# Clinical Studies Using Synthetic Materials for Meniscus Replacement

David D Lin BSc MBBS MRCS, Natasha E Picardo BSc MBBS MRCS, Adetola Adesida PhD, Wasim S Khan PhD

**Abstract**

Meniscal injury is a common problem among sportsmen and increasingly seen in the older more active population. The traditional treatment options include a partial meniscectomy, which provides good mechanical and pain relief to the patient. However, the focus of treatment is shifting towards repairing meniscal tears where possible and replacement of the lost meniscal tissue where appropriate. Replacement can be total or partial. Total Meniscal replacement using an allograft, is usually reserved for young patients, who meet certain criteria and who have undergone several subtotal menisectomies or a single stage total meniscectomy and are still symptomatic. Partial meniscal replacement can be utilized in conjunction with a partial meniscectomy to fill the resulting space left by the resection. Collagen based implants and biological scaffolds have entered the European market but have demonstrated mixed results in clinical trials. Tissue engineering to create an implant that mimics the biomechanical properties holds much potential for future research.

**Keywords**

## Introduction

The menisci are semilunar discs of fibrocartilaginous tissue, which play critical roles in knee joint biomechanics. They are primarily composed of an interlacing network of collagen fibres (predominantly type 1 collagen) interposed with cells and an extracellular matrix (ECM) of proteoglycans and glycoproteins [1].

The collagen fibres are orientated circumferentially from the anterior horn insertional ligament to the posterior horn insertional ligament and help to absorb energy by converting axial loading forces across the joint into hoop stresses within the tissue. There are also radial fibres, which prevent longitudinal splitting of the circumferential fibres [2]. In this way the menisci, which were once thought to be a functionless embryonic remnant, are now known to increase joint congruency and absorb shock to optimize force transmission across the knee. This means that the load imposed on the knee joint during daily activities is dissipated and therefore lower energy is transmitted to the chondral surface, reducing biomechanical wear. The menisci also provide lubrication and nutrition to the knee joint and act as secondary stabilisers, taking over as primary stabilisers in the ACL deficient knee.

The blood supply to the menisci holds important implications for the potential healing of a meniscal tear. Supply is from the periphery via the medial and lateral geniculate arteries. A cadaveric study has revealed that only the peripheral 10-25% of the meniscus actually receives a blood supply in the mature skeleton [3]. Two zones exist which are known as the red-red vascular zone in the periphery and the white-white avascular zone centrally. These zones are separated by a red-white region, which has attributes from each zone. The clinical implications are that tears involving the white zone are unlikely to generate a healing response.

With an ageing population and an increased focus on higher physical activity, preservation of joint health is increasingly important. The mainstay of treatment of meniscal tears that have not responded to conservative management has hence been a partial meniscectomy with resection of the torn meniscus to a stable border. This procedure is successful in alleviating the mechanical symptoms of locking and instability and also reduces pain. It does however predispose the knee to further chondral damage

and accelerated osteoarthritis [4,5]. Meniscal repair is another treatment strategy but the main obstacle here is the degree of vascularization and the eventual development of immunological reactions caused by the introduction of biomaterials [6].

Research into biomaterials has been undertaken to replace or repair meniscal tears. Biological scaffolds are protein-based extracellular matrices, which usually derive from human or animal connective tissues. Their advantages include optimum integration into host tissues and high porosity but limitations include inflammation, which can lead to implant rejection, low mechanical properties and degradation [7].

In this review, we will first consider the current widely used treatment options in the form of conservative based therapy and then the surgical options. We will consider the evidence for popular surgical management in the form of meniscectomies and meniscal repair. We will then introduce the concept of meniscal substitution and consider the current strength of evidence supporting the two available partial meniscal replacement therapies and allograft total meniscal replacement. Finally we will touch on some of the biological therapies in preclinical trials.

**Current treatment options for meniscal tear**

The management of meniscal tears is unique to each patient. A myriad of factors should be considered before treatment is offered. These can be considered as patient specific, surgeon specific or factors related to the nature of the tear itself.

Patient factors like age, existing knee joint stability, weight, current mobilization requirements for activities of daily living and likely compliance to post rehabilitation instructions are crucial in the decision making process. Surgeon related factors take into account the experience of the surgeon in meniscal repair or replacement. Complex surgeries like meniscal repair/ replacement will only be performed routinely in high volume centres to ensure best patient outcomes.

If surgery is considered, the nature of the tear itself is important. Surgeons should consider the zone of injury (red-red, red-white, white-white), stability and type (radial/ horizontal/ longitudinal) before deciding on the form of surgery offered. Meniscal repairs

for example tend to be offered to patients with vertically orientated tears in the peripheral zone.

The financial costs of meniscal replacements will also influence whether they can be offered to patients as hospitals might not be able to afford these costly implants estimated at almost 2000 Euros per unit.

The treatment offered is hence dependent on a combination of all the above factors. In the acute setting, conservative management in the form of immediate rest/ ice and compression with elevation of the injured limb combined with suitable NSAID based analgesia is almost universal.

Subsequent physiotherapy focusing on range of movement exercises and knee stabilization exercises are also important and should be part of the management of every meniscal injury. Physiotherapy without subsequent surgery seems to provide a satisfactory clinical outcome in stable, longitudinal lesions that are less that 1cm in length and occur in the vascular zone. It is also recommended in patients older than 45 years with degenerative lesions. A Finnish study comparing arthroscopic partial meniscectomy with sham surgery for degenerative meniscal tears interestingly did not demonstrate any significant difference in functional improvement between the patients undergoing surgery or those randomized to physiotherapy alone[8].

**Meniscectomy and Repair**

Most operations undertaken for meniscal tears are partial meniscectomies. Indeed, this is the most commonly undertaken procedure in sports medicine [8]. When a meniscectomy is undertaken the meniscal tissue should be preserved as much as possible to avoid biomechanical consequences. The torn tissue is resected enough to ensure that the remaining tissue is stable. The biomechanical effects of meniscectomy on load distribution within the knee have been well understood since the 1970s. Fairbank et al. demonstrated that the contact pressures within the tibial plateau increase proportionally with the amount of meniscus resected [4]. A direct correlation has been reported between meniscus resection and the risk of development of radiographic osteoarthritis (OA) in the longterm [9, 10, 11]. Although many patients generally experience pain relief and

improved function in the initial period post meniscectomy, many still report persistent pain in the affected joint line without the presence of a remaining tear. This proportion of patinets increases as follow-up time increases. Hede et al. found that Lysholm scores were fair to poor ( score <77) in 14% of patients 7.8 years after partial or total meniscectomy [9]. Long-term, the results are worse. Englund et al used a retrospective controlled cohort study using the Knee injury and Osteoarthritis Outcome (KOOS) questionnaire [11]. 50% of the patients suffered from symptomatic OA 16 years post meniscectomy compared to 19% in the control group in the same period. There were no differences between partial and subtotal meniscectomy and the risk of developing OA was in fact higher in the case of degenerate rather than traumatic lesions. This raises an interesting question about whether this patient group with degenerate tears in particular may benefit from meniscal substitutes.

Meniscal repairs were first reported in 1980 and research has been undertaken into improving techniques and results [12]. It has previously been recommended that repair be undertaken ideally in young patients with peripheral and longitudinal meniscal injuries [13, 14]. More recently however, satisfactory results have been reported after the repair or more complex and multiplanar injuries which extend into the avascular zone and even chronic injuries [15, 16]. The failure rates of meniscal sutures have declined over the years and the reoperation rate has decreased from 23% in 2003 to approximately 12.5% more recently. However, a systematic review of the outcomes of meniscal repair at greater than five years postoperatively demonstrated a failure rate of 22.3%-24.3% for all techniques investigated [17]. Furthermore, more modern all-inside repair devices have not been shown to have improved outcomes [18].

Due to these high failure rates, research groups are investigating how to improve fixation with safer devices and how to apply biological therapies directly to the site of injury ( i.e. growth factors) to increase the healing rate after repair. Nevertheless, as not all meniscal tears can be repaired, experimental and clinical studies are being undertaken to find safe substitutes for irreparable injuries – i.e. meniscal replacement.

**Partial meniscal substitutes**

Over the last few years, there have been two companies that have offered solutions for patients suffering from post-meniscectomy pain. The indications for this type of procedure are restricted to adults with post meniscectomy symptoms with chondral injuries up to grade 2 according to the International Cartilage Repair Society (ICRS) criteria, stable knees or knees stabilized in the same procedure and a preserved meniscal rim and periphery [19]. The treatment strategy involves measurement of the void arthroscopically and then filling the resected space with a custom sized, porous material, which serves as a scaffold to regenerate meniscal tissue within its structure. Patients not eligible for this type of treatment include those with a high body mass index ( BMI) greater than 35, total meniscal loss or for unstable peripheral zone tears. It is also not suitable for patients with multiple zones of meniscal wear, a misalignment or a chondral grade of ≥3. Most research using these techniques has taken place in Europe. The two licensed scaffolds commonly in use are a collagen matrix (Menaflex Collagen Meniscal Implant) produced by Regen Biologics Inc and the Actifit Polyurethane Non collagen Implant by Orteq Bioengineering, Ltd. A third total meniscal implant NU Surface by Active Implants is currently recruiting into a Phase 1 trial in the USA and is a potential alternative for meniscal allografting.

**Menaflex Collagen Matrix Implant (CMI)**

This implant was developed in the Unites States and is available in certain European countries. It is a biocompatible and degradable implant comprising type I collagen fibres which have been purified from bovine achilles tendon and are supplemented with glycosaminoglycans via γ-irradiation. In vitro, it promotes fibrochondrocyte migration with the help of fibronectin. Disadvantages include inflammation caused by bovine tissue and the implant is expensive [6].

Clinical studies into this implant have demonstrated mixed results on functional scores. Zaffagini et al. [20] published a small study demonstrating improved clinical results in the replacement arm of the trial in both Cincinnati Knee Rating Scale (CKRS) scores and International Knee Documentation Commuttee (IKDC) scores. However, three patients had a re-arthroscopy within the 6-8 year follow up period and it was observed that all had a significantly reduced implant size or complete degradation of the implant.

Zaffagini went on to publish a prospective cohort study of 33 patients comparing medial meniscal implantation with meniscectomy alone. The choice of treatment was decided by the patient and the cohort was followed up for 10 years. Again IKDC and Short Form Health survey (SF-36) scores were higher in the implantation group and importantly weight bearing radiographs evaluation showed significantly less medial joint space narrowing in the implantation group when compared to the meniscectomy group (0.48 ± 0.63 mm vs 2.13 ± 0.79 mm; P = .0003) [21].

These promising results were not however fully mirrored in a large multicentre prospective randomized controlled trial involving 311 patients [22]. This important trial involved two study arms, one consisting of 157 patients who had had no prior surgery on the involved meniscus (the "acute" arm of the study) and one consisting of 154 patients who had had prior meniscal surgical procedures i.e. the "chronic" arm. Patients in each arm were then randomized either to receive the collagen meniscus implant following partial meniscectomy or to serve as a control subject treated with a partial meniscectomy only. The mean duration of follow-up was fifty nine months. In the acute arm of the study there was no significant difference in any of the functional scores between implant and meniscectomy whereas in the chronic arm, the Tegner scored reached significant difference favouring the CMI implant. The study required all 141 patients receiving the implant to have a 2nd look arthroscopy and interestingly reported that patients receiving the CMI had significantly (p = 0.001) increased meniscal tissue compared with that seen after the original index partial meniscectomy.

A trial looking at longterm outcomes of CMI versus partial meniscectomy in patients with concomitant ACL reconstruction has demonstrated improved postoperative clinical scores in both groups at a mean follow-up of 9.6 years with no significant difference

found between between the two groups [23].  Despite this, the chronic subgroup of patients had significantly less postoperative knee pain compared to patients treated with partial medial meniscectomy and acute lesions treated with medial CMI showed less knee laxity.

Trials looking at the follow up of patients receiving the CMI implant have agreed on a few aspects. Firstly complication and reoperation rates are low and there is no difference in outcome between medial and lateral CMI [24]. However magnetic resonance imaging (MRI) studies have shown that the size of the CMI implant seems to decrease over time [25] and the regenerated meniscal tissue does not exhibit the same signal as native meniscus.  This has led Spencer et al. to postulate that the regenerated tissue might not be fibrocartilaginous in nature [26]. Further studies looking at the histological nature of the regenerated tissue will be important to ascertain the degree to which the tissue can exhibit the same biomechanical and hence chondroprotective characteristics of the native menisci.  Correlation between MRI findings and gross CMI appearance has also not yet been reported.


**Actifit noncollagen matrix scaffolds**

The second commercially available implant is the Actifit, which is a synthetic bioabsorbable scaffold engineered from polyurethane. The synthetic nature of Actifit has been marketed to favour implant customization. It has a highly porous surface that has been demonstrated to attach to the vascular zone of the meniscus and facilitates the penetration of neomeniscal tissue.  Tissue integration occurs in 97.7% of patients [12].   It is manufactured differently for the medial and lateral menisci.


Clinical trials have demonstrated improved functional scores in patients who have been implanted with Actifit [27, 19].  Baynat et al. published a case series of 18 patients who successfully underwent implantation of the Actifit implant. The team demonstrated improved Lysholm scores in their cohort but careful analysis of this paper revealed that

two thirds of their patients also had concurrent knee stabilization surgery in the form of ACL reconstruction and/or tibial realignment surgery, which may have confounded the results [27]. Histological examination of the meniscal substitute biopsies at 1 year after implantation showed polymer ingrowth by normal chondrocytes and fibrochondrocytes and no damage to the implant.

Verdonk et al. carried out a single arm multicentre case series involving 52 patients with a 24 month follow-up. The study demonstrated statistically significant improvements in all the assessed functional scores including visual analogue scale (VAS), / IKDC and KOOS which improved further over time. There was also a stabilization or improvement of the articular cartilage condition which suggested that the implant had a protective effect against cartilage degeneration [19].

Midterm follow-up of the Actifit implant has also been encouraging. Schuttler et al. have demonstrated good functional scores 48 months postoperatively with no significant changes to the articular cartilage seen on MRI scan [28].

One group has looked at preoperative meniscal extrusion and shown poorer results in patients with Actifit implantation who have evidence of preoperative meniscal extrusion in the coronal plane [29]. The recommendation is that these patients are instead considered for allograft replacement.

However all these results should be interpreted with caution as there was a lack of a control group in these studies. Moreover the Verdonk study did demonstrate an alarmingly high rate of failure (17.3%) with more specifically a failure rate of 33% in the subgroup of replacements for the lateral meniscus and a reoperation rate of 17.3% [19]. The reasons for this are unclear.

Studies looking at the sequential MRI images of patients being implanted with Actifit have demonstrated good structural integrity and tissue ingrowth at a mean of 19 months post surgery [26]. However, again, the signal of the regenerated tissue did not resemble fibrocartilage but showed instead an oedema-like signal, casting some doubt on the nature of the tissue.

In summary, although Actifit seems safe, randomized controlled trials are needed to support its true clinical value against standard partial meniscectomy alone. Evidence is lacking regarding the efficacy of CMI in acute irreparable lesions and in all knees, it is still doubtful whether the CMI or Actifit implanted knee actually functions better than a knee that has undergone meniscectomy alone. Further longterm randomized studies are needed to assess the effects of both implants.

## Total Meniscal Substitutes

On occasion, repeated partial meniscectomies result in a subtotal meniscectomy not suitable for partial replacement. Rarely, large traumatic tears are encountered that dictate a total meniscectomy. In both these instances, leaving the patient without any form of meniscal replacement greatly increases the progression of osteoarthritis and pain in the knee [30].

The treatment options are then a meniscal allograft or a synthetic meniscal replacement. Meniscal allografting has been trialled since the early 1980s. Contraindications to meniscal allografting include an Outerbridge score of grade 3 or 4 articular damage, diffuse arthritic changes, squaring or flattening of the femoral condyle or tibial plateau, significant osteophyte formation, untreated tibiofemoral subluxation, inflammatory arthritis, synovial disease, a history of joint infection or marked obesity [31]. The meniscal allograft can be cool ( 4°C), fresh-frozen (-80°C), cryopreserved or lyophilized ( freeze-dried). Most surgeons used prolonged fresh or deep frozen grafts as previous studies have shown that donor cells are repopulated with recipient DNA even without complete cell viability [32]. The fixation of the anterior and posterior horns is one of the essential steps in the technique and in particular, the proximity of the horns of the lateral meniscus is of special importance. The most commonly used method for the lateral meniscus is the construction of a bone bridge.

Meniscal allografting has been demonstrated to significantly improve initial functional outcomes in recipients during the first few years of follow-up. Improved function after meniscal allografting is due to an increase in intra-articular contact area and a decrease in

peak contact pressures across the bone [31]. Human retrieval studies have shown that the transplants are partially repopulated by host cells [33, 34].

A large meta-analysis of 44 trials has, however, demonstrated that these improvements are not sustained when reviewed over a 20 year time frame and there is no data to support the chondroprotective effect of donor menisci in the knee [35]. Histological evaluation of allograft tissue which has been removed has also shown that there is decreased cellularity and growth factor production which perhaps accounts for the high rate of allograft tears [36]. In a retrospective review of 172 patients who had undergone meniscal allograft, McCormick et al. reported an reoperation rate of 32% at a mean of 21 months, although most of these were simple arthroscopic debridement [37].

Again, evidence in the literature for meniscal allografting has a limited scope due to the absence of control groups.

There are many problems related to obtaining suitable allografts for patients post meniscectomy. There must be accurate sizing of the meniscal allograft to the native meniscus, especially when using a bone bridge or plugs. This is often achieved using radiographs, MRI or computed tomography ( CT ) scans [31]. Oversized allografts can lead to greater forces across the articular cartilage, which may lead to extrusion with inadequate transmission of compressive loads across the joint. Conversely, undersized allografts can lead to excessive load and poor congruity with the femoral condyle.

Allografts also carry a risk of disease transmission, although the central component of meniscal tissue is thought to be immunoprivileged [38]. High costs of preparing the implants have also limited their use [12].

These limitations have driven the research into synthetic meniscal replacements. Initial implants made of Teflon and Dacron demonstrated severe deformation and accelerated intra articular accumulation of wear particles in animal models with associated synovitis and knee joint remodelling [39, 40]. Later polyvinyl alcohol (PVA) was trialled as a non porous permenant replacement. This again caused extensive damage to the articular surface in large animal model testing and showed no benefit in comparison to meniscal allografting [41].

More recently a free floating polyethylene reinforced polycarbonate urethane (PCU) meniscal implant has commenced clinical trials in the USA. The NU Surface meniscal replacement by Active Implants has shown promise for safe use in animal models and is in its first year of recruitment in the VENUS trial. A pilot study of 3 patients implanted with the NUsurface implant revealed that the knee maintained its static kinematic properties following surgery [42]. Preliminary MRI images show restoration of the joint space and maintenance of cartilage signal intensity at one year postoperatively [30]. Further results are anticipated over the next year.

**Future directions**

This paper has focused on clinical studies documenting techniques being currently utilized in meniscal injury. Several groups continue research into developing a synthetic meniscal substitute but it is difficult to mimic the function of the human native meniscus. For example, Balint et al. have developed a fibrous scaffold for total meniscal replacement composed of quasi-circumferentially wrapped collagen-polymeric fibres to convert compressive loads into hoop stresses like the native meniscus. Unfortunately, the lack of supportive bulk material results in weak compressive properties in preliminary testing [Balint]. Work has also been undertaken investigating the potential of silk scaffolds for partial meniscal regeneration. A multilayered silk scaffold model was developed but the tensile moduli of the layers was lower than the native meniscus [44].

Other research groups are investigating tailoring the individual properties of implants, for example by balancing scaffold porosity with material properties, improving tissue infiltration and optimizing integration into the surrounding environment. It is known that extracellular matrix molecules play an important role in regulating cell behaviour. Studies have demonstrated the positive effect of growth factors (e.g. TGFβ, BMP-2, PDGF etc), low oxygen tension and cell-cell interactions on meniscal tears.

A number of other meniscus scaffold materials have been tested in the preclinical setting ranging from acellular allografts, porcine submucosa and a wider range of synthetic and natural polymers. Further work is needed to integrate new materials into clinical practice

and evaluate their efficacy in controlled trials to prove superiority over current treatments available.

**List of abbreviations**

None

**Conflict of interest**

None

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None

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