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Role of Scaffolds in the Reconstruction of Anterior Cruciate Ligament of Knee-Systematic Review

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ABSTRACT

AIM: To analyse the functional outcome after the use of biological/synthetic scaffolds in patients with anterior Cruciate Ligament injuries.

BACKGROUND: Injuries to the anterior cruciate ligament are common. Due to low cell density and poor regenerative capacity, primary surgical repair can lead to failure. There is a critical need for scaffolds that can replace or provide adequate strength and enhance healing potential. The purpose of this paper is to review the basic science and clinical understanding of scaffolds, which are currently used for anterior cruciate ligament reconstruction.

METHODS: A search was performed using EBSCO Hosted Medline, CINAHL, Cochrane and PubMed using various combinations of the keywords 'anterior cruciate ligament', 'scaffold', 'biological scaffold' and 'synthetic scaffold' over the years 1966–2015. The studies that are most relevant to the research question are selected. All articles relevant to the subject were retrieved, and their bibliographies hand searched for further references in the context to biomaterials for anterior cruciate ligament reconstruction.

RESULTS: Numerous biomaterials are available as scaffolds for the repair/reconstruction of anterior cruciate ligament injuries. The use of LARS ligament for anterior cruciate ligament injuries are safer and successful when compared to other commercially available scaffolds.

CONCLUSION: Biomaterial for tendon augmentation and/or replacement is an emerging field, which has huge implications in the management of injuries to anterior cruciate ligament. Available studies support the idea that these biomaterials have the ability to provide an alternative for the available techniques, however studies with long term follow-up concentrating on patient safety, effectiveness and cost-benefit analysis is the need of the hour.

Key words: ACL; Anterior Cruciate Ligament; Scaffolds; Biological Scaffolds; Synthetic Scaffolds

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INTRODUCTION

The anterior cruciate ligament (ACL) is critical to the normal functioning of the knee. Its disruption can lead to joint instability, functional impairment, injury to the meniscus and can finally lead to early onset osteoarthritis[1]. Every year in the United Kingdom there are about 30 ACL injuries for every 100,000 people[2]. ACL injuries account for around 40% of all sports injuries[2].

The treatment of ACL injury involves arthroscopic or open surgery. Historically direct repair associated with the ACL has been proven to be unsuccessful and is not being used anywhere[3]. This is because of the fact that this ligament has a poor blood supply and due to high re-rupture rate, almost 100%. The reconstruction of the ACL is commonly done using autografts or sometimes allografts[3]. The problems that are associated with harvesting autografts are shortening and contracture of the patellar tendon leading to patella baja, graft failure approximately 1% however this is smaller when compared to the allografts, patella fracture and/or patella tendon rupture[4]. The other option is to use allograft, however the biomechanical studies have shown that allograft from a cadaver is not as strong as the patient's own tissue and this is not suitable for patients planning to participate in high demand activities[3,5]. Although the allograft decreased the operative time and reduces the morbidity, it still carries a significant risk of disease transmission and infection transmitted by the graft[5]. The graft is potentially weak because of sterilisation storage techniques and they also exhibit slower healing and remodelling when compared to the autografts[5].

All these issues have necessitated the use of biological and synthetic scaffolds for reconstruction ACL. Though these biomaterials are manufactured to restore normal function, several characteristics of the scaffolds like mechanical property, host tissue integration/reaction, biodegradability, patient safety, design, indications and cost effectiveness were not clearly evident. Also most of the studies available in the literature were industry driven and are sparsely available. This review was performed to analyse various biological and synthetic scaffolds available in the market and their effectiveness in the management of anterior Cruciate Ligament injury.

MATERIALS AND METHODS

A comprehensive search was performed using EBSCO Hosted Medline, CINAHL, Cochrane and PubMed between 1966 and 2015, using various combinations of the keywords 'anterior cruciate ligament', 'scaffold', 'biological scaffold' and 'synthetic scaffold'. These databases were searched as they contain articles relevant to medicine, nursing, dentistry, the health care system, pre-clinical sciences and allied health journals. The period 1966 to 2015 was chosen because the use of biomaterials in orthopaedics started from 1970 and was then withdrawn around 1980 due to complications associated with them. The biomaterials with improved quality came to market around 2000 and are used till date.

The studies that are most relevant to the research question are selected. All articles relevant to the subject were retrieved, and their bibliographies hand searched for further references in the context to biomaterials for repair of anterior cruciate ligament. The search was limited to articles in English (including the articles where English translation is available) literature which are peer reviewed. Letters to editors, literature reviews and expert opinions were excluded from the review. Grey literature was searched in World Wide Web and System for Information on Grey Literature in Europe (SIGLE), however most of the information was by the industry/industry sponsored, so they were excluded from the review to reduce the bias. The initial selection is based on the title, abstract and key words. These studies were then further filtered based on full text. Strict inclusion and exclusion criteria were followed (Table 1) in including the study for review.

Table 1 Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Complete or partial rupture of anterior Cruciate Ligament;	Tendinopathy/other disorders with intact tendon or ligament;
Synthetic and/or biological scaffold;	Expert opinion, letter to editors, case reports and literature review;
Clinical studies in human being.	Experimental studies on animals;
	Lost to follow-up if > 20%;
	Additional secondary procedures.

Appendix 1 Search History.

Search	Keyword	Results
S1	Anterior cruciate ligament	15978
S2	Synthetic scaffold	242
S3	Biological scaffold	227
S4	Scaffold	15908

S5	S1 and S2	11
S6	S1 and S3	13
S7	S1 and S4	86

A search was performed looking for evidence using EBSCO Hosted Medline and CINAHL using a number of key words: (Performed on 07/03/2015). Websites searched for evidence include:
<http://www.cochrane.org/reviews>
<http://www.ncbi.nlm.nih.gov/pubmed/>
www.nice.org.uk

RESULTS

In the literature search (Appendix 1) 15,978 studies were identified related to the Anterior cruciate ligament injuries of which 110 were related to the use biological/synthetic scaffolds in the repair of torn anterior cruciate ligament. Of the 110 studies 14 were related to the use of biological scaffolds and the remaining were related to the use of synthetic scaffolds. After applying strict inclusion and exclusion criteria to the selected studies, none of the studies fit the criteria for the biological scaffolds and 15 were selected for the synthetic scaffolds for review (Table 2).

Study/year	Scaffold used	Clinical indication	Sample size/ Follow up	Failure rate	Outcome	Adverse events
Lavoie <i>et al</i> /2000	LARS	ACL rupture	47/8-45 months	3/47	Persistent knee instability in spite of good patient satisfaction	No
Nau <i>et al</i> /2002	LARS	ACL rupture	27 Autograft (AG) 26 LARS / 24 months	0/27 AG; 1/26 LARS	Results comparable to autograft (gold standard)	No
Liu <i>et al</i> /2010	LARS	ACL rupture	32 AG; 28 LARS/ 48 months	0/32 AG; 0/28 LARS	Results comparable to autograft (gold standard)	No
Gao <i>et al</i> /2010	LARS	ACL rupture	159/36 to 62 months	3/159	Good functional outcome	One synovitis
Macnicol <i>et al</i> /1991	Leeds-Keio	ACL rupture	20 / 2-4 years	16/20	Instability	Synovitis in 16/20
McLoughlin and South/1992	Leeds-Keio	ACL rupture	25 / 5 years	NA	20/25 good to excellent	No
Engström <i>et al</i> /1993	Leeds-Keio	ACL rupture	55 / 28 months	NA	Instability significantly greater in Leeds Keio	No
Ochi <i>et al</i> /1993	Leeds-Keio	ACL rupture	62 / 8-36 months	NA	Ligament did not act as scaffold	No tissue ingrowth
Denti <i>et al</i> /1995	Leeds-Keio	ACL rupture	50 / 5-7 years	5/50	Instability 25/50	No
Radang and Peterson/1995	Leeds-Keio	ACL rupture	24 / 2 years	3/24	13/21 unstable	No
Murray and Macnicol/2004	Leeds-Keio	ACL rupture	18 / 13.3 years	28% rerupture	51% instability	No
Sugihara <i>et al</i> /2006	Leeds-Keio	ACL rupture	13 / 12 months	NA	Good outcome	No
Ghalayini <i>et al</i> /2010	Leeds-Keio	ACL rupture	26 AG, 24 Leeds-Keio / 5 years	NA	Good outcome	No
Fukubayashi and Ikeda/2000	Gore-Tex patch	ACL rupture	123 / 5-11 years	26/123	50% loosen, 63% arthritis	Tunnel lysis
Muren <i>et al</i> /2005	Gore-Tex patch	ACL rupture	17 / 13-15 years	NA	15/17 tunnel lysis	Tunnel lysis and widening

NA: Non-Available.

SYNTHETIC SCAFFOLDS CURRENTLY USED ARE

1. Ligament Advanced Reinforcement System (LARS, Dijon, France)

LARS is a second-generation, nonabsorbable synthetic ligament device made of terephthalic polyethylene polyester fibres[6]. The ligament is cleaned to remove potential machining residues and oils to further encourage soft tissue in-growth and reduce the risk of reactive synovitis. The intra-articular portion, or scaffold, of the ligament consists of multiple parallel fibres twisted at 90 degree angles and this gives good mechanical strength to the ligament. Besides, this design aims to prevent the fibre breakdown that was previously seen in grafts made from woven materials and is thought to facilitate even tensioning of the graft fibres during knee movement[6]. The scaffold provides a meshwork for the injured ligament to heal and repair. One in-vitro laboratory study has demonstrated cellular growth after six months, subsequent to seeding of human fibroblast and osteoblast like cells onto the LARS[6].

Lavoie *et al* in a cohort study evaluated patient satisfaction scores for knee stability following ACL reconstructive surgery using LARS[7]. Their study population consisted of 47 subjects with ACL rupture and included associated pathologies such as meniscal tears. All the patients were reviewed 8-45 months after surgery using Knee and Osteoarthritis Outcome Score for patient satisfaction, a modified International Knee Documentation Committee form for clinical knee stability, and a Telos stress radiography for PA stability. This study concluded that the LARS could be considered as a viable option for ACL reconstruction in terms of patient satisfaction. Interestingly, in spite of positive patient satisfaction scores, ongoing knee laxity were reported (average posterior-anterior displacement scores of 7.3 mm).

Nau *et al* performed a randomised clinical trial comparing two methods of reconstruction of the anterior cruciate ligament[8]. They compared bone-patellar tendon-bone autologous graft with LARS in a population of chronic, symptomatic, ACL ruptures. This study demonstrated that LARS was comparable to the gold standard bone patella bone reconstruction in terms of subjective functional scores over a two year period. The authors commented on the high likelihood of return to high-level activity in the LARS group, however did not provide statistical analysis to support this contention. There were no long term studies to confirm these findings.

Liu *et al* in a retrospective study compared the effectiveness of the LARS to matched controls who had received traditional ACL reconstruction using a four-strand hamstring autologous graft[9]. In a mean follow-up of 49 months

both the LARS and the four-strand hamstring autologous graft can result in improvements in functional outcomes. In this study all the subjects had a period of more than four months since time of injury to time of surgery, so the efficacy of the graft in acute setting is not known. Besides, it carries the disadvantages of the retrospective case series.

Gao et al in a retrospective, multicentre case series assessed the clinical outcome of LARS reconstruction[10]. In this study 159 patients with ACL rupture underwent arthroscopic ACL reconstruction with LARS artificial ligament at 4 orthopaedic sports medicine centres in China and they were retrospectively followed up for 50 +/- 6 months (range, 36 to 62 months). LARS surgery was only performed on subjects who had a viable ACL stump for the LARS to pass through. Prior to surgery, subjects gave consent for the LARS procedure but were informed that without a viable stump a more traditional approach, either BPB or hamstring tendon autologous graft would be performed. LARS artificial ligament rupture occurred in 3 patients; knee synovitis developed in 1 of these patients. This study concluded that LARS performed in subjects presenting surgically with a viable stump can be a suitable option for ACL reconstruction in terms of function and pain outcomes.

2. Leeds-Keio or Poly-tape (Xiros plc, Neoligaments, Leeds, UK; Yufu Itonaga Co., Ltd, Tokyo, Japan)

The Leeds-Keio or Poly-Tape is made of polyester (ethylene terephthalate) and was developed by the University of Leeds and the Keio University. The Leeds-Keio was specifically designed for ACL reconstruction with stiffness of 200 N/mm, similar to that of natural ACL[11].

Macnicol et al from Edinburgh first reported the early results of using Leeds-Keio ligament in anterior cruciate ligament reconstruction[12]. All the patients were evaluated post operatively using Tegner activity scale and the Lysholm knee score. At a follow-up of two to four years all the 20 patients were less disabled by instability, however under anaesthesia the pivot shift sign was still positive in half of the patients. Arthroscopy in 16 patients failed to show the development of a functional neoligament, histological assessment from 10 of these 16 ligaments showed a common appearance of an inflammatory synovial reaction in all specimens.

McLoughlin and Smith analysed twenty-five patients who had surgical reconstruction, at an average follow-up period of almost five years[13]. The patients were assessed in terms of function (pre injury level of activity), clinical examination (range of movements) and residual laxity. In their study the results showed that four could be classified as excellent, 16 good, and four poor. Fifty-two percent of patients returned to their pre injury level of activity, and there did not appear to be any evidence of increasing laxity with time. All patients had a good range of flexion with no extension loss. They concluded that this prosthesis along with its unique method of fixation, offers a simple alternative to patellar tendon or soft tissue reconstructions in the chronic anterior cruciate-deficient knee.

A prospective study from Sweden compared the effectiveness of Leeds-Keio prosthesis to autogenous patellar tendon graft in 60 patients[14]. At a mean follow-up of 28 months both the pivot shift and the anterior laxity were significantly greater ($P < 0.01$) for the Leeds-Keio group. The study concluded that the Leeds-Keio ligament does not fulfil the requirements for a satisfactory result in ACL reconstructive surgery with regard to knee-joint stability.

62 patients, who underwent anterior cruciate ligament (ACL) reconstruction with the Leeds-Keio artificial ligament, had an arthroscopic second look and biopsy of the reconstructed ACL at 8-36 months postoperatively[15]. Results demonstrated that the implanted ligament had the capacity for tissue induction, however no statistically significant correlation was observed between any two results among the arthroscopic, histologic, and clinical data. In their study, within the time span of the experiment, there was no conclusive evidence that the L-K ligament functioned as a scaffold type of artificial ligament. The authors suggested that more convincing results must be attained before any firm recommendation can be made for the use of the Leeds-Keio ligament as a substitute ACL over the autograft or allograft.

A long term study by Denti et al analysed the effectiveness of the Leeds-Keio prosthesis at a follow-up of 5-7 years in 37 patients[16]. All the patients were evaluated using Lysholm score, Lachman's test and KT 1000 test. Five patients developed failure of the prosthesis, which was clinically assessed using Lachman's test and KT 1000 test. The Lachmann test was 1+ in 15 patients, 2+ in 7, 3+ in 2, and negative in 13; KT 1000 test at 30 lb side to side was < 3 mm in 23 patients, 3-5 mm in 6, 6-10 mm in 6, and > 10 mm in 2. In view of these results, authors suggested that this procedure should no longer be performed as an ACL substitute.

Rading and Peterson observed 24 consecutive patients with symptomatic chronic anterior cruciate ligament ruptures who had ligament reconstructions with the Leeds-Keio artificial ligament for a minimum of 2 years or until ligament failure, whichever came first[17]. Three patients underwent reoperation because of a rupture of the artificial ligament leading to instability and another six patients developed significant subjective instability, even during ordinary activity. Only eight patients had a subjectively stable knee. The high incidence of unstable knees, due to insufficiency of the artificial ligament in this study strongly suggests that the Leeds-Keio artificial ligament is not an effective device for the reconstruction of the anterior cruciate ligament.

The study by Murray and Macnicol[18].., is a long term follow-up of 20 patients who had earlier reconstructions from Edinburgh[12]. At a mean follow up of 13.3 years (range 10-16 years) all patients experienced some degree of

symptoms from their knee but functional impairment varied widely. In the study 28% have ruptured their Leeds-Keio ligament and 56% had increased laxity compared with their opposite knee but no correlation could be shown between rupture, increased laxity and poor function. Interestingly all post-operative knees had radiographic signs of degenerative change compared with a rate of 39% in the contralateral knees.

Sugihara et al used a bioactive Leeds-Keio ligament to improve tissue induction, cell proliferation and cell attachment to artificial fibres[19]. Thirteen cases were reviewed in a year's time and knee stability was regained after reconstruction without any complications such as joint effusion and chronic synovitis. Postoperative arthroscopy of one patient at 8 weeks showed that the reconstructed anterior cruciate ligament was completely covered with newly formed tissue. Biopsy of this anterior cruciate ligament revealed abundant fibroblasts, collagenous fibers, and vessels around the artificial fibers without marked inflammatory findings. Electron microscope study showed abundant thin collagen fibres, with regular orientation to some extent. Thus this result suggests that bioactive Leeds-Keio is superior to Leeds-Keio in tissue induction and maturation.

A recent prospective, randomised controlled trial compared anterior cruciate ligament reconstruction using middle third patellar tendon graft to synthetic Leeds-Keio ligament[20]. There were no significant differences between functional outcomes between the groups at 5 years. The authors concluded that the results of Leeds-Keio ligament ACL reconstruction are as acceptable as those using middle third patellar tendon graft.

3. Gore-Tex patch (Gore and Associates)

Fukubayashi and Ikeda analysed the results of use of Gore-Tex ligaments in 123 patients[21]. At a follow up of 5-11 years, the ligaments were totally ruptured in 26 cases. Graft loosening occurred in half of the patients, and osteoarthritic change was identified in 62% of the cases. Besides, tunnel osteolysis was observed in most of the cases. The authors concluded that the Gore-Tex ligament should not be used for anterior cruciate ligament reconstruction.

Muren et al followed up 17 patients for 13-15 years, after their anterior cruciate ligament were reconstructed using a Gore-Tex ligament prosthesis[22]. They identified progressive widening of the bone tunnels in 15 patients and suggested to use this implant with caution.

DISCUSSION

The use of synthetic and biological scaffolds in the repair of torn ligaments and tendons is an emerging field in Orthopaedics[11,23]. These scaffolds are aimed to enhance and accelerate the biology of tissue repair. They also help in host cell infiltration and constructive tissue remodelling so that the tendons and ligament can withstand the normal forces exerted on them. In addition to this, the scaffold decreases the mechanical forces on the repair during the post-operative healing phase, it prevents the failure of repair and the gap formation and it helps the biology of healing so that the scaffold is reorganised by the host tissue over time[11,23].

The use of synthetic scaffolds was started in the 1980's however the use was discontinued after a few years because of poor material quality and decreased biocompatibility[23]. However, the recently developed synthetic scaffolds are more biocompatible and have superior mechanical property. These synthetic scaffolds are made of polyester, polypropylene, polyarylamide, dacron, carbon, silicone and nylon[11,23]. The synthetic scaffolds have much better biomechanical properties when compared to the biological scaffolds. However, the compatibility with the surrounding tissues is less when compared to the biological scaffolds. The commonly used synthetic scaffolds are LARS ligament, Leeds-Keio, Gore-Tex patch WL, Artelon and sports mesh[11,23]. The Lars ligament is non-absorbable synthetic ligament device which is made of terephthalic polyethylene polyester fibres. The Leeds poly tape is made of polyester and this ligament was developed by the University of Leeds and the Keio University. This ligament was specifically designed for ACL reconstruction as this has the stiffness of about 200 newtons per millimetre which is similar to the natural ACL ligament. The Gore-Tex patch WL is composed of expanded polytetrafluoroethylene[11,23]. This ligament has micro-porous structure allowing host tissue incorporation. This ligament is more elastic and has been used to augment rotator cuff repairs. The Artelon and sports mesh are made of biodegradable polyurethane urea polymer (Valentin et al., 2006, pg 2673-2686). Animal studies conducted by the company suggested that the Artelon fibre is slowly degraded and is capable of stimulating host cell ingrowth[24].

The Gore-Tex Cruciate Ligament Prosthesis (1986), Stryker Dacrone Ligament Prosthesis (1988) and 3M Kennedy Ligament Augmentation Device (1987) were initially used in ACL reconstruction. Though the short-term studies showed satisfactory results, the long-term follow up revealed many complications like implant degeneration, device failure, severe synovitis, inflammatory response with foreign body reaction and osteolysis[21,22]. All the three prostheses were retracted from the market and a study by Guidoin et al revealed that the factors contributing to prosthesis failure are; inadequate fibre abrasion resistance against osseous surfaces, flexural and rotational fatigue of fibres and loss of integrity of the textile structure due to unpredictable host tissue infiltration[25]. Interestingly, the use of Gore-Tex in a retrospective clinical study on 28 rotator cuff tears showed a great improvement in pain relief, muscle strength and function of the shoulder[26]. Another study by Kollender et al used Gore-Tex strips for reconstruction of the patellar tendon and showed a good-to-excellent functional outcome at 2

years follow up[27]. Both the studies showed no evidence of inflammatory response or infection at the follow ups. These studies show that Gore-Tex though not suitable for ACL reconstruction, can be used in rotator cuff reconstruction. The failure of Gore-Tex occurred in bone graft junction in ACL reconstructions, on the contrary in rotator cuff reconstructions it bridged the gap between torn edges of tendons and did not elicit any immune response[21,22].

Lars Ligament is extensively used in the reconstruction of anterior cruciate ligaments. Promising results were reported in several studies using LARS Ligament for ACL reconstruction[7-10]. A prospective, randomised, controlled trial found no differences regarding the failure rate, functional score and satisfaction between the autograft and the LARS group at the 2 year follow up[8]. Unlike other synthetic scaffolds severe complications like synovitis, osteolysis, and foreign body rejection leading to failure of the graft have not been found in LARS. Histological studies on retrieved LARS prosthesis showed complete cellular and connective tissue in growth at six months time[6].

Leeds-Keio graft is extensively used for ACL reconstruction in the UK. The results following the use of Leeds-Keio ligament for ACL reconstruction were controversial. Studies reported in 1990's and the early 2000's reported adverse events like re-rupture, tunnel enlargement, synovitis associated with polyester particles, greater pivot shift and laxity[12,14,16-18]. However, the recent studies were more favourable for its use in tendon and ligament reconstruction[19,20]. The recent study by Ghalayini et al is a prospective randomised controlled trial the results showed no significant differences between functional outcomes between the groups at 5 years[20]. The controversial findings may be due to the use of newer generation Leeds-Keio ligament for ACL reconstruction and improvement in surgical techniques. However long term studies are necessary to evaluate the biology of Leeds-Keio ligament.

Artelon and Sportmesh are biodegradable polyurethane urea polymer. The animal studies conducted by the company showed that this fibre is slowly degraded, biocompatible and capable of stimulating host cell ingrowth[11,23]. However, there were no clinical studies regarding its use in the repair of anterior cruciate ligament injuries.

PROPERTIES OF COMMERCIALLY AVAILABLE SCAFFOLDS

Strength

The scaffolds should have better mechanical properties when compared to the host tissue so that they can protect the host tissue from the stress produced during normal activities. Besides a strong scaffold can protect the host tissue during the early rehabilitation and physiotherapy so that the complications like joint stiffness, disuse atrophy of the tissues and surrounding muscle wasting can be avoided.

Interestingly, the mechanical strength of most of the scaffolds available today in the market is far lower than the normal tendons and ligaments. In vitro studies on human cadaveric tendons and ligaments, demonstrated, the ultimate strain of an intact ACL is 1,246 +/- 243 newtons[28]. The studies on biological scaffolds by Barbra et al showed that the mean load to failure of GraftJacket is 229 newtons, Zimmer Patch is 128 newtons, Tissue Mend is 76 newtons, Restore is 38 newtons and Cuff Patch is 32 newtons[29]. Synthetic scaffolds had a higher mean load to failure when compared to biological scaffolds. For Leeds-Keio ligament it is 780 +/- 200 newtons and for Lars ligament it is 998 +/- 148 newtons[23]. These values suggest that the mechanical property of the scaffolds available needs to be greatly improved to serve the function they are supposed to do.

DEGRADATION

Ideally the scaffolds used for tendon and ligament reconstruction should undergo degradation when inducing tendon regeneration. Of the commercially available biological scaffolds, Restore Patch was completely degraded after 112 days in animal studies, while GraftJacket, Cuff Patch and Tissue Mend were partially degraded and Zimmer Patch did not undergo any degradation at all[24]. Most of the synthetic scaffolds available in the market today degrade much more slowly, or not at all. A study by Debnath et al showed that the synthetic scaffolds were present in the knee joint even after 15 years of implantation[30].

The tissue induction capability of the synthetic scaffolds is poor when compared to the biological scaffolds. Guidoin et al examined 117 surgical failed ACL prostheses and found that the healing inside the synthetic ACL was poorly organised, incomplete and unpredictable[25]. Interestingly, the extent of collagenous infiltration into the scaffold did not increase with the duration of implantation. These facts reveal that the synthetic scaffolds do not possess the capability to induce host tissue ingrowth.

Host tissue induction/integration

Even though the biological scaffolds are more capable of inducing host tissue ingrowth, the induction ability is uncontrolled and non-specific. On the contrary, synthetic scaffolds are composed of macromolecules from random coils and they lack a well defined three-dimensional microstructure that allows host cell in-growth. The other issues

with the synthetic scaffolds are when they degrade they produce a local environment which is not conducive for the tissue in-growth[11,23].

Synthetic scaffolds elicit a sequence of events which starts with acute inflammatory response followed by chronic inflammation and particularly the material is non-degradable granulation tissue and fibrous capsule formation[31]. Biodegradable synthetic scaffolds made from aliphatic polyesters typically degrade over a period of several months forming lactic acids and fatty acids which are normally present in the body. However, non-degradable synthetic scaffolds such as polycarbonate, polyurethane and Teflon usually persist for the life of the patient[11,23].

SCAFFOLDS FOR THE FUTURE

Nano technology

The future of the scaffolds depends on improving the mechanical property and the biological compatibility of the scaffolds. Electrospinning is a new technology which uses an electrical charge to draw very fine fibres from a liquid[32]. The advantage of this is that it can easily produce a nanostructured extracellular matrix scaffold with controlled mechanical properties and a three dimensional microstructure that resembles the extracellular matrix of the tissue. This experiment by Matthews et al., has shown that the electrospun collagen promotes cell ingrowth and penetration of cells into the engineered matrix, in addition to the better mechanical property[32]. The structure, material and the biological properties of the electrospun collagen may represent a nearly ideal tissue engineering scaffold. The other major advantage of the nanofibers is they provide high surface area to volume ratios leading to increase in the contact area between the cells and the fibres offering a huge potential to deliver substances like growth factors at the area of repair or regeneration[32,33].

Laurent, et al studied multilayer braided biodegradable co-poly(lactic acid co-ε-caprolactone) fibres for its potential towards ACL reconstruction[34]. Their mechanical properties, biochemical nature, and morphology can be favourably altered using the tissue engineering techniques. They concluded that this scaffold closely mimics the geometry of the real scaffold and the pore size distribution is also good. The advantage of the scaffold is that the size of the pores can be adjusted by playing on the process parameters and can be matched to the ideal pore size reported for tissue ingrowth.

Tissue engineering

The other options the present commercially available scaffolds can be coated with growth factors like fibroblast growth factors which promote healing and bone morphogenic proteins which can also help in healing at the bone scaffold interface[35]. An interesting study by Murray et al observed the effects of several growth factors on cell migration, proliferation and collagen production in human ACL cells[36]. The addition of transforming growth factor Beta 1 led to increased cell population as well as increased collagen and smooth muscle actin production in human ACL cells. Supplementation with platelet derived growth factor resulted in increased cell proliferation rates within the scaffold and increased collagen production. The addition of fibroblast growth factor-2 resulted in increased cell proliferation rates and slowed rates of scaffold shrinkage when compared with the control group. The authors proposed that the addition of selected growth factors to an implantable scaffold may facilitate ligament healing in the gap between the ruptured ends of the human ACL.

Recently many studies have stressed the importance of use of gene therapy and growth factors to enhance tendon and ligament healing[35]. However, they are still in the experimental stage and have not reached the clinical studies.

Degradation of the scaffolds leads to loss of mechanical strength, however host tissue deposition and remodelling can concomitantly strengthen the repair. The sequence of remodelling events, including the rate and extent of the scaffold degradation, incorporation and host tissue deposition, is not well established for most of the available scaffolds devices. Future work should be aimed to address these questions so that the sequence of the interplay between scaffold degradation and remodelling can predict the clinical course. Besides it can also help to devise optimal rehabilitation protocol, leading to good functional outcome. Presently most of these studies focus mainly on extracellular matrix reconstruction where the scaffolds are produced to mimic the extracellular matrix of the tendon or ligament to stimulate cell proliferation and tissue ingrowth. However, the healing process at the graft bone interface has not been evaluated at large. In the majority of the failures the causes usually are osteolysis at the graft bone junction or the scaffold pull out. This reinforces the fact that healing at the bone graft junction is an important role in evolution of biological and synthetic scaffolds. Furthermore, studies are needed to understand and promote the healing of bone graft junction.

CONCLUSION

Several biologic and synthetic scaffolds are available in the market for the repair of anterior cruciate ligament injuries. Of the available scaffolds, LARS ligament has produced consistently good results in the reconstruction of

anterior cruciate ligament injuries. Large controlled randomised trials with longer term follow-up are needed to prove the efficacy and safety of these commercially available scaffolds. The incorporation of techniques tissue engineering can be helpful in improving the mechanical property and biological behaviour of the scaffolds.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest with regard to the present study.

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