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Review Article

Single-step scaffold-based cartilage repair in the knee: A systematic review

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ABSTRACT

Chondral lesions are difficult-to-treat entities that often affect young and active people. Moreover, cartilage has limited intrinsic healing potential. The purpose of this systematic literature review was to analyse whether the single-step scaffold-based cartilage repair in combination with microfracturing (MFx) is more effective and safe in comparison to MFx alone.

From the three identified studies, it seems that the single-step scaffold-assisted cartilage repair in combination with MFx leads to similar short- to medium-term (up to five years follow-up) results, compared to MFx alone. All of the studies have shown improvements regarding joint functionality, pain and partly quality of life.

1. Introduction

A chondral or osteochondral lesion is a debilitating condition. Besides the older people (with degenerative cartilage damage), the young and active persons, especially, are likely to acquire chondral or osteochondral lesions, mainly caused by traumatic events (e.g. sport injuries). Due to the low intrinsic healing capacity of human articular cartilage, spontaneous healing of the damaged tissue cannot be expected. In addition to pain and functional impairment, resulting in a reduced quality of life, cartilage lesions can lead to the development of osteoarthritis and a further progression can lead to the requirement of a joint replacement.[1,2]

There are numerous treatment options for chondral lesions, starting with conservative treatment and followed by surgical interventions. Generally, the treatment of chondral or osteochondral lesions aims at pain reduction, regaining joint mobility, reactivation of the affected area, preventing/slowing of the progression and prevention of osteoarthritis, and eventually avoiding total joint replacement.[2–4]

For small cartilage lesions, microfracturing (MFx) alone is considered as the first-line treatment for focal cartilage defects. MFx is a repair surgical technique that works by means of creating tiny fractures (e.g. by drilling) in the subchondral bone. The underlying idea is to promote cartilage regeneration from a so-called "super-clot" (after bleeding from the bone marrow). However, the procedure seems less effective in treating older patients, overweight patients, or cartilage lesions larger than 2.5 cm^2.[1,2,5,6]

For larger defects, the autologous chondrocyte implantation (ACI) is indicated, which may also be used in combination with a matrix (MACI).[2,7] ACI is performed in different steps. In the first step, intact cartilage is sampled arthroscopically, preferably from a non-weight-bearing area of the affected cartilage. The generated cells are then cultured in vitro until there are enough cells to be re-implanted into the cartilage lesion. These autologous cells should adapt themselves to their new environment by forming new tissue. If chondrocytes are applied onto the damaged area in combination with a membrane (tibial periosteum or biomembrane) or pre-seeded in a scaffold matrix, this technique is called MACI. However, for (M)ACI, two surgeries are needed, resulting in higher costs.[5,8,9]

To overcome the disadvantages of MFx and (M)ACI, a new treatment option has evolved: the single-step scaffold-based treatment of cartilage defects. During this approach, a matrix is implanted in the area of the damaged cartilage to cover the blood clot after a bone marrow stimulation technique (e.g. MFx). This technique is also called autologous matrix-induced chondrogenesis (AMIC). The scaffolds are implanted arthroscopically or by a mini-arthrotomy for "in situ" repair, permitting the ingrowing of mesenchymal stem cells (MSCs) to differentiate into the chondrogenic lineage. The used matrix acts as a temporary structure to

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Table 1
Product overview.

Product	Manufacturer	Main component(s)
BST-CarGel®	Primal Enterprises Limited, Canada	Chitosan solution
CaReS®-1S	Arthro Kinetics AG, Germany	Collagen type I
Chondro-Gide®	Geistlich Pharma, Switzerland	Porcine collagen type I/III
Chondrotissue®	BioTissue Technologies GmbH, Switzerland	Polyglycolic acid fleece and freeze-dried sodium hyaluronate
GelrinC	Regentis Biomaterials Ltd., Israel	Hydrogel of polyethylene glycol di-acrylate (PEG-DA) and denatured fibrinogen
Hyalofast®	Anika Therapeutics, Inc., USA	Biodegradable hyaluronan (HYAFF®)
Maioregen™	Fin-Ceramica Faenza S.p.A., Italy	Deantigenated type I equine collagen
MeRG®	Bioteck S.p.A., Italy	Microfibrillar collagen membrane

References: individual manufacturers' websites.

Table 2
Inclusion criteria.

Population	• Adult patients with indications for surgical cartilage repair in the knee • Grade III–IV (Outerbridge classification) localised cartilage damages/defects/disorders in the knee • Grade III–IV (ICRS classification) (osteo)chondral lesions • Osteochondritis dissecans (OCD) • ICD-10 codes: M24.1, M94.8, M94.9, M93.2
Intervention	• Single-step, cell-free, scaffold-based cartilage repair in combination with microfracturing
Control	• Microfracture surgery/microfracturing alone (main comparator) • Autologous chondrocyte implantation/transplantation (ACI/ACT) • Matrix-induced autologous chondrocyte implantation (MACI)
Outcomes	
Efficacy	• Mobility/joint functionality • Pain • Return to daily activities/sports/physical activity • Quality of life • Necessity of total joint replacement
Safety	• Adverse events • Mortality (up to 10 days postoperatively) • Re-operation/additional surgery
Study design	
Efficacy	• Randomised controlled trials • Prospective non-randomised controlled trials
Safety	• Randomised controlled trials • Prospective non-randomised controlled trials • Prospective uncontrolled trials ($n > 50$ pts., follow-up > 24 months)

allow the cells to be seeded. The fixation of the matrices can be done by e.g. suturing or glueing. This cartilage repair technique is done within one single surgery and can be used for larger defect sizes than 2.5 cm^2.[7,10]

The single-step scaffold-assisted cartilage repair is mainly an enhancement of the standard MFx technique, used to induce reparative marrow stimulation.[11,12] Thus, we exclusively focus on one approach, where the implantation of the scaffold is combined with MFx.

A total of eight products from eight manufacturers that can be used for the single-step scaffold-assisted cartilage repair and are commercially available were identified. An overview of these products is shown in Table 1.

The aim of this report was to assess the clinical effectiveness and safety of the single-step matrix-assisted cartilage repair in the knee joint (combined with MFx), compared to MFx alone or (M)ACI.

2. Methods

2.1. Research questions

This systematic review should answer the following two questions:

(1) Is the single-step scaffold-based cartilage repair in combination with MFx more effective and safe in comparison to MFx alone in patients with indications for cartilage knee surgery concerning the outcomes listed in Table 2?
(2) Is the single-step scaffold-based cartilage repair in combination with MFx as effective, but safer, in comparison to two-step cartilage repair procedures (autologous chondrocyte implantation or matrix-induced, autologous chondrocyte implantation) in patients with indications for cartilage knee surgery concerning the outcomes listed in Table 2?

2.2. Search strategy

To answer the research questions, a systematic literature search was conducted between 13th and 15th of January 2016 in the following databases: The Cochrane Library, CRD (DARE, NHS-EED, HTA), Embase, Medline via Ovid and PubMed. Additionally, a search was conducted by hand and using Scopus, and manufacturers of the most common products were contacted (see Table 1). The literature search was limited to articles published in English or German.

2.3. Selection of studies

Two reviewers independently screened and selected the literature based on the criteria listed in Table 2. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow Diagram depicting the flow of records from identification to inclusion is shown in Fig. 1.