Arch Orthop Trauma Surg (2013) 133:95–109
DOI 10.1007/s00402-012-1624-2

ARTHROSCOPY AND SPORTS MEDICINE

Meniscus reconstruction: today's achievements and premises for the future

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Received: 27 April 2012 / Published online: 18 October 2012

Abstract Injuries of the meniscus remain a burden for the development of premature cartilage degeneration and osteoarthritis. This review surveys all treatment options and focuses on the recent development of tissue engineering. Tissue engineering of the meniscus means a successful combination of cells, scaffolds and specific stimuli. Each element of the combination can be subject to variation. Studies investigating the optimum meniscus implant and previous steps in producing these implants are presented in this article. A comprehensive search of the English and German literature was performed in PubMed to retrieve appropriate manuscripts for review. Based on the literatures, autografts and allografts can delay the progress of osteoarthritis for a restricted time period, but several concerns persist. The biomechanical properties of the native meniscus are not copied entirely by the current existing autografts. Congruence, fixation, biocompatibility and potential infection will always remain as limitations for the users of allografts. Long-term results are still not available for meniscus prosthesis and even though it permits fast recovery, several aspects are questionable: bioincompatibility and a lack of cellular adhesion are likely to compromise their long-term fate. Currently, there is no ideal implant generated by means of tissue engineering. However, meniscus tissue engineering is a fast developing field, which promises to develop an implant that mimics histological and biomechanical properties of the native meniscus. At present several cell sources and scaffolds have been used successfully to grow 3-dimensional constructs. In future, optimal implants have to be developed using growth factors, modified scaffolds and stimuli that support cellular proliferation and differentiation to regenerate the native meniscus more closely.

Keywords Meniscus · Prosthesis · Tissue engineering · Scaffold · Collagen

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Introduction

A variety of pathological disorders, such as congenital anomalies, inflammatory disorders, metabolic disorders, degenerative conditions and tumours all lead to the loss of integrity of the meniscus [1]. Traumatic conditions of meniscal disorders are the most common leading to reconstructive procedures.

The biomechanical importance of the meniscus as a stabilizer and shock absorber in the knee joint has been outlined by several authors [2–6] and the necessity of saving the integrity of this organ has also been

demonstrated [7–9]. Once the meniscus is injured partially or in total, a complex inflammatory response occurs within the joint. A damaged meniscus may cause progressive chronic joint degeneration and osteoarthritis (OA) [10–15].

Meniscectomy may be beneficial in reducing the acute symptoms of a meniscus lesion such as pain, swelling and mechanical blockade of the joint [16], but several chronic syndromes are likely to present later on [17–19] including chronic pain, biomechanical malfunction of the knee, malalignment of the limb [20], quadriceps atrophy [21, 22], instability of the joint [23].

For two decades, to minimize the inevitable degeneration of the joint following meniscectomy, experimental and clinical studies have been striving to find a safe substitute for an irreparably torn meniscus. Autografts, allografts, prosthesis and lately, tissue engineered constructs which were generated with the use of a combination of cells, engineering and materials methods, and suitable biochemical and physio-chemical factors, provided the main option of treatment, but so far the long-term benefit is only evident for fresh frozen meniscus transplantation following total meniscectomy and mainly for the lateral meniscus [24, 25]. Still, the failure rate for the lateral meniscus transplantation is reported to be 20 % [26]. Some benefits from a collagen meniscus implant have been reported for chronic lesions after 7 years. However, tissue engineering has potential in the future curing one of the most common sports injuries, as the use of allografts remains limited.

The intention of this review is to present all the options of meniscal implants together with their benefits and shortcomings. Possible substitutes for meniscal tissue, including autografts, allografts, prosthesis, cell therapy and tissue engineering are presented and summarized. However, this discussion focuses primarily on engineering the meniscus, which is divided into three parts: cells, scaffolds, and culture conditions.

Methods

A comprehensive search of the English and German literature was performed in PubMed using Endnote X3 (Thomson Reuter Inc., Carlsbad, USA) to retrieve appropriate manuscripts for review. The keywords used were meniscus, autograft, allograft, prosthesis, engineered, cells, stem cells, BMSC, MSC, fibroblasts, scaffold, collagen, synthetic, stimulation, factors, growth, mechanic, hypoxia. When these searches were combined, more than 500 abstracts were extracted. Keywords were used in 2- to 4-words combinations to provide the references for each chapter. Each one was reviewed and papers were obtained if the abstract was relevant to the review.

Anatomy and function of the menisci

The menisci are a pair of "C" shaped and semicircular fibro-cartilage that perform important functions in the knee joint. Both the medial and lateral menisci play roles in weight bearing, tibia-femoral joint stabilization (especially in the ACL-deficient knee [27]), load transmission, joint congruency improving, rotation of the opposing articular surfaces enhancement, and the improvement of lubrication and nutrition in the articular cartilage [27–30].

The lateral meniscus is more mobile compared with medial one. It may displace up to 11 mm with knee flexion. This may explain why meniscal injuries occur less frequently on the lateral side. The posterior horn of the lateral meniscus is attached to the meniscofemoral ligaments. And the central region of the lateral meniscal posterior horn was attached to popliteomeniscal fascicule [31, 32]. Normally, the meniscofemoral ligaments or the popliteomeniscal fasciculi may not be restored when lateral meniscus transplantation is applied, which may bring negative biomechanical consequences [33]. In contrast, the medial meniscus is attached firmly to the coronary ligaments and the deep medial collateral ligament. In addition, the medial meniscus is attached to the capsule circumferentially [34].

Meniscal fibrocartilage is rich in circumferentially- and radially-oriented collagen fibrils and extracellular matrix proteoglycans [35, 36]. In normal condition, physiological load of several times body weight appears within the knee, 50–100 % of which can be transmitted by menisci [37, 38] through its dense network of circumferentially aligned collagen [11, 14, 39, 40].

Autografts

Autografts derived from the fat pad [41, 42], tendon [43–47], cartilage [46], periosteum [48], synovial flap [6, 49, 50] and perichondrium [51] were used to reconstruct the meniscus. However, satisfactory results were reported rarely (Table 1).

Fat pad

Kohn et al. [52] replaced the medial meniscus with autogeneous fat pad in 15 sheep after meniscectomy. The medial half of the infrapatelar fat pad in each sheep was removed and used to replace the medial resected meniscus of the same sheep. All sheep were operated by the same surgeon. The implant was sutured with non-resorbable thread to tibia in the posterior intercondylar area and to the joint capsule. Another five sheep had their medial menisci resected without any replacement. Six months after the implantations all knees had developed osteoarthritis (OA) and after 12 months the grafts had disintegrated. The joint

Table 1 Studies with autograft meniscal substitutes

Authors	Autograft	Type of study	Study period
Milachowski et al. [42]	Fat pad	Clinical	12 months
Kohn et al. [52]	Fat pad	Experimental, in vivo	6 months
Kohn et al. [45]	Tendon	Experimental, in vivo	12 months
Kohn et al. [44]	Tendon	Clinical	12 months
Lecumberri et al. [46]	Tendon	Experimental, in vivo	24 weeks
Johnson and Feagin, Jr. [43]	Tendon	Clinical	9–24 months
Pressel et al. [47]	Tendon	Clinical	4–17 years
Lecumberii et al. [46]	Articular cartilage	Experimental, in vivo	24 weeks
Walsh et al. [48]	Periosteum	Experimental, in vivo	12 months
Cisa et al. [49]	Synovial flap	Experimental, in vivo	48 weeks
Yamazaki and Tachibana [6]	Synovial flap	Experimental, in vivo	16 weeks
Bruns et al. [53]	Perichondrium	Experimental, in vivo	12 months

cartilage only seemed to be protected due to the autograft for a short period of time. It was concluded that the fat pad is not an adequate resource for replacing the meniscus.

Tendon and cartilage

Lecumberri et al. [46] investigated patellar tendon and cartilage that were used as meniscal implants in rabbits. In one group, after total medial meniscectomy, a strip of patellar tendon was implanted replacing the original meniscus. In the other group, a fragment of cartilage was implanted the same way. The existence of meniscal regeneration after total meniscectomy and the behavior and integration of implants after meniscoplasty were investigated. Another 15 rabbits with meniscectomy only served as controls. All three groups showed development of fibro-cartilaginous tissue within 6 months. It was concluded that meniscal regeneration happens and the tendon and cartilage could be used for substitution of meniscus. A clinical study by Johnson et al. showed in five patients after a follow-up of 9–24 months that the semimembranosus tendon is by far not an ideal substitute [50]. In their study, there was minimal or no clinical improvement and the joint surface deteriorated. In the study of Pressel et al. [22], 34 patients accepted meniscus replacement by autogenous quadriceps tendon was investigated. Results were compared with menisc-ectomised knees or meniscal allografts reported in the literature. X-rays showed in most cases a clear or severe osteoarthritis of the knee. Clinical and radiological findings demonstrated similar results in comparison with meniscectomy. It was also found that meniscus replacement with quadriceps tendon was inferior to meniscal allografts. Even though, patients after meniscal allograft transplantation also show increasing degenerative changes of the respective joint.

Periosteum and synovial flap

Walsh et al. [48] proved, in an experimental study in New Zealand rabbits, that periosteal grafts are not satisfactory source for meniscus reconstruction, as ossification of the graft and accelerated joint degeneration occurs within 12 months compared with controls who had meniscecto-mies. Several experimental studies have reported promising results with synovial flaps as a meniscal substitute. Cisa et al. [49] tried to repair the meniscus in 44 rabbits using a pedunculated synovial flap. After 48 weeks, healing with vascularisation of an originally avascular zone was observed in 75 % of the experimental animals.

Perichondrium

Bruns et al. [51, 53] investigated meniscus replacement with perichondral tissue in sheep. After 3 months, the new tissue resembled the native meniscus in size and shape. The orientation of collagen fibres and cell characteristics were similar to native tissue. All perichondral menisci had central areas of a cellular differentiation similar to hyaline-like cartilage but were associated with areas of central calcification. No cartilage degeneration was observed in the implant-group except one, but in controls the phenomenon occurred. Inferior vascularisation and mechanical properties were observed compared with the native meniscus; however, the results were superior compared with knees that were treated with meniscectomies.

Allografts

Allograft transplantation of the meniscus is now a widespread treatment option for knees that are subjected to total or near total meniscectomy. The current indications for meniscal transplantation are [26] as follows:

- Total meniscectomy with early arthritis.
- Loss of anterior cruciate ligament.
- Concomitant osteotomy.
- Prophylactic transplantation.

In the patients with severe degenerative changes in the knee joint, accompanied by radiological changes like femoral condyle flattening or marked osteophyte formation, meniscal transplantation is considered to be contraindicated. In addition, instability, malalignment and history of infection in the knee joint should not be included in the list of candidate [26].

However, there is no common opinion on the benefits of allografts transplantation. Even though decellularized meniscus scaffold remained functional with maintenance of biomechanical properties [54], and meniscus allografts show good short term clinical results (less pain and better functionality) [55], but the following shortcomings do exist:

- Graft processing weakens the biologic, chemical and mechanical properties [56]
- Costs of processing and storing are high [57].
- Potential transmission of infectious disease [58].
- Difficult sizing and potential incongruence [59, 60].
- Immunological reactions [61, 62].
- Shrinkage [63].

In a study using human cadavers, meniscal allografts did not restore the normal contact mechanics at the time of implantation, but there was an improvement when compared with meniscectomy without meniscal substitute [64]. In order to have acceptable knee contact parameters, the meniscal allograft needs to be in the range of 10 % smaller or larger than the original meniscus [59].

Evaluation of transplanted meniscal allografts on animal models was done as well. Normally, lyophilized, gamma-sterilized and deep-frozen meniscal transplants were utilized. Milachowski et al. [65] investigated such meniscal allografts in a sheep model. Uneventful capsular healing was observed 6 weeks after transplantation. Same animal model was used in the study of Aagaard et al. [66]. They found the ingrowth of the transplants in only 50–75 % of the periphery in three specimens. The menisci tended to extrude peripherally towards the capsule, with the suture anchor being partially pulled out especially in the posterior horn. In addition, changes in tissue consistency, colour, and shape were seen in some of the transplanted menisci. On the whole, it can be announced that the healing of meniscal allografts has been found, but degenerative changes are observed in the meniscal tissue itself.

Clearly, variables such as animal species, graft geometry and size matching, allograft material properties, restored joint kinematics, and surgical transplantation technique will play an important role in the overall success of the procedure, and future studies may be directed at optimizing these parameters to improve surgical outcome.

Prosthesis

Various types of meniscal prosthesis have been tested but most of them obtain unfavorable results (Table 2). Messner et al. [67] implanted meniscal prosthesis in 22 rabbit knees. The groups consisted of meniscal prosthesis made from Dacron® coated with polyurethane, Teflon® coated with polyurethane, and uncoated Teflon®. These were compared with knees which had meniscectomy alone. Similar articular cartilage degeneration was observed in both prosthesis group and meniscectomy group. The same study group tried to obtain better results by covering Teflon® with a periostal flap [68]. This prosthesis was implanted in rabbit knees and it was compared with autologeous transplanted meniscus and untreated controls. Despite healing and good integration, substitution of the medial meniscus with artificial–biological grafts or autografts failed because of form changes of the substitutes, which were especially discovered at the attachment sites. In the prosthetic group, knees had osteoarthritic changes and synovitis, which were similar to knees undergoing meniscectomy only.

Cell therapies

The procedure of injecting mesenchymal stem cells (MSCs) selected from bone marrow (or simply bone marrow stromal cells—BMSCs) obtained by bone marrow aspiration may be a very useful tool for the healing of an injured joint. Agung et al. [71] showed some encouraging results regarding mobilization and differentiation of MSCs in a damaged knee joint of the rat (anterior cruciate ligament, meniscus and cartilage damages). They used two groups of rats: within each group the injured knee joint was compared with the contralateral healthy knee joint. Both joints in each group were treated either with 1 million or 10 million cells. Using fluorescence markers and immunohistochemistry, it could be proven that the group with an injured knee injected with 10 million cells, had MSCs recruitment that fostered tissue regeneration that included meniscus regeneration. Histology showed an extracellular matrix around the cells and chondrogenic differentiation was promoted. Unfortunately, the injected cells generated scar tissue and free bodies, a factor that limits its clinical application.

Table 2 Studies with prosthetic meniscal substitutes

Authors	Type of prosthesis	Type of study	Study period
Messner et al. [67]	Dacron® coated with polyureande, Teflon® coated with polyureande and uncoated Teflon®	Experimental, in vivo	3 months
Messner [68]	Teflon® covered with periostal flap	Experimental, in vivo	3 months
Kobayashi et al. [41, 69]	Poly-vinil-alcohol hydrogel (PVA-H) with a high grade of polymerisation and 90 % water content	Experimental, in vivo	24 months
Verdonk et al. [70]	Actifit (polyurethane scaffold)	Clinical	24 months

Platelet rich plasma therapies

Platelet rich plasma (PRP) can influence the cell microenvironment for meniscal regeneration

Platelet rich plasma may provide a valuable tool by which the cell microenvironment may be manipulated to enhance tissue regeneration. Ishida et al. [72] reported that meniscal cells cultured with platelet rich plasma displayed enhanced proliferation as well as an increased extracellular matrix synthesis. They also presented evidence that in vivo, rabbit meniscal defects treated with gelatin hydrogel associated with PRP showed an improved healing with the repair tissue that histologically resembled the inner part of the meniscus. On the contrary, a study by Zellner et al. [73] revealed no significant improvements when PRP was used with a hyaluronan-collagen composite matrix for treatment of similar defects.

Meniscal regneration by application of platelet rich plasma

For the meniscal regeneration, the application of PRP is still in its infancy. However, studies evaluating the effects of PRP on regenerating cartilage defects may provide important insight. Sun et al. [74] treated full thickness osteochondral defects with autologous PRP loaded poly (lactic-co-glycolic acid) (PLGA) scaffolds in a rabbit model and observed a qualitative and quantitative enhancement of the new cartilagenous matrix formed. This is in addition to an increased volume of the subchondral bone as opposed to the control defects. Furthermore, in a sheep model, Milano et al. [75] demonstrated that PRP used in conjunction with microfractures as intra-articular injection resulted in the formation of a more mechanically competent repair tissue that was histologically well-differentiated. In the latter study, the authors showed that although the regenerated cartilage tissue was of superior quality, it was not hyaline. Owing to the fact that the meniscus is fibrocartilagenous, PRP could be greatly beneficial for the treatment of meniscus lesions. Wu et al. [76] showed that PRP provided an ideal three-dimensional support as cell carrier for chondrocytes when used for intra-articular injections in rabbits. The use of PRP allowed the technique to be micro-invasive and increased the precision of the in vivo procedure.

Tissue engineering

The old and new frontier in medicine is the engineering of artificial organs in vitro or in vivo: tissue engineering. Laurencin et al. [77] defined tissue engineering as "the application of biological, chemical, and engineering principles towards the repair, restoration or regeneration of living tissues using biomaterials, cells, and factors alone or in combination". In orthopaedics and trauma surgery, this area has developed with impressive speed over the last decade. A great number of studies are focusing on creating artificial organic substitutes for injured menisci, bone and cartilage defects and even injured ligaments or tendons. An engineered meniscus is the result of a successful combination of cells, matrix and specific stimuli (media, cytokines, physical stimuli) [17]. There are two main options for achieving this goal:

- Implantation in vivo of an acellular matrix and migration of cells from the periphery;
- Cell seeding on the matrix in vitro with further tissue maturation in vivo.

Cells

The main cell sources for tissue engineering of meniscus are meniscal cells (fibro-cartilaginous cells) or MSCs [78]. Staining with the monoclonal antibody in meniscal cells confirmed their mesenchymal origin [79]. MSCs obtained from bone marrow aspiration are also named BMSCs [78], which can differentiate along multiple lineages such as osteoblasts, chondrocytes, adipocytes, and hematopoiesis-supportive stroma [78]. Other cells with similar properties are adipose derived stem cells (ADSCs) [80].

Differentiated cells have been used for meniscus regeneration as well, including fibrochondrocytes, chondrocytes, synovial membrane cells, fat pad cells and even allogenic chondrocytes (Table 3). But there is still no consensus concerning the best cell resource for the regeneration of meniscus.

Zellner et al. [73] investigated the role of BMSCs in tissue engineering of the meniscus in a rabbit model. BMSCs were seeded in hyaluronan-collagen scaffolds and implanted into punch defects in the avascular zone. After 12 weeks, meniscus-like repair tissue was observed. Marsano et al. [81] studied human inner meniscus cells, fat pad cells, synovial membrane cells and articular chondrocytes (AC). Results showed only AC generated tissue contained relevant amounts of glycosamonoglycan (GAG) and cell phenotypes compatible with those of the inner and outer meniscus regions. The other investigated cell sources formed tissues resembling only cells of the outer region of the meniscus. The ability of grafts based on AC to reach the complex structural and functional organization typical for meniscus tissue still has to be determined.

Weinand et al. [82] seeded articular and auricular chondrocyles as allogenic or autogenic chondrocytes on a vicryl mesh scaffolds for 9 days and implanted to repair bucket-handle lesions of the avascular zone of meniscus in the swine model. After 12 weeks, menisci were harvested and evaluated. Complete or partial healing was observed in the autogenic and allogenic group, and there were no significant differences. However, no healing was seen in the control group.

Scaffolds

There is a very broad variety of scaffolds, ranging from synthetic to biological materials (Table 4).

Stone et al. [99] defined the basic requirements for scaffolds used to reconstruct the meniscus as follows:

- Biocompatibility.
- Physical shape similar to that of the normal meniscus or an ability to be shaped at the time of implantation.
- Porous structure that would facilitate cellular ingrowth.
- Initial mechanical strength suitable for fixation.
- Permeable to macromolecules.
- Initial in vivo stability in function as a template.

One other prerequisite for an ideal scaffold is the creation of optimal pore geometry and pore interconnectivity to facilitate tissue ingrowth and simultaneously to ensure adequate mechanical proprieties. The study of Klompmaker et al. gives a clear recommendation concerning these aspects [15]. This research group could demonstrate that the macropore size must be in the range of 150–500 μm diameter to have complete ingrowth and incorporation of partial or total meniscus prosthesis. The volume percentage of macropores was 48–55 % and total pore volume was 84–86 %. Buma et al. [103] alluded to the need for large interconnectivity between macropores to facilitate cellular and vascular penetration.

The scaffold used in engineering meniscus can be classified into non-collagen matrix and collagen matrix.

Table 3 Types of cells used for the engineered meniscus

Authors	Type of cells	Differentiation	Scaffold	Type of study
Marsano et al. [81]	Chondrocytes, meniscal inner cells, synovial membrane cells, fat pad cells	TGF-β1, PDGF-BB, FGF-2	Pellet culture and hyaluronan-based scaffold	In vitro and in vivo
Kon et al., (2012)	Chondrocytes	TGF-β1	Hyaluronic acid/ polycaprolactone	In vivo
Weinand et al. [82]	Allogenic and autogenic chondrocytes	–	Vicryl mesh	In vitro and in vivo
Aufderheide and Aandasiou [83]	Fibrochondrocytes	Mechanical stimulation	Poly (glycerol adipate) polymers (PGA)	In vitro
Kang et al. [84]	Allogenic fibrochondrocytes	–	PGA-PLGA	In vitro and in vivo
Martinek et al. [85]	Fibrochondrocytes	–	Collagen meniscal Implant (ReGen Biologics, Inc.)	In vitro, and in vivo
Zellner et al. [73]	Bone marrow stem cells	–	Hypaluronan-collagen scaffold	In vitro, and in vivo
Mandal et al. [86]	Fibroblasts and chondrocytes	TGF-β3	Silk	In vitro
Saliken et al. [87]	Bone marrow stem cells and meniscus cells	TGF-β1	Pellet culture	In vitro
Cui et al. [88]	Bone marrow stem cells and meniscus cells	TGF-β3	Pellet culture	In vitro
Matthies et al. [89]	Bone marrow stem cells and meniscus cells	Different oxygen tension	Pellet culture	In vitro

Table 4 Types of scaffolds used for the engineered meniscus

Authors	Type of scaffold	Type of study	Study period
Aufderheide and Aandasiou [83]	PGA	Experimental, in vitro	7 weeks
Stewart et al. [90]	PGA	Experimental, in vitro	39 days
Ionescu et al. [91]	Polycaprolactone (PCL)	Experimental, in vitro	8 weeks
Kang et al. [84]	PGA-PLGA	Experimental, in vivo	36 weeks
Tienen et al. [92]	Polyurethane-based polymers	Experimental, in vivo	6 months
Yan et al. [93]	Silk fibroin	Experimental, in vitro	30 days
Gastel et al. [94]	Collagen matrix—small intestinal	Experimental, in vivo	24 weeks
Welch et al. [95]	submucosa (SIS)	Experimental, in vivo	6 months
Tan et al. [96]		Experimental, in vivo	1 month
Stone et al., Rodkey et al., Steadman et Rodkey [97–99]	Collagen-glycosaminoglycans (GAGs) matrix	Clinical	2–6 years
Zaffagnini et al. [100]	Collagen matrix	Clinical	6–8 years
Reguzzoni et al. [101]	Collagen matrix	Clinical	6 months
Martinek et al. [85]	Collagen matrix	Experimental, in vitro and in vivo	3 months
Pabbruwe et al. [102]	Collagen matrix	Experimental, in vitro	40 days

Non-collagen matrix

AufderHeide and Athanasiou [83] showed that a non-woven polymer made from polyglycolic acid (PGA, Albany International Research, Mansfield, USA) can be efficiently seeded with cells. Fibrochondrocyte cell numbers in this culture increased 22 times compared with cells that were grown in an agarose scaffold after 7 weeks. A greater production of GAG and collagen type I and III was seen within the PGA scaffold compared with agarose. The modulus of agarose was better than that of PGA at all measured time intervals: 1, 5 or 7 weeks. The mechanical tests showed that modulus of PGA decreased with the time. The authors conclude that this effect was a result of the non-biodegradability of agarose and biodegradability of PGA rather than that of extracellular matrix (ECM) production. The cells in agarose exhibited reduced synthesis of ECM compared with PGA.

Tienen et al. [92] reported a biodegradable polymer meniscus scaffold that was made from estane. The scaffolds were implanted unseeded in knees of dogs after meniscectomy. Knees with meniscectomy alone served as controls. Regeneration was based on the idea that synovial membrane would provide cellular ingrowth and the periphery of the meniscus will provide vascularisation. After 3–6 months the synthetic matrix was completely infiltrated by fibrovascular tissue, later additionally with fibro-cartilaginous tissue and was completely integrated with its periphery. The implant was firmly attached to the capsule and the popliteal tendon was moving freely, but in three cases the popliteal tendon entered in the joint space and damaged the meniscal implant. Abundant matrix consisted mainly of collagen I, and later it progressed to collagen II and proteoglycans. Slight inflammatory reaction with macrophages and giant cells was observed and this was interpreted as a result from the implant, but no clinical signs of inflammation were seen. Unfortunately, the implant was not capable of stopping degeneration of the articular cartilage. No improvement was seen compared with the controls. Biomechanical properties were clearly inferior to native meniscus. The authors speculated that in the long term the implant would improve its biomechanical properties and therefore would be a means to limit cartilage degeneration.

The same authors [104] compared the behaviour of two different polyurethane-based scaffolds: estane (BF Goodrich Chemical NV, Belgium) and an aliphatic 1,4-butane-diisocyanate based polyesterurethane (PCLPU). They were implanted unseeded in the knees of dogs according to the protocol mentioned previously. After 6 months, no differences regarding tissue regeneration were seen. Both groups developed a "meniscus-like tissue" which was more fibrotic in the periphery and cartilaginous centrally. The compression curve was similar in both types of implants with some improvement with time but still a long way from the compression curve of the native meniscus. A less intense immune reaction was seen in knees with PCLPU implants. In our previous study, the cellular compatibility of a novel polyurethane meniscus scaffold was investigated (Fig. 1) [105].

Mandal et al. constructed a novel meniscus scaffold with three silk layers with different pore sizes and orientations.

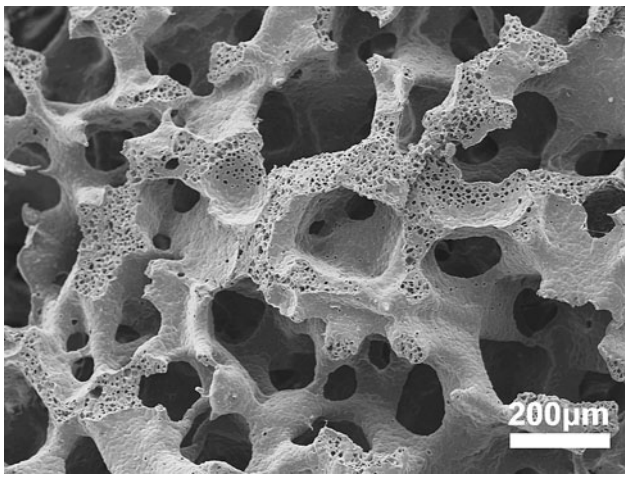

Fig. 1 SEM microphotographs of an 80/20 % poly(ε-caprolactone)/urethanes porous polymer meniscus scaffold with micropores (0.7–12 µm) and larger macropores (80–370 µm). This polymer scaffold is from a published study of our group

The scaffolds were seeded with fibroblasts and chondrocytes. In the presence of TGF-b3, cell-laden constructs increased in cellularity and the content of ECM. The chondrocytic phenotype was maintained according to high levels of sulfated glycosaminoglycans and collagen types I and II. And scaffold mechanical properties were improved along with ECM alignment with time in culture [106].

Collagen matrix

For two decades, it has been known that an artificial collagen matrix can support new tissue formation [107–109]. Cook et al. treated 29 dogs with partial meniscectomy of the posterior horn with unseeded small intestinal submucosa (SIS) matrix and compared them with 22 dogs with partial meniscectomy without further treatment [22]. The SIS group developed a more mature and better filling tissue with less articular cartilage damage after 6 and 12 months. There was no further progression of articular damage in the SIS group from 6 to 12 months. At 12 months the femoral articular cartilage in both groups proved to be less stiff than the contralateral unoperated knees. Histological assessments demonstrated that in the SIS group there was a better regeneration (meniscus-like tissue) after 6 and 12 months. Histological examination of the tibial and femoral condyles showed a wide range of appearances, from normal articular cartilage to severe erosive and degenerative changes.

According to the results, the authors concluded the following principles for the successful use of the scaffold:

1. The meniscal defect should extend to the vascular zone.
2. A source for initial clot formation should be present or created.
3. The SIS implant should be adequately stabilized in the meniscal defect.
4. The SIS implant or meniscus should be protected during the initial phases of healing.

Gastel et al. [94] obtained similar results in a study with 12 rabbits with a defect in the lateral meniscus which was treated with unseeded porcine SIS. The contralateral lateral menisci with a corresponding defect served as control. Gross appearance showed that shape, contour, consistency and colour of native meniscus had been reproduced and histological studies demonstrated the presence of meniscus-like cells and a good integration in the periphery of the remaining meniscus.

Contradictory results were obtained by Welch et al. [95] after porcine SIS was implanted for 6 months in dogs with 4 mm circular defects in medial meniscus. Each medial meniscus had two similar defects: one filled with SIS and other with no treatment. The regeneration of the meniscus was seen only in 4 out of 16 defects. In another three defects, immature fibrous tissue formation was found. The biomechanical properties, permeability and hydroxy-proline content did not differ statistically between SIS-treated and control defects. It was concluded that this implant did not promote tissue regeneration in induced meniscal defects.

The collagen meniscus implant (CMI) (ReGen Biologics Inc., Redwood, USA) is the first clinical application of a tissue engineered construct. Steadman, Stone, Rodkey et al. [97–99] made two pilot studies (phase I and II) in 10 and 8 patients respectively. The studies proved after 2, 3 and 6 years that CMIs are biocompatible through biopsy analysis (no immune reaction, cell conductivity and inductivity, new tissue formation and maturation, but slow integration), activity/pain evaluation and second-look arthroscopy confirmed the survival of the new tissue. However, some aspects of the study are concerning. MRI evaluation had shown a rapid shrinkage after 6 weeks. And one patient on the second trial had fragmentation of the posterior horn. Even if the gross appearance of cartilage after 2, 3 and 6 years showed limited cartilage damage or exuberant tissue growth, there are no long-term results available. In phase II, the clinical scores from 3 to 6 years showed no major improvement, even a slight decrease of the scores (especially pain). For future directives concerning CMI more studies with control groups are needed. There is a prospective, randomised trial underway that will give further insight to the usefulness of CMI. Also, it is not known if some other factors (like growth factors, or in vitro seeding of cells) can ameliorate the results.

Other prospective studies of CMIs in humans showed similar results [100, 101], but once again the histological status of the joint was not thoroughly analysed. 6–8 years

after implantation, patients showed mild or no effusion, good or very good joint stability, range of motions, pain scores and clinical scores (Cincinnati Knee Rating Scale) [100]. However, second-look arthroscopy proved that the implants had diminished in size. X-Ray and MRI examinations revealed no or slight increase in joint degeneration. Reguzzoni et al. [101] focused more on the morphological aspects of the implants in a small series of four patients, but only 6 months after implantation. The connective framework of the scaffold is still evident in biopsies. The invasion of the lacunae of the scaffold framework by vessels, fibroblast-like cells and connective tissue, as well as the absence of phagocytes and macrophages supports the biocompatibility of CMI material.

The experimental study made by Martinek et al. [85] showed that seeding the CMI scaffold before implantation shows favourable results compared with cell-free implantation. Autologous fibrochondrocytes were seeded and cultured for 3 weeks in CMI scaffolds and then implanted in meniscectomized knees in a sheep model. The medial meniscus was removed subtotally leaving 2 mm of a peripheral meniscal ridge intact. In the seeded CMI group there was less cartilage degeneration after 3 months than in the controls with meniscectomy only.

Culture conditions

An important aspect in the creation of the artificial organic meniscus is the influence of environmental factors such as perfusion with media, addition of specific growth factors, mechanical stimulation, possible vascularisation of the neo-tissue, level of oxygenation and specific properties of the scaffold. There is still limited knowledge of the influence of these factors on developing new tissue.

Growth factors

The accelerated proliferation of cells by growth factors can be a very useful tool in the complex process of engineering a meniscus (Table 5). Bovine meniscal cells from zones of the meniscus behave differently when they are stimulated with a range of cytokines [110]. The DNA synthesis in the cells of the outer meniscus was higher in the presence of 10 % serum in comparison with cells of the middle or inner meniscus. Recombinant human platelet-derived growth factor-ab (rhPDGF-AB), bone morphogenic protein-2 (BMP-2), hepatocyte growth factor (HGF) stimulated the DNA synthesis in all meniscal cells. Migration was stimulated by rhPDGF-AB and HGF in cells derived from all zones of the meniscus, while interleukine-1 (IL-1) stimulated migration only in cells from the outer meniscus. Epidermal growth factor (EGF) stimulated the migration of cells in the inner and outer zones and BMP-2 and insulin-like growth factor-1 (ILGF-1) stimulated the migration of meniscal cells from the middle zone. Gunja et al. [111] studied the effects of TGF-β1 on the ability of meniscus cells to produce ECM. TGF-β1 was found to increase collagen and GAG deposition in the scaffolds 15-fold and 8-fold, respectively.

Meniscal injuries treated with HGF and PDGF obtained better results than controls [112]. The synthesis of proteoglycans and collagen was higher in those groups. Cell number, migration, and alignment were superior. The study was made in vitro on meniscal explants.

Not only the type but also the concentration of an individual growth factor affects the results. However, up-regulation of extracellular matrix production in monolayer cultures of meniscal fibrochondrocytes can be obtained with transforming growth factor-beta-1 (TGF-β1) at either 10 or 100 ng/mL [113]. Basic fibroblast growth factor (bFGF), PDGF-AB and ILGF-1 at different concentrations were used in comparison. Similar results were induced by the same growth factors when meniscal fibrochondrocytes were cultured on PGA scaffolds [123]. Labels of (3H)-proline and (35S)-sulfate were used to measure uptake of collagen and glycosaminoglycan (GAG) components, respectively. TGF-β1 (10 and 100 ng/ml) aroused both productions of the components of collagen and GAGs, showing a dose-dependent response for both and a temporal response for GAG production. ILGF-I (5 ng/ml) and bFGF (25 and 100 ng/ml) showed an increase only in the synthesis of collagen components. PDGF-AB did not show notable increases. Considering the economical reasons, it was stated that TGF β1 at 10 ng/ml is the most effective growth factor and therefore it is recommended for use in scaffold-based approaches to tissue engineer the knee meniscus.

Petersen et al. [114] assumed that healing of meniscus tears in an avascular zone can be promoted by the local application of the angiogenic factor: vascular endothelial growth factor (VEGF). Unfortunately, such tears of meniscus did not show any improvement 6 weeks after refixation with a VEGF coated suture. TGF-β1 showed in Imler's study much more effective stimulation on bovine meniscus explants to produce proteoglycans and proteins compared with bFGF, ILGF-I or PDGF-AB, whereas bFGF was the least effective stimulator [115]. In a recent report, it was demonstrated that the combination of catabolic enzyme chondroitinase-ABC and TGF-β1 could enhance the biochemical and biomechanical properties of agarose scaffold seeded with articular chondrocytes and meniscus cells [124].

Gene transfer

Healing the avascular zone of the meniscus or improving the tissue engineering results may be supported by the transfer of genes encoding appropriate growth factors. Goto et al. [119] reported that the transfer of genes encoding TGF-β1 to

Table 5 Studied growth factors on the meniscal cells

Authors	Culture conditions	Studied effect
Bhargave et al. [110]	r-hPDGF-ab, BMP-2, HGF, IL-1, EGF, ILGF-I, serum	Proliferation, migration and alignment
Bhargave et al. [112]	HGF, PDGF	Citokynes diffusion, cell proliferation, migration and aligment, proteoglycan content
Pangborn et al., Gunja [111, 113]	Different concentrations of TGF-β1, bFGF, PDGF-A, B and ILGF-1	Collagen and glycosaminoglycan (GAG) components
Petersen et al. [114]	Vascular endothelial growth factor (VEGF)	Healing the tears in avascular part of meniscus
Imler et al. [115]	TGF-β1, bFGF, ILGF-I or PDGF-ab	Proteoglycans and total proteins
Shin et al. [116]	IL-1, mechanical stimulation	Total proteins, NO, and proteoglycan synthesis, pathways of modulation
Fermor et al. [117]	Tumor necrosis factor (TNF)-α, mechanical stimulation	Total proteins, NO, PGE2 and proteoglycan synthesis, pathways of modulation
Hidaka et al. [118]	Gene transfer encoding HGF	Blood vessel formation, histology, collagen and proteoglycan content
Goto et al. [119]	Gene transfer encoding TGF-β1	Collagen, non-collagen proteins and proteoglycans
Gunja et al. [111]	TGF-β1	Collagen and glycosaminoglycan (GAG) components
Fox et al. [120]	Basic fibroblast growth factor (bFGF), TGF-β1 and insulin-like growth factor (IGF-1)	Collagen and aggrecan
Riera et al. [121]	IL-1, TNF-α, TGF-β1	Cell proliferation
Baker et al. [122]	Mechanical stimulation	Cell differentiation and collagen component

meniscal cells was able to stimulate the matrix synthesis by these cells. In this study, the synthesis of collagen and proteoglycans could be increased 8–15 times. In addition, the TGF-β1 gene increased the synthesis of all types of collagen without altering the ratios between them and synthesis of non-collagen proteins showed a moderate increase.

It is known that the lack of vascular supply is associated with an insufficient healing response. Gene transfer using an adenovirus vector encoding the hepatocyte growth factor gene (AdHGF) was used to induce blood vessel formation in tissue-engineered meniscus with calf meniscal cells on a PGA scaffold [118]. Expression of marker genes and HGF was detectable after gene transfer for a limited period of time and the gene treated tissue contained fourfold more vessels than controls after 2 weeks following implantation of the constructs in subcutaneous pouches of athymic mice. Histology after 8 weeks showed the appearance of a fibro-cartilage, with abundant matrix and collagen and proteoglycan formation. Collagen fibres were less extensive and less organised than those observed in native menisci. This animal model provides an abundant vascular surrounding, but has a lack of biomechanical stimulation. This may explain the observed limited compressive strength (15 %) compared with the native meniscus.

Mechanical stimulation

Different mechanical stimulation protocols have been applied to obtain better proliferation, better differentiation of cells or higher amounts of ECM. Aufderheide and Athanasiou [18] applied mechanical stimulation on meniscus explants to analyse the ECM expression. Mechanical stimulation of 2 % oscillatory strain, 1 Hz, 4 h/day, was applied for 4 days to the explants. In medial meniscus samples, dynamic compression up-regulated aggrecan expression at 4 and 76 h by 51 %, but not collagen II expression, compared with static controls. No difference in gene expression was observed for lateral meniscus explants. In a previous study of our group, a cyclic compression of 10 % strain, 0.5 Hz, 4 times/days, 2 h/time was applied to polyurethane meniscus scaffolds laden with bone marrow stem cells. Results demonstrated that the proliferation of cells was enhanced by the mechanical stimulation (Fig. 2) [105].

Upton et al. [125] showed that the meniscus responds differently to static and dynamic compression, with selective inhibition of mRNA levels for the ECM proteins, decorin, types I and II collagen, but not biglycan, cytoskeletal proteins or aggrecan whose mRNA levels remained unchanged. The gene expression results presented by the authors also suggest that transcription of types I and II collagens as well as decorin, which is believed to play a structural role in stabilizing the collagen fibril, may be regulated by common mechanical stimuli. An analysis of mechanical stimuli at both the transcriptional and post-transcriptional levels is crucial for elucidating regulatory mechanisms in meniscal cells and their ability to maintain and repair the ECM.

Imler et al. [115] reported static mechanical compression shows inferior results compared to dynamic stimulation.

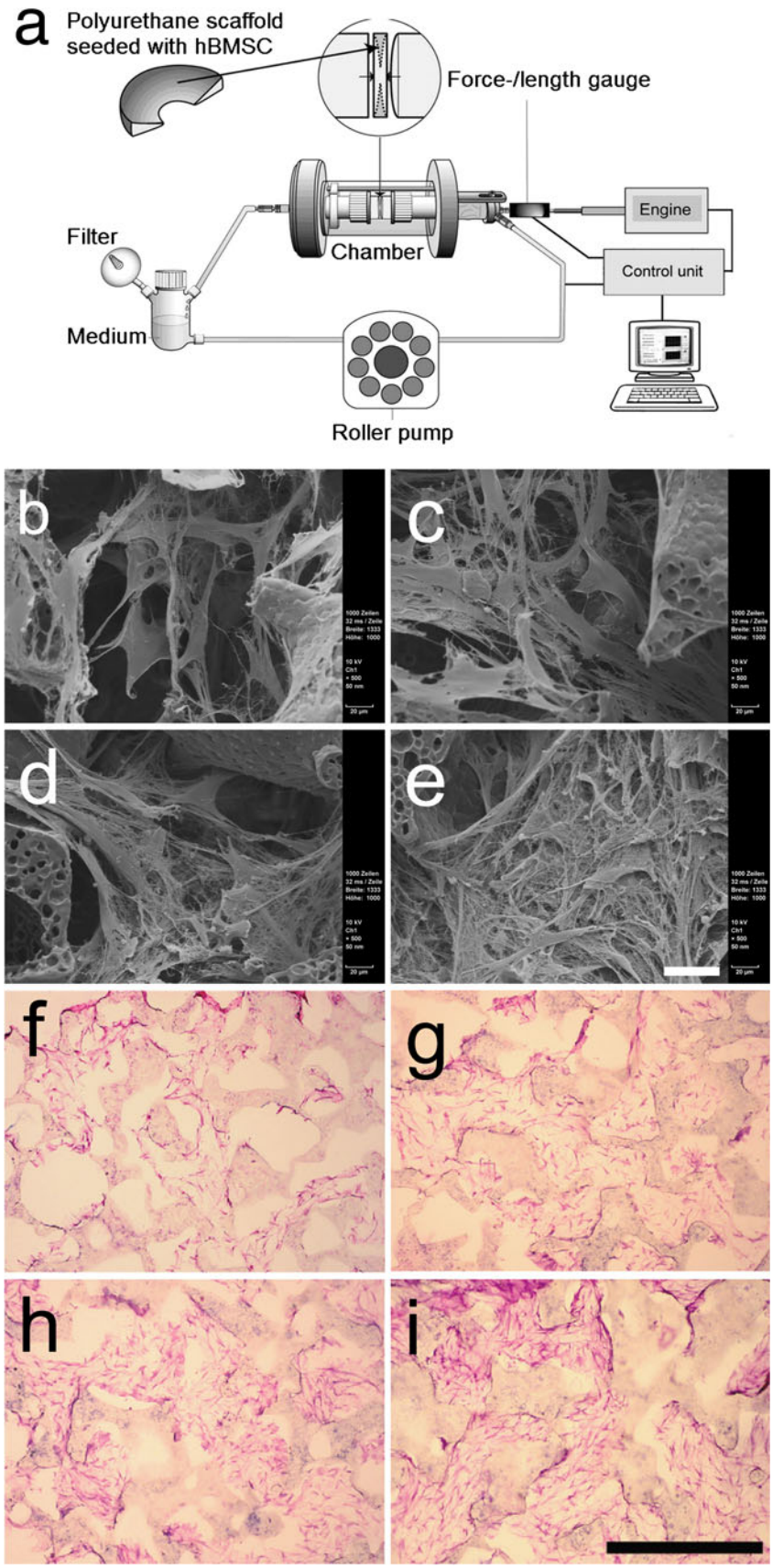

Fig. 2 Schematic shows the cyclic compression stimulation bioreactor system (**a**). SEM and HE staining graphs shown cell proliferation under static culture (**b**, **c**, **f**, **g**) and cyclic compression stimulation culture (**d**, **e**, **h**, **i**), which were obtained after 1 week (**b**, **d**, **f**, **h**) and 2 weeks (**c**, **e**, **g**, **i**). The parameter of cyclic compression: 10 % strain, 0.5 Hz, 4 times/days, 2 h/time. These figures are from a published study in our group. *Bars* are 40 (**e**) and 150 (**i**) μm

Static mechanical stimulation inhibits matrix production in the presence of each anabolic factor (bFGF, PDGF-AB, ILGF-I, TGF-β1). Mechanical stimulation in rotating wall culture could not enhance the matrix production compared with static culture when fibrochondrocytes were seeded on PGA or agarose scaffolds [83].

Bimen et al. investigated the effect of mix medium with different Reynolds number on alginate scaffold seeded with meniscal fibrochondrocytes. They found mix media stimulation could increase mechanical and matrix accumulation in constructs. The collagen accumulation and compressive modulus appeared to peak in Re 2.9 group [126].

Conclusion

Autografts and allografts can delay the progress of osteoarthritis for a restricted time period, but several concerns still persist. The biomechanical properties of the native meniscus are not reached by the current existing autografts. Congruence, fixation, biocompatibility and potential infection are limitations for the use of allografts. Long-term results are still not available for meniscus prosthesis and even though it permits fast recovery, several aspects are questionable: bio-incompatibility and a lack of cellular adhesion are likely to compromise their long-term outcome.

At present several cell sources and scaffolds have been used successfully to build 3-dimensional constructs, but to achieve the goal of engineering a meniscus that copies the properties of the native meniscus both histologically and biomechanically, better scaffolds, cell sources and cultivation protocols have to be found.

Acknowledgments This paper has been written entirely by the authors and was supported by "Deutsche Arthrosehilfe" and "Gesellschaft für Orthopädisch-Traumatologische Sportmedizin (GOTS)". Chaoxu Liu received financial support from the China Scholarship Council (CSC). Ionel Cristian Toma was supported by the Romanian Government and the Trauma Foundation.

Conflict of interest The authors declare that they have no conflict of interest.

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