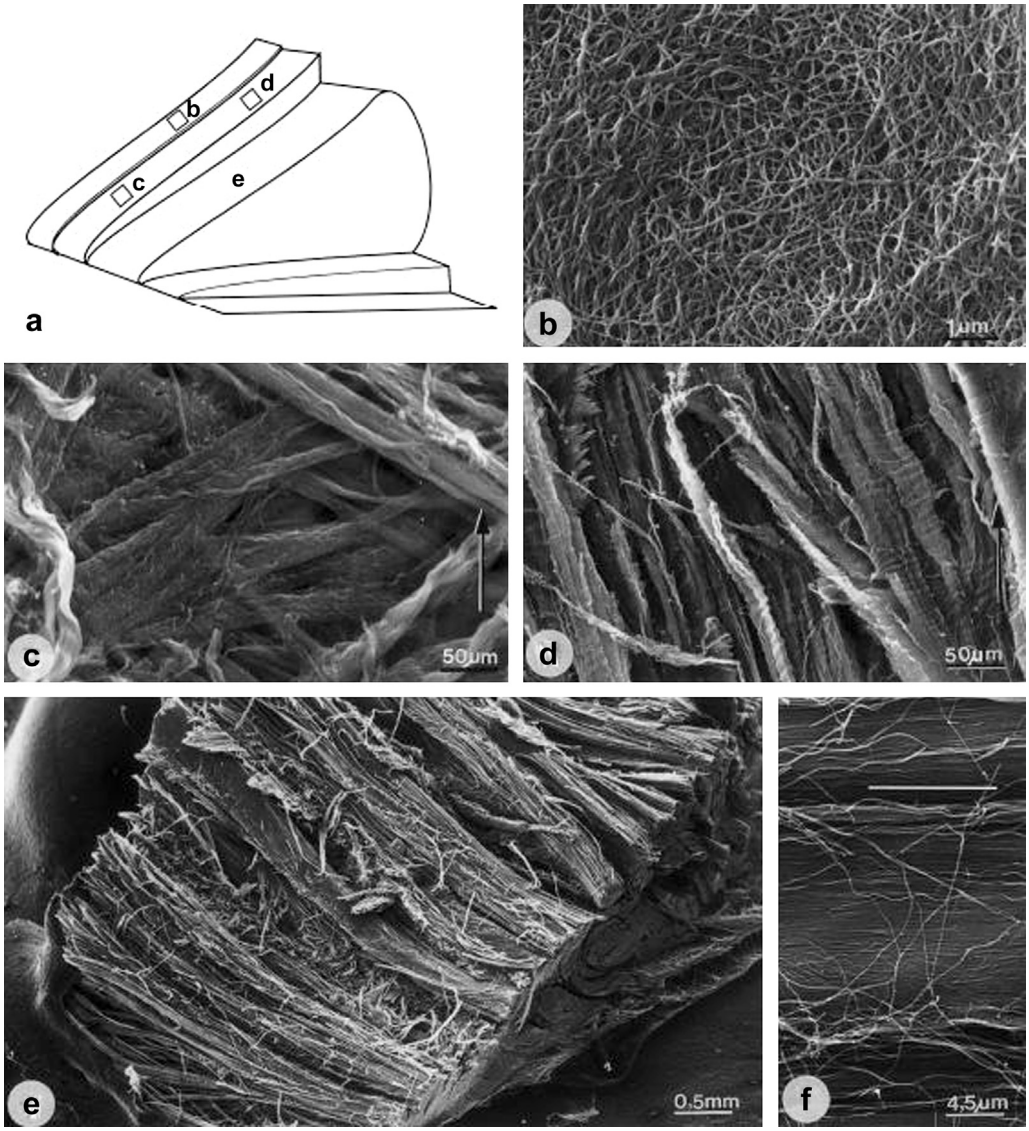

Fig. 3. Scanning electron microscopic results of collagen fibers. Scanning electron microscopic results. a Schematic drawing of a posterior segment of a medial meniscus that indicates the location of the following detail micrographs. b Meniscus surface, detail from the femoral surface (b in a). The meniscus surface is covered by a network of delicate fibrils with a diameter of approximately 35 nm. The fibrils do not show a preferred orientation. Male, 45 years. c Superficial layer of the femoral surface (c in a). The collagenous network of the meniscus surface has been removed mechanically. Collagen fibrils are arranged in tight, approximately 20–50-mmwide lamellar bundles and form a superficial fibril layer. In this area the fibril bundles intersect at various angles. The arrow points to the internal circumference. Male, 53 years. d Superficial layer of the femoral surface (d in a). The collagen fibrils run in a radial direction. The arrow points to the internal circumference. Male, 53 years. e Central main layer (e in a). The central layer forms the main part of the meniscus. In the entire meniscus the prime orientation of the collagen fibrils is circular in the external as well as in the internal circumferences. Female, 57 years. f Detail from the central main layer. The circular collagen fibrils are divided into small bundles by a network of thin fibrils. Female, 57 years (reprinted from Ref. [37]).

which to date researchers have not been able to mimic artificially. With respect to a meniscal substitute, two types of directions can be observed: first, the construction of a permanent prosthesis, and secondly to produce a scaffold which allows tissue ingrowth and is biodegradable, encouraging the body to replace its lost tissue.

5. Resorbable natural polymers

In the early 90's Stone et al started investigating on a resorbable collagen template for meniscal regeneration [63]. The rationale and basis for the use of these resorbable scaffolds was the pioneering work of Yannas et al in the replacement of human skin and the regeneration of nerves [64,65]. Collagen is a naturally occurring matrix polymer which is highly conserved across species. It is the predominant extra-cellular matrix component of most connective tissues within the mammalian body, comprising one third of all protein found within tissues. Collagens are part of the extracellular matrix and mainly caries out a structural role in which density, and orientation results in varying mechanical properties.

Purified type I collagen from bovine achilles tendon was used to fabricate a porous collagen meniscus, which was interspersed with glycosaminoglycan molecules [66]. The collagen fibers were ordered both circumferentially and radially, with the density of the fibers being substantially uniform in which the glycosaminoglycan molecules provided cross links between the fibers. With respect to biomechanical and anatomical properties, it was hypothesized that weight bearing would orient the newly formed collagenous fibers along the lines of stress, and that the initial ability of the swollen matrix to conform would allow it to be implanted, be attached, and adapt to the geometry required for the meniscus to provide joint stability without joint abrasion or disruption [63,67].

Early studies, both in vitro and in vivo, demonstrated the ability of this new implant to support new tissue ingrowth [63]. Based on preliminary results in dogs that, compared to (sub-) total meniscectomy, the scaffold was able to provide some degree of protection to articular cartilage damage, authors assumed adequate biomechanical functioning [63]. However, at final evaluation after 12 months, no such significant difference was observed [67]. Substantial meniscal like regeneration was noted in 63% of the joints implanted with the scaffold. Whereas meniscectomized controls spontaneously regenerated nearly complete menisci in 25% of the joints. This modest success made the authors suggest that effective meniscal regeneration can be stimulated by the implantation of the scaffold. Which led the way for commercially funded (ReGen Biologics, Redwood City, California) clinical feasibility trials in humans, in which the collagen scaffold was defect-sized and implanted after removal of only the irreparably damaged meniscal tissue and making sure that it reached the vascular zone [68,69]. Although limited, several implant characteristics were determined; the pore size ranged from 75 to 400 μm and the suture pullout strength averaged 2.5 kg. Results demonstrated that the scaffold formed a stable interface with the host meniscus rim, and that it progressively invaded and replaced by new collagen and cells typical of meniscal tissue. Immunological evaluation revealed no apparent immune responses to the collagen implant. The implant tissue construct shrank during the first weeks after implantation, and after 12 months remnants of the collagen scaffold were still observed while maturation process was ongoing. Authors concluded that feasibility was demonstrated. Next, a prospective randomized trial comparing the collagen meniscal implant (here called Menaflex; ReGen Biologics, Hackensack, New Jersey) with partial meniscectomy confirmed the ability to support new tissue ingrowth on the collagen graft [70]. Based on their results, authors concluded that the scaffold enhanced meniscal function as evidenced by improved clinical outcomes in patients with a chronic meniscal injury (patients who had undergone more than one prior surgical procedure on the involved meniscus). Within the acute patients (with no prior surgery on the involved meniscus) no such was observed. Critically, it has to be noted that improvement in clinical outcomes was apparent for both partial meniscectomy and the chronic collagen meniscal implant group. However, authors put emphasis on a larger regained activity as denoted by Tegner index in the chronic collagen meniscal implant group compared to the partial meniscectomy group; respectively 42% and 29% regained lost activity compared to pre injury. On the other hand, improvement in pain scores, patient self assessment scores, but also Lysholm functional scores were not different between the two groups. Other clinical studies have been adopted but lack a design of similar scientific quality [71–73]. Currently, the scaffold is named CMI (Collagen meniscus implant) and is distributed by Ivy Sports Medicine (ISM) (formerly known as ReGen Biologics). (Fig. 4) Overall, it is remarkable that although it has been shown to be feasible and safe to implant the collagen meniscal implant, it is only assumed that it will lead to better knee function and protect the articular cartilage from damage compared to partial meniscectomy. The observation that the implant is biomechanically stable (e.g. withstands the forces about the knee joint) doesn't automatically imply that it put forth adequate biomechanical properties. Moreover, the implant dependence on the peripheral vascularized rim of the native meniscus, may limits its usability. The longer follow up of the randomized clinical trial will offer interesting results.

Another natural occurring polymer applied in meniscal tissue engineering is Silk. Silks are fibrous proteins and are characterized by modular units linked together to form high molecular weight, highly repetitive proteins. These modular units or domains, each with specific amino acid sequences, provide specific functions. Mechanically, the toughness of silk fibers produced by spiders and silkworms are superior to synthetic fibers [74,75]. Although important insights into silk protein self-assembly have been achieved over the past decade the lack of full comprehension of processing steps has limited the ability to artificially create fibers with identical properties to those of native fibers [76].

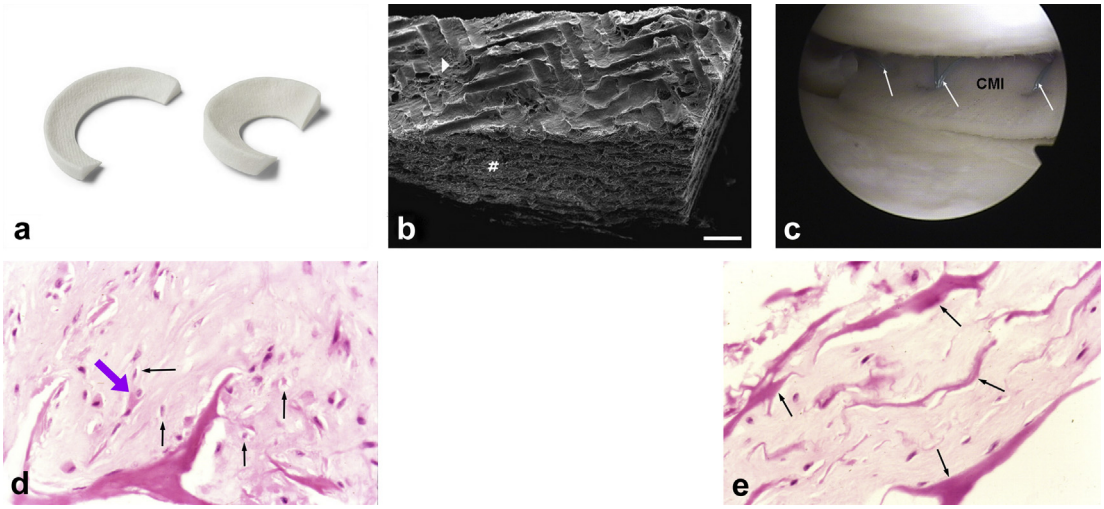

Fig. 4. The collagen meniscus implant. a) From left to right: Collagen Meniscus Implant (CMI®) Medial and Lateral, reprinted with permission of Ivy Sports Medicine GmbH. b) Scanning electron microscopy of the CMI. On the top surface (triangle) some regular cristae are interposed with herringbone grooves that are about 70 μm wide. The lateral surface (number sign) shows lacunae 60–90 μm wide, formed by collagen laminae interconnected by thinner fibrils (bar = 250 μm).(reprinted from Ref. [137]) c) The collagen meniscus implant (CMI) is sutured to the host meniscus remnant with non absorbable sutures (white arrows) and an inside-out technique. (reprinted from Ref. [70]). d) human biopsy specimen, obtained at one year, it can be seen that part of the collagen meniscus implant has been resorbed or assimilated into the new matrix. The arrows point to darker staining structures that are remnants of the collagen meniscus implant (hematoxylin and eosin; original magnification, ×100). (Reprinted from Ref. [70]) e) Human biopsy specimen, obtained at one year demonstrating meniscus-like fibrochondrocytic matrix production within the collagen meniscus implant. The collagen meniscus implant was integrated into this tissue as it was assimilated and/or resorbed (large purple arrow). Cells that appear to be meniscus fibrochondrocytes (small black arrows) are noted to be surrounded by lacunae, suggesting that they are viable and active cells (hematoxylin and eosin; original magnification, ×100). (Reprinted from Ref. [70]). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The outstanding mechanical properties as well as its demonstrated biocompatibility, versatile processability, and its use in studies of chondrogenesis were motivation for Mandal et al to use silk fibroin obtained from the *Bombyx mori* silkworm cocoons in meniscal tissue engineering [77]. (Fig. 5) A silk fibroin solution (9 w/v %) was obtained from cocoons after extracting the glue like sericin proteins and wax that bind the fibroin fibers [78]. By using a multilayered silk scaffold, composing of three individual layers with different pore sizes and orientations, authors aimed at aiding both cell migration (large pores) and aligned deposition of collagen and extra cellular matrix (smaller pores). Using freeze drying for the, bottom, third layer created pores ranging between 60 and 80 μm. Whereas salt leaching created pores in the range of 350–400 and 500–600 μm for the for the first and second layer respectively. Pores were highly interconnected, but the total percentage of porosity was not determined. The compressive modulus, determined via non confined testing on hydrated specimen at a rate of 5 mm/min, ranged between 294, 348 and 165 kPa for the first, second and third layer respectively. The tensile modulus, determined on hydrated specimen with 0.1% strain per second, ranged between 1.3, 1.4, and 0.23 MPa for the first, second and third layer respectively. Moreover, the individual layers supported robust cell growth with aligned meniscus like extracellular matrix deposition. Still, initial mechanical properties will have to be tailored to meet values comparable to the native human meniscus. Yan et al showed that it is possible to alter mechanical and structural scaffold properties by altering initial silk fibroin concentrations [79]. In which mechanical properties of the silk fibroin scaffolds increased with increasing silk fibroin concentration. However, in turn, porosity and interconnectivity decreases. In vivo studies will have to demonstrate the feasibility to manufacture and implant an anatomically alike scaffold. However, the group of Kaplan is currently focused more on how to treat the meniscal disorders than on further meniscus biomaterials strategies (personal communication). But, next to silk obtained from the *Bombyx mori* silkworm cocoons, another research group is exploring the usability of spider silk technology (Oxford Biomaterials Ltd, UK) for meniscal repair. Experimental studies are to be expected (http://www.onemedplace.com/database/list/cid/12315/).

Bodin et al proposed a gel of bacterial cellulose, grown statically in corn steep liquid medium, as an attractive material for consideration as a meniscal implant [80]. (Fig. 5) Cellulose is an organic polysaccharide consisting of a linear chain of several hundred to over ten thousand linked glucose units, and is an important structural component of the primary cell wall of green plants, many forms of algae and the oomycetes. Main arguments for the authors were that the material is inexpensive, can be produced in a meniscus shape, and promotes cell migration. The feasibility for implantation was explored using a pig model. Although inferior to the native pig meniscus (21 kPa), the compression modulus of the cellulose scaffold (1.8 kPa) at 10% strain was higher compared to the collagen meniscal implant (0.23 kPa). Detailed description of material characteristics is lacking.

6. Resorbable synthetic polymers

Already in the mid eighties Veth et al started research applying synthetic polymers for meniscal tissue engineering. Their aim was to provide a scaffold to replace the whole meniscus. Experience obtained in the search for a vascular prosthesis in cardiovascular surgery led them to the use of polyurethanes in meniscal tissue engineering.

Polyurethanes, all polymers that contain urethane, urea or other isocyanate derived functional groups, form a highly versatile class of polymers. The wide range of possibilities in synthesis gives rise to an equal wide range of. Segmented polyurethanes, one of the major group, can be considered as multiblock copolymers (made up of blocks of different polymerized monomer species) consisting of a

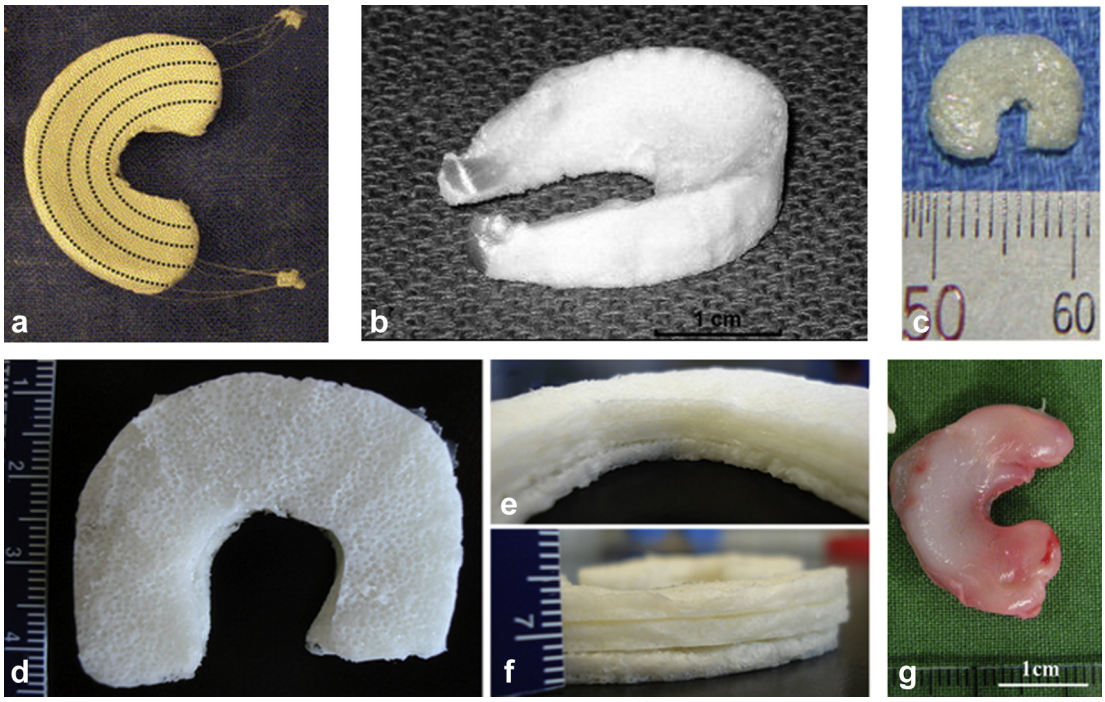

Fig. 5. Resorbable meniscus scaffolds. a) The PCL and HYAFF total meniscus scaffold augmented with circumferential PLA fibers (sheep model). (reprinted from Ref. [102]) b) Fiber weaved meniscus scaffold from bovine dermal collagen reinforced by a network of degradable tyrosine-derived polymer fibers to a ovine model. (reprinted from Ref. [110]) c) Meniscus-shaped PGA mesh scaffold of a rabbit model (The scale is in millimeter). (reprinted from Ref. [107]) d-f) Silk scaffolds with three stacked layers with different porosities (scale in centimeters). (reprinted from Ref. [77]) g) Meniscus scaffold composed of bacterial cellulose to a pig model. (reprinted from Ref. [80]).

hard and soft segment. Their properties are determined by the choice of this hard segment (a diisocyanate and an extender) and soft segment (usually a polyol).

Experience with Poly (urethane)-Poly (L-lactide) (PU-PLLA) as a scaffold for tissue engineering was obtained during the search for a vascular prosthesis in cardiovascular surgery. Studies had already demonstrated its biodegradability, biocompatibility, micro porous structure and elasticity related to its porosity. For meniscal tissue engineering grafts were prepared from 95:5 PU–PLLA which were reinforced with carbon fibers. In unconfined testing with hydrated specimen, the Young's modulus was 42.5 MPa and the elastic modulus at 2% compression was 11 kPa. Unfortunately, although tissue ingrowth was demonstrated, carbon particles induced synovitis. Subsequently, different series and compositions of polyurethane foams (PU-PLLA (with and without PLLA fiber reinforcement) and PU (Estane 5701 F)) were tested in dogs. It was concluded that larger macropores (200–300 um), high interconnectivity between macropores, and a high total pore percentage had a positive effect on cell and tissue ingrowth. Whereas PLLA fibers (tensile strength 0.5–1.2 GPa; Young's modulus 6–15 GPa) retarded both the degradation process and the ingrowth of fibrocartilaginous tissue [81–83].

Next, authors determined whether a PU scaffold (Estane 5701F) with improved structural properties (porosity 78%, compression modulus at 20% strain of 300 kPa) could be used as a scaffold. Tissue ingrowth was observed. However, even after 6 months of implantation, mechanical properties were still not comparable to that of the native meniscus, and although less compared to meniscectomized controls knees, damage to articular cartilage was not prevented. Notably, damage to articular cartilage was more prominent in the tibial plateau than in the femoral condyles, which might be explained by initial insufficient tribologic properties [84].

Further development and refinements of polyurethane foams followed, more so because Estane was thought to potentially release carcinogenic compounds upon degradation and concerns had raised over the relative fast degradation profile [85–87]. A polyurethane based on poly ε-caprolactone and 1,4 butanediisocyanate/1,4-butanediol was developed (PCLPU) [85]. In rats, this new scaffold showed faster tissue ingrowth compared to Estane scaffold [88]. Comparing the two scaffolds as substitute for a whole meniscus in dogs showed comparable results. Again, damage to articular cartilage was not prevented, which was observed more on the tibia than on the femur, and although compressive characteristics improved after tissue ingrowth they were still not comparable to the native meniscus [89]. A longer follow up study of 24 months demonstrated that, although not noticeably degraded in mass, the PCLPU scaffold was disintegrated by fragmentation. Differentiation into the typical organization of the native meniscus was not observed, lacking also specific collagen fiber orientation. Compression modulus of the implant was increased after tissue ingrowth but did not change from 6 to 24 months. However, in the light of scaffold fragmentation the authors suggested that stiffer tissue had formed over the time period. Damage to articular cartilage was observed, with similar patterns, but significantly more in comparison to meniscectomized control knees [90,91]. Initial insufficient mechanical characteristics, insufficient tribologic properties, and extrusion of the implant during loading were suggested as possible causes. Under while, the polyurethane implant became commercialized and named Actifit (Orteq Ltd, London, United Kingdom). (Fig. 6) In order to overcome at least part of the problems encountered during previous studies Orteq Ltd subsequently switched the implants main aim from total towards partial meniscal replacement [92].

A sponsored study about joint contact mechanism demonstrated that with the Actifit (porosity of 80% and pores that range in size from 150 to 355 μm): contact area increased and average and peak contact pressures decreased relative to the partly meniscectomized knee [92]. However, values were not restored to that of the intact native knee. To note, the scaffold was manufactured so that it was ±2 mm thicker than the native tissue, which led to a higher modulus and hence a better ability to carry and distribute loads across the plateau. Next, the Actifit implant was tested in vivo in an ovine meniscal defect [93]. No statistical differences were observed in damage to articular damage between scaffold and partial meniscectomy after 12 months. In contrast to Tienen et al [89] no specific damage of articular cartilage was observe underneath the

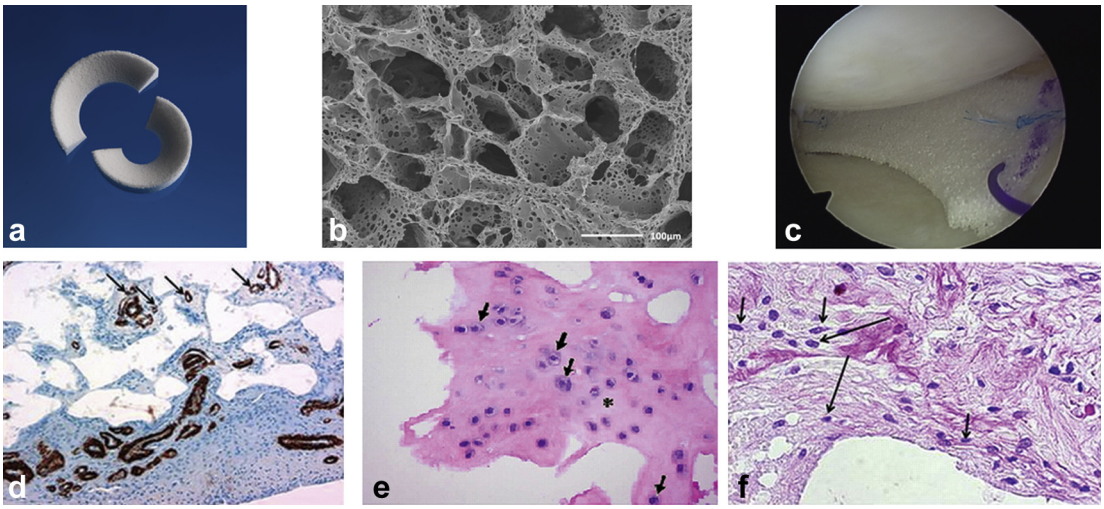

Fig. 6. The actifit meniscus implant. a) The medial and lateral Actifit® meniscus implant (reprinted with permission of Orteq Sports Medicine). b) Porous, spongy structure of the Actifit scaffold implant in a microscopic cross-section (reprinted from Ref. [138]) c) The Medial Actifit scaffold is sutured to the host meniscus remnant with nonabsorbable sutures and an inside-out technique (reprinted from Ref. [139]) d-f) Histologic Results From 12-Month Biopsy Specimens in human, biopsy from the center of the inner free edge of the implanted scaffold. 3 distinct layers were observed in the biopsy specimens. Going from the superficial area toward the center of the specimen: layer 1(d) consists of vascularized fibrous tissue (CD34 immunohistochemistry showing the presence of vessel "sprouts" (arrows)), layer 2 (e) consists of nonvascularized, hypercellular, loose collagenous tissue (Sirius red stain illustrating a loose extracellular matrix, and a mixture of fusiform fibroblast-like cells (short arrows) and more polygonal fibrochondroblast-like cells (long arrows)), and layer 3 (f) consists of immature cells in a nonvascularized immature and fibrinous tissue (hematoxylin and eosin stain showing chondroblast-like cells) (reprinted from Ref. [94]).

scaffold, but more in proximity of the midline of the joint. Comparing these two studies is not justified due to the different nature of the implant dimensions and fixation. However, damage to the articular cartilage in the central zone could also signal insufficient load transfer and the accumulation of peak stresses in the articular cartilage not covered by the implant.

Galley et al investigated the frictional behavior of the implant, before and after tissue ingrowth. Compared to native tissue the Actifit showed inferior initial frictional behavior which tended to normalize after tissue ingrowth [58]. The initial improper frictional behavior may in part be explained by the implants porosity which limits the ability to maintain a pressurized fluid film at its surface.

Recently, the first proof of principle study in humans was conducted. Using the scaffold in patients with an irreparable medial or lateral meniscal tear or partial meniscus loss with intact peripheral rim. The treatment objective was to provide pain relief and restore lost meniscus functionality. The study illustrated successful tissue ingrowth, and demonstrated biocompatibility [94]. Although the end product is different from the first initial aim, the bulk of research has significantly improved knowledge about meniscal tissue engineering. However, further (randomized) controlled clinical trials will have to show its superiority to other techniques and long term follow up is required to assess its chondroprotective effect.

Chiari et al developed a biomaterial consisting of hyaluronic acid and polycaprolactone (PCL) to serve either as a partial or a total meniscus substitute, and tested it in sheep. The scaffold was a porous composite of PCL and HYAFF®. The former is prepared by ring opening polymerization of ε-caprolactone and is subjected to biodegradation via hydrolysis (Fig. 5). Extensive in vitro and in vivo biocompatibility and efficacy studies had already been performed, which resulted in US Food and Drug Administration approval for its use in several medical applications [95–97]. PCL loses its molecular weight in vivo considerably slower than other aliphatic polyester but more importantly it loses its mechanical stability much earlier [98,99]. HYAFF (HYAFF® Fidia Advanced Biololymers – F.A.B Abano Terme, Italy) is a commercialized polymer obtained by esterification of hyaluronic acid with different alcohols [100]. It has been demonstrated to be biodegradable via de-esterification within 3–4 months [101]. Additionally, the PCL-HYAFF scaffold was reinforced with circumferential polylactic acid (PLA) fibers in the total meniscus substitute and with a polyethylene terephthalate (PET) net in the partial meniscal substitute. Pores of 200–300 μm were created via salt leaching. In vivo, after 6 weeks tissue integration and ingrowth was observed. Damage to articular cartilage was observed on both femur and tibia, and to a higher degree in the total meniscal substitute compared to the partial meniscal substitute, signaling implant(-ation) related causes. Moreover, implant extrusion as well as irregularities and wrinkles on the implant's surface were observed [102]. Insufficient biomechanical properties and fixation related problems of the implanted scaffold were supported by subsequent results at 6 months [103]. A foreign body giant cell response to the implant was observed, which was attributed as a part of the physiological resorption process. At 12 months follow up, implant dislocation, slight extrusion and wrinkling of the scaffold in the posterior region was again observed repeatedly [104]. Damage to articular cartilage was not prevented, but was less pronounced compared to meniscectomized controls. Unfortunately, biomechanical properties were not described throughout the subsequent publications. Whereas the unfavorable mechanical degradation kinetics of the PCL and the relatively fast degradation of HYAFF put significant interest in the mechanical behavior of the scaffold during implantation.

Poly (α-hydroxyacids), including poly (glycolic acid) (PGA), poly (lactic acid) (PLA), and their copolymer poly [(lactic acid) -co-(glycolic acid)] (PLGA), are widely used synthetic polymeric materials in tissue engineering [105]. These polymers are well characterized and have gained FDA approval for several applications (e.g., sutures and meshes). In line, these polymers have also been used in meniscus tissue engineering. Although the porous scaffold composed of PGA (95% porosity) demonstrated successful fibrochondrocytes seeding, mechanically it lacked sufficient properties (aggregate modulus of 2.6 ± 0.6 kPa after 5 weeks of culture) [106]. By physically bonding adjacent PGA fibers with PLGA mechanical properties could be improved [107], demonstrated by a 28-fold higher compressive modulus and a 50-fold higher yield strength of bonded meshes compared to unbonded meshes (239 versus 9 kPa and 75 versus 1.5 kPa respectively). Despite this reinforcement, in rabbits, scaffolds not seeded with cells demonstrated early partial degradation already after 36 weeks without signs of meniscal tissue regeneration. Therefore, biomechanical analyses were omitted. However, damage to articular cartilage was not prevented.

Pezzin et al used a blend of poly (L lactic acid) and poly (p-dioxanone) to produce a porous meniscus scaffold to replace the whole meniscus and tested it in rabbits [108]. The rationale for using these materials was not argued. Although results and scaffold characteristics were presented scarcely, authors dare to conclude that this bioresorbable scaffold allowed tissue ingrowth, induced fibrocartilage formation, had a significant protection of cartilage, and suggested that this material has great potential to be used as a meniscal prosthesis. However, a follow up study has not been published so far.

Disturbed by the long degradation time, but attracted by the mechanical properties of poly (lactic acid), Esposito et al synthesized a poly (L-co-D,L-lactic acid) (PLDLA) copolymer. This polymer had similar mechanical properties to poly(lactic acid) but a faster degradation profile [109]. To enhance interaction with cells and tissues the polymer was additionally made more hydrophilic via the addition of poly (caprolactone-triol) (PCL-T). The subsequent PLDLA/PCL-T (90:10) polymer, with a compressive modulus of 9.5 ± 1.0 MPa (strain rate 1 mm/min), was implanted in rabbits. Notably, authors determined the modulus in the first linear region (toe region) of the stress strain curve. However this region was only linear up to a strain of 0.3%. The subsequent, second region, estimated between strains of 2% up to 35%, showed a significant lower modulus. With the disappearance of a foreign body granulomatous response at 24 weeks the authors assumed complete polymer degradation between 12 and 24 weeks. Damage to articular cartilage was assessed only by determination of the amount of chondrocytes in the hyaline cartilage of femoral condyles, which showed favorable higher amounts in implanted groups compared to meniscectomized knees. Further scaffold development and more elaborate in vivo experiments are necessary to demonstrate its ability to be suited as a meniscal scaffold. Currently, the authors are evaluating a terpolymer scaffold and the effects of seeding with mesenchymal stem cells (personal communication).

Balint et al developed a resorbable meniscal scaffold in which emphasize was put on the tensile mechanical behavior [110]. They used a continuous fiber of a degradable tyrosine-derived polymer, poly (desaminotyrosyl-tyrosine dodecyl ester dodecanoate), which was weaved in a quasi circumferential three dimensional pattern, and subsequently enclosed and crosslinked with a 1% w/v acid-insoluble bovine dermal collagen dispersion (Fig. 5). Collagen was chosen for its unique biochemical and mechanical properties, its high cellular affinity, and opportunities to adjust structural properties. The fiber was chosen for its relatively high ultimate stress and low modulus of elasticity. Testing different fiber compositions demonstrated that the tensile load, generated in the scaffold in response on axial loads across the knee joint, increased with

increasing fiber density (e.g. continuous fiber length). Stiffness of the scaffold containing 90 m of continuous fiber was comparable to the native medial ovine meniscus. Authors hypothesized that the increase in tensile stresses may decrease compressive loads on the tibial plateau, protecting the cartilage from damage. Further in vivo testing in a large animal model would be required to determine feasibility and its effect on articular cartilage.

7. Non resorbable synthetic polymer

One of the first research papers reporting on a permanent meniscus substitute using polymer based materials was by Toyonaga et al in 1983. They used a Teflon (polytetrafluorethylene (PTFE)) net made out of fibers which was subsequently folded and rolled into a cylinder and finally inserted into the knee joint of dogs. Teflon (DuPont) is a commercial polymer formed by the polymerization tetrafluorethylene, it has a high molecular weight and is hydrophobic. Compared to any other solids, Teflon has a very low coefficient of friction [62]. Implementing the Teflon implant, folded and rolled into a cylinder, did not prevent damage to articular cartilage although it seemed less compared to meniscectomized controls. Authors suggested that the lateral extrusion of the implant was in part responsible for these disappointing results. Moreover, a transient inflammatory response to the Teflon fibers was observed. Most probably, mechanical and tribologic properties of the folded implant were not in line with native tissue. The limited processability of the material at the time may have impeded further research.

Sommerlath et al evaluated a permanent prosthesis consisting of dens wove Dacron (Polyethylene terephthalate, PET) felt with a polyurethane coating, provided by Stryker inc, in rabbits [111]. (Fig. 7) Rationale for product design was not provided. Dacron is a commercial polymer and its fibers have outstanding crease and abrasion resistance. Polyurethanes had been used as coatings to improve abrasion, tear and impact resistance [62]. Whereas tissue ingrowth did not seem a problem upon implantation, synovitis was observed repeatedly, and, although less compared to meniscectomy, the implant was not able to prevent damage to articular cartilage. Dacron tissue demonstrated a lower stiffness when compared to the native meniscus. Authors suggested sizing related issues as well as inferior material characteristics as reasons for the disappointing results. Changing size of the Dacron implant did however not reduce damage of articular cartilage, nor the occurrence of synovitis. Moreover, compressive results were more close to the native meniscus with Teflon instead of Dacron implants [112]. Subsequently using a Teflon felt prosthesis showed that it was prone to wear, resulting in debris formation and synovitis [113]. Moreover, the prosthesis lost its shape soon after implantation. Coating it with a polyurethane was not able to prevent synovitis, nor damage to articular cartilage [114]. Although unsuccessful, even an autologous periostal graft coating was used with the mechanical superior Teflon prosthesis in attempt to improve its strength and wear. After these disappointing results, use of these materials in meniscal implant constructing was omitted.

Kobayashi et al developed an artificial meniscus using poly (vinyl alcohol) hydrogel (PVA-H) which had been studied earlier as an artificial cartilage substitute and already demonstrated biocompatibility [115]. (Fig. 7) Hydrogels are polymer networks capable of absorbing and retaining large amounts of fluids. The properties of hydrogels are determined by their monomer composition, crosslinking density, and polymerization conditions [116]. Due to crosslinking the polymer remains insoluble in solution. Poly (vinyl alcohol) has a relatively simple structure and is produced by the polymerization of vinyl acetate to poly (vinyl acetate), followed by hydrolysis to poly (vinyl alcohol). The high water content and elastic characteristics of hydrogels give them the ability to mimic human tissue. Kobayashi et al used poly (vinyl alcohol) hydrogel with a water content of 90% and with a degree of polymerization of 17500 and cross linked and crystallized it at low temperature. The implant was tested in rabbits, replacing the whole lateral meniscus. In a 2 year follow up study they demonstrated that their implant was not able to prevent damage to articular cartilage but was able to reduce its progression compared to meniscectomy. Mechanical compression testing was performed, demonstrating that the samples of human menisci had a lower modulus of elasticity than that of the hydrogel, although exact numbers were not provided [117–120].

After these fair results in small animals another research group subsequently assessed the PVA-H (Salumedica, Inc, Atlanta, Ga) as a meniscal substitute in a larger animal, performing a ovine animal experiment [121]. Its functioning in situ was compared to sham operation, allograft implantation and meniscectomy. Remarkably, complete radial tears were observed in the posterior aspect of all implants at 1 year, signaling insufficient mechanical properties. Other then MRI data, in contrary to 2 and 4 months, no detailed histological information on cartilage was denoted at 12 months.

Although less in comparison to meniscectomy, the hydrogel implant was not able to prevent damage to articular damage which was apparent already after 4 months. The degree of damage was comparable to that observed in the allograft implant group. However, in contrary to the allograft, the hydrogel implant showed more damage to the articular cartilage in the periphery underlying the hydrogen implant. This observation was emphasized by MRI results at 1 year in which, next to wear in the central margin of the joint, marked wear of cartilage and osteophyte formation over the peripheral margin of the knee was observed. Insufficient intrinsic mechanical properties of the meniscal implant, insufficient fixation of the implant causing excessive movement, and improper tribologic properties of the implant surface may have contributed to both implant failure and increased articular damage. Further development and reinforcement of the PVA-H scaffold seems

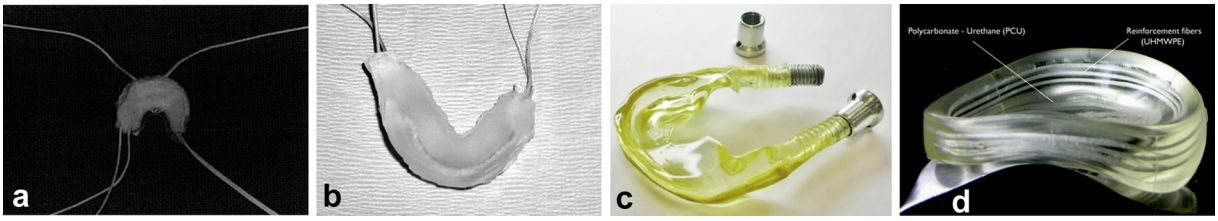

Fig. 7. Non resorbable meniscus implants. a) The meniscal prosthesis made of Dacron with polyurethane coating in which the sutures are attached to the horns and to the central part of the prosthesis. (reprinted from Ref. [111]) b) Hydrogel meniscus construct with sutures woven through the construct for anterior and posterior horn attachment (reprinted from Ref. [121]) c) Polycarbonate-urethane meniscal implant, with the stainless steel fixation bolt in the unfastened and fastened state (reprinted from Ref. [123]) d) The Nusurface meniscal implant composed of a polycarbonateurethane PCU matrix, reinforced with circumferential polyethylene, PE fibers. (reprinted from Ref. [124]).

necessary before it can be used as a meniscal implant. Holloway et al demonstrated the possibility to improve mechanical properties of the PVA-H by varying freeze thaw cycles, which increases crosslinks, and addition of fibrous reinforcement with polypropylene and ultrahigh molecular weight polyethylene [122]. The compression modulus reached 0.24 ± 0.03 MPa after six cycles of freeze thawing, and fibrous reinforcement increased the tensile modulus from 0.23 MPa without any reinforcement to 8.2 and 258.1 MPa with 10% polypropylene and 29% ultrahigh molecular weight polyethylene, respectively. Currently Holloway et all are optimizing the design of their implant before commencing ovine studies in early 2014 (personal communication).

Zur et al tested an artificial Polycarbonate-urethane (Bionate 80A, Polymer technology Group (PTG-DSM), CA, USA) meniscal implant in a study which was supported by Active Implants Corporation [123]. (Fig. 7) Bionate® is a thermoplastic elastomer formed as the reaction product of a hydroxyl terminated polycarbonate, an aromatic diisocyanate, and a low molecular weight glycol used as a chain extender. These polyurethanes have been broadly used in the medical device industry because of their combination of outstanding physical properties, in vivo biostability, and biocompatibility. The PCU meniscus implants were reinforced circumferentially with Kevlar fibers (DuPont) embedded in the peripheral rim of the implant to mimic the oriented collagen network of the native meniscus. Authors evaluated the effects 3 and 6 months after implantation in sheep. The main aim of the study was to test the hypothesis that the implant could provide a chondroprotective effect on the cartilage. Statistical differences in damage to articular cartilage between the implant and non operated control stifles were not observed, but this seems merely a statistical power issue regarding the limited number of animals used per time point ($n = 3$). Moreover, macro and microscopical analysis were only described for the inner tibial and femur cartilage, omitting the cartilage underlying the implant. Although the animal experiment had several limitations and critical questions regarding the implant remained unanswered, a clinical trial was started. However, not before the meniscal implant was re-designed for this purpose, by using finite element modeling and experimental validation in a cadaver knee [124]. (Fig. 7) Instead of rigid trans tibial fixation, the implant (now called Nusurface meniscal implant, Active Implants) became free floating (not fixated) and embedding circumferential polyethylene fibers (elastic modulus 98 GPa). It was demonstrated that this meniscal implant can redistribute loads in a similar pattern to the natural meniscus under static axial conditions. Interestingly, the compression of the implant, composed solely of PCU, resulted in relatively large distortion of the implant and peripheral extrusion. Reinforcement with circumferential fibers was able to decrease this distortion, it reduced circumferential expansion under load by ±95% to ±2 mm. Redistribution of loads resulted in such forces that integrity of the material and its reinforcement fibers was not at risk.

Viscoelastic properties were determined using the whole implant after simulated use in a knee model [125]. Under low compressive loads, the implant was fairly flexible, and able to deform relatively easily, attributed to the mechanical properties of PCU. With a strain of only 2% the modulus was in the range of 0.92–1.31 MPa. However, although the applied load was not described for this strain, it will have been well below 150N. During physiological vertical loading of 1500N, simulating normal gait, a strain of 60% was observed, and the modulus was in the range of 2.61–3.08 MPa. This increase in stiffness was attributed to the straightening of reinforcement fibers. Authors state that their implant has an agreeable modulus at 2% strain with the native meniscus as reported by Chia and Hull [53]. However, this comparison is tricky to make. Chia and Hull observed these similar compressive modulus at a physiological strain rate of 12%, which in their experiment was the estimated strain of the native meniscus during physiological loading [126]. Thus, a more valid comparison would have been to compare these values with compressive modulus observed during the vertical loading of 1500N. During this load the implant displays high resistance to strain, and demonstrate a 2–3 fold higher modulus, showing that the implant is stiffer then the native meniscus. A non-randomized, single group assignment, safety study is currently recruiting patients (ClinicalTrials.gov Identifier: NCT01712191). Notably, the implant is intended for the medial side only. The design offers several interesting features and we await clinical results with interest.

The group of Buma and van Tienen are developing an anatomically shaped, non-resorbable total meniscus substitute by using a thermoplastic elastomer [127]. Authors aim for an implant suitable to replace the severely damaged meniscus in the knee joint with starting osteoarthritis, in which it should be chondroprotective, relieve pain and stabilize the knee joint. An animal experiment is scheduled to assess implant performance under long-term loading conditions together with its chondroprotective capacity.

8. Discussion

Many attempts have been made to construct a substitute to replace, a part of, the irreparably damaged meniscus. To date, only the meniscus allograft has found its way into clinical practice as an substitute, but merely to pursue short-term benefits in the symptomatic young aged patient using tailored patient selection criteria [128–130]. Moreover, next to inherent limitations (e.g. availability of donor tissue and sizing problems [131,132]), concerns do exist over the longevity of the allograft and it remains unknown whether it reduces the risk of progression of osteoarthritis. Which creates the need for a new meniscal substitute.

The main goal of the this substitute will depend on its target population, and will aim for: (1) reducing the risk for developing osteoarthritis in, young, patients with a acute traumatic irreparable meniscal lesion with no signs of damage to articular cartilage; (2) relieving enduring symptoms and preventing or delaying the progression of damage to articular cartilage in patients who already underwent a, partial, meniscectomy; (3) relieving enduring symptoms and delay the progression of, symptomatic, osteoarthritis in patients with irreparable degenerative meniscal pathology and signs of damage to articular cartilage. Grossly, two categories of substitutes are brought forward. First, a resorbable scaffold which depends on the tissues capacity to populate the scaffold and organize itself in such a way that a new meniscal tissue is formed while slowly degrading. Second, a non resorbable, permanent implant which mimics the biomechanical function of the native meniscus. So far, research has not led to a substitute able to completely prevent damage of articular cartilage after meniscectomy in animals. On the other hand, several have demonstrated reduced damage to cartilage compared to that observed after total meniscectomy. Overall. it is remarkably that the gross of the literature is concerning biodegradable tissue engineered solutions, whereas there has been only relatively little effort in the design of a permanent implant.

Further elaborating on the basic requirements for a meniscal substitute set forth by Stone et al [68], the following requirements can guide meniscal tissue engineering. **(1)** The initial mechanical properties should resemble that of the native meniscus as close as possible, the compressive modulus should be in the range of 75–150 kPa, and the tensile modulus should be in the range of 75–150 MPa. More accurately, there is need to compare mechanical properties of the material of interest against the native meniscus within the same experimental set up. A too stiff construct will

impede ingrowth of fibro-cartilaginous tissue and might even directly cause damage to the articular cartilage, whereas a too pliant construct will insufficiently transfer load and increase peak stress accumulation. The latter may show good short term results on clinical symptoms, but will likely provide less optimal long follow up results up on damage of articular cartilage. Interestingly, the ability to process a non linear elasticity regime in the scaffold would increase the resemblance to its native counterpart. **(2)** The initial tribologic properties should resemble that of the native meniscus as close as possible, we assume that a friction coefficient of $\leq$0.05 should be pursued. As such it will aid in the prevention of early abrasion and joint disruption until the new organized tissue produces its own surface zone proteins. This may either be achieved by reducing the porosity of the scaffold at its surface by which it will able to maintain a pressurized fluid film at its surface and/or by adding lubricating and/or anti adhesive substances, like lubricin, to its surface. **(3)** If the construct is to mimic the shape of the meniscus then the size should mimic its native counterpart as closely as possible. Most preferably, the substitute will be custom made taking into account the specific anatomic boundaries of its host. If the latter is not feasible, choosing one out of a range of pre sized products may be an alternative only if respecting a size of $\pm$10% of the native meniscus [131]. Here, it is advised to select a transplant that is slightly larger rather than too small. Under sizing will lead to increased stress on the construct making it susceptible for failure. Whereas over sizing will increase peak forces across the articular cartilage. Shrinking or size alterations of the construct in situ should either be intrinsically prevented or taken into account during size determination. **(4)** The material and its degradation products used should be non-cytotoxic or carcinogenic. **(5)** The scaffold should allow cell adhesion and provide a framework for restoration of vascular, cell and matrix elements. **(6)** To promote tissue ingrowth the scaffold should have large macropores ($\pm$200–300 μm), high interconnectivity by smaller micropores ($\pm$10–50 μm), and a high total percentage of porosity ($\pm$70% or higher). Embedding an anisotropic architecture of these pores can guide extracellular matrix deposition to mimic its native counterpart [133]. Although most authors describe high interconnectivity based on visual μCT images, the μCT data can also be used to quantify this interconnectivity. The latter through assessment of its accessible pore volume, which is the volume that can be reached from the outside of the imaged scaffold by simulating the permeation of a spherical particle [134]. The limitation of porosity is that it inversely influence the scaffolds' mechanical properties, this will have to be taken into account on material selection and synthesis. **(7)** The degradation profile should take long enough time for adequate tissue ingrowth and organization in such way that itself can provide mechanical support. Too fast degradation, losing the framework before adequate tissue ingrowth and organization, will have more deleterious effects than too long, in which a remaining skeleton provides additional mechanical support. A surface degradation profile (in which size and mass of the scaffold decrease in time, whereas molecular weight and mechanical properties of the polymer itself remain unchanged) is more attractive compared to a bulk degradation profile (in which polymer chain scission occur throughout the specimen, losing its mechanical properties before its mass, but retaining its external dimensions until disintegration at a critical time point). The time available for total degradation is critically linked to tissue formation and organization, we advise a surface degradation profile of at least 12 months. **(8)** The surgical technique should be as minimal invasive as possible, preferably via arthroscopy. Moreover, we recommend that this aim should be adopted in animal related experiments as well. Because we believe that the surgical procedure by open arthrotomy itself is a risk factor for damage to articular cartilage. Surgical fixation techniques should allow for rigid enough fixation to be able to withstand extrusive forces and the generation of hoop stresses during loading, on the other hand limited movement of the scaffold should be allowed to meet the knee joints' dynamics during flexion. Next, the implementation of both a randomized sham and an allograft receiving group during the animal experiment, in which the scaffold is tested for its chondroprotective properties, is necessary to be able to put observed changes in articular cartilage into perspective. **(9)** Although beyond the scope of the current review, cell seeding, the addition of growth factors and mechanical stimulation during scaffold processing offer interesting future perspectives as they might accelerate tissue organization before and after implantation [135].

Concerning non degradable permanent implants, the guidelines are less comprehensive, mainly because they do not depend on tissue ingrowth and degradation. Here, most important is that the implant is non-cytotoxic, intrinsically stable and mimic the biomechanical and tribologic function of the native meniscus as close as possible (as mentioned earlier). The implants should be able to transfer loads over the knee joint and prevent the accumulation of peak stresses. Merely the displacement of the peak stresses itself will likely contribute to a relief in experienced symptoms. If the implant aims to mimic the anatomy of the native meniscus, then the same requirements as mentioned before apply as well.

9. Conclusion and future directions

Although many biomaterials have been used in the search of a meniscal substitute, none have demonstrated its chondroprotective effect in humans. The first human clinical trials are currently enrolled and their results are looked out for with great interest. However, it is to be expected that scaffold and implant properties will have to be optimized. With different products emerging on the medical market, all with commercial interests, the need for unbiased randomized clinical trial will arise in the near future. Even earlier, an independent study uniformly testing and comparing mechanical characteristics off all scaffolds and implants currently available would be highly valuable.

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