# Cartilage repair in the degenerative ageing knee

## A narrative review and analysis

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Submitted 2016-03-13. Accepted 2016-10-09.

**Background and purpose —** Cartilage damage can develop due to trauma, resulting in focal chondral or osteochondral defects, or as more diffuse loss of cartilage in a generalized organ disease such as osteoarthritis. A loss of cartilage function and quality is also seen with increasing age. There is a spectrum of diseases ranging from focal cartilage defects with healthy surrounding cartilage to focal lesions in degenerative cartilage, to multiple and diffuse lesions in osteoarthritic cartilage. At the recent Aarhus Regenerative Orthopaedics Symposium (AROS) 2015, regenerative challenges in an ageing population were discussed by clinicians and basic scientists. A group of clinicians was given the task of discussing the role of tissue engineering in the treatment of degenerative cartilage lesions in ageing patients. We present the outcomes of our discussions on current treatment options for such lesions, with particular emphasis on different biological repair techniques and their supporting level of evidence.

**Results and interpretation —** Based on the studies on treatment of degenerative lesions and early OA, there is low-level evidence to suggest that cartilage repair is a possible treatment for such lesions, but there are conflicting results regarding the effect of advanced age on the outcome. We concluded that further improvements are needed for direct repair of focal, purely traumatic defects before we can routinely use such repair techniques for the more challenging degenerative lesions. Furthermore, we need to identify trigger mechanisms that start generalized loss of cartilage matrix, and induce subchondral bone changes and concomitant synovial pathology, to maximize our treatment methods for biological repair in degenerative ageing joints.

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Degeneration is by definition a deterioration of a tissue or an organ where its function is reduced or its structure is degraded. Joint cartilage degeneration can be seen after trauma, or it can be generalized in ageing cartilage and as part of the osteoarthritic process (Richmond et al. 2013). It is important to understand that while a degenerative ageing joint is not necessarily an osteoarthritic joint, the reverse is certainly true: joint tissue degeneration is a key factor in osteoarthritis (OA). OA has been described as degenerative arthritis, degenerative joint disease, or osteoarthrosis, and it is a type of joint disease that results from breakdown of articular cartilage and the underlying subchondral bone (Poulet and Staines 2016). An initial degeneration may progress to a pre-OA state that may be reversible, spontaneously or through preventive measures, and if it is not stopped, continues on to early OA and finally established OA (Ryd et al. 2015).

There is an increasing frequency of OA in the elderly population (Greene and Loeser 2015). Changes that are seen in the articular cartilage during the development of OA are the result of an age-related loss in normal joint homeostasis. A disturbed balance promotes increased production of matrix degrading enzymes by chondrocytes, such as matrix metalloproteinases, aggrecanases, and other proteases, which degrade the cartilage matrix. Similar changes can also occur in ageing cartilage and appear to contribute to the loss of homeostasis (Goldring and Marcu 2009, Loeser 2009, Greene and Loeser 2015).

In the cartilage of elderly individuals, matrix biosynthesis is inhibited by static loading while cyclic loading is stimulatory (Plumb and Aspden 2005). This knowledge is important for tissue engineering approaches to repair of osteoarthritic cartilage, where the source of the replacement tissue or cells must be considered. Although the tissue response appears to be dif-

ferent from that in young individuals, these findings still support the importance of exercise in the elderly to regulate the biosynthetic activity of the tissue (Plumb and Aspden 2005). However, the same information is of importance when trying to use tissue engineering to restore or replace a degenerative and osteoarthritic joint surface.

As the world population continues to age, osteoarthritis is increasingly being recognized as a significant cause of disability in the elderly population (Rahmati et al. 2016). Estimates are wide-ranging, but a study done in 2008 by the National Health and Nutrition Examination Survey (NHANES) estimated that approximately 27 million American adults had been clinically diagnosed with osteoarthritis (Lawrence et al. 2008), and up to 46 million had reported a history of osteoarthritis (Ma et al. 2014). Because of these numbers, therapies aimed at preventing the development of advanced disease are of vital importance to orthopedics and society.

In this paper, we will look at various techniques that are normally used for focal cartilage repair, and discuss the possibilities and the means by which these techniques could be applied to patients with OA.

## Methods

All the co-authors were responsible for their own areas of expertise in cartilage repair and they all evaluated and discussed their chosen papers on cartilage repair related to ageing degenerative and osteoarthritic joints. The databases Medline, PubMed, Cochrane Systematic Reviews, and Clinical Keys were then searched by the first author (MB) to check that all papers of relevance to the area studied were included. The clinical cartilage repair papers evaluated have been presented with a level of evidence grading (LOE 1–5) (Obremskey et al. 2005). The risk of bias (RoB) in the clinical cartilage repair papers presented has been calculated using the Jadad scale with scoring from 0 to 5 points (Jadad et al. 1996, Jadad and Enkin 2007) and the RoB has been classified as low (4–5 points), moderate (2–3 points), or high (0–1 point). RoB in the papers was calculated by 2 of the authors (MB and JF) and was finally agreed upon by all the authors.

### The cartilage defects

There are several methods to repair traumatic cartilage defects, but the natural course of such lesions is still not well known (Grieshober et al. 2016). Similarly, the natural course of degenerative lesions is not well characterized, even though it is associated with increased cartilage loss. It has been shown that cartilage defects tend to progress over 2 years in people with symptomatic OA, with only a small percentage decreasing in severity (Davies-Tuck et al. 2008).

Isolated cartilage lesions are often related to subchondral bone marrow lesions (BMLs). Baseline BMLs are predictive of site-specific defect progression and cartilage volume loss in

a dose-response manner, which suggests that BMLs may have a local effect on cartilage homeostasis. Such baseline defects are predictive of site-specific BML progression, which may represent increased bone loading adjacent to defects (Dore et al. 2010). These results suggest that BMLs and cartilage defects are closely related and may have key roles in knee cartilage volume loss. As such, both cartilage defects and bone marrow lesions should be considered targets for intervention. Furthermore, knee cartilage defects in older adults are common but less likely to regress than in younger individuals (Carnes et al. 2012). Baseline factors found to be associated with increase in defect score over 3 years were radiographic osteoarthritis, tibial bone size, BMI, and being female (Carnes et al. 2012). However, the clinical decision to perform cartilage repair is based on the degree of pain caused by the lesion in a healthy joint, or even in an early OA joint.

The established cartilage repair methods were developed for focal traumatic defects, most frequently in an otherwise healthy joint. Those methods also have limited application in early degenerative joints, such as those with chronic instability and meniscal loss. Cartilage lesions in these patients are characterized not only by existing biomechanical problems but also by occasionally severe biochemical changes that may negatively influence the cartilage repair (Ferruzzi et al. 2014). The use of such methods in joints with more severe OA is, however, rare.

### Repair methods

The goal is to fill a symptomatic cartilage defect with a durable repair tissue that will provide patients with pain relief and functional recovery. The techniques could be either procedures that only address cartilage repair, or osteochondral procedures to treat both cartilage and subchondral bone.

Classically, the different repair technologies include:
- Bone marrow stimulation techniques—in isolation or augmented
- Cartilage tissue-based repair
- Chondrogeneic cell-based repair
- Synthetic or metal-based repair
- Pharmacologically stimulated repair

Normal cartilage repair is very much dependent on the presence of an intact surrounding shouldering cartilage. Lesions in a degenerative environment have much less healthy surrounding cartilage, and the cartilage thickness surrounding such a lesion varies substantially. There is not one repair technique that addresses all types of lesions equally well, and considerable knowledge about the repair of focal defects in normal cartilage is necessary before initiating treatment for early osteoarthritic lesions.

From here on, we will discuss the biological surgical methods that are available and have been used to some extent for the treatment of degenerative and/or OA joints, with the aim of inducing a repair tissue.

Table 1. Bone marrow stimulation of degenerative and/or osteo-arthritic joints

**≥ 45 years without any reference to the joints being diseased**
- Miller et al. 2004, therapeutic case series        LOE 4  RoB high
- Bae et al. 2013, therapeutic case series           LOE 4  RoB high
- Solheim et al. 2014, case series                   LOE 4  RoB high
  *Summary:* Younger age was beneficial for the outcome.

**Reports on pure OA patients treated by bone marrow stimulations**
- Bae et al. 2013, case series                       LOE 4  RoB high
  *Summary:* Half of the patients (62) had undergone total knee arthroplasties (TKA) at a follow-up of 12 years after the index procedure.
- Miller et al. 2004, therapeutic case series        LOE 4  RoB high
  *Summary:* Significant improvement in outcome scores but 1/5 had complications needing extra surgeries.
- Sakata et al. 2013, case series                    LOE 4  RoB high
- Kaul et al. 2012, case series                      LOE 4  RoB high
  *Summary:* Results suggest that arthroscopic marrow stimulation might not improve clinical symptoms for the long-term due to poor repair tissue formation.
- Sterett et al. 2010, case series                   LOE 4  RoB high
  *Summary:* 91% survivorship at 7 years after a combination of high tibial osteotomy and microfracture. Eleven percent of the patients were operated on with artificial arthroplasty after mean 81 months.

**Bone marrow augmented techniques for degenerative and/or osteoarthritic joints**
- Gille et al. 2013, prognostic study                LOE 4  RoB high
  *Summary:* Three age groups were studied with less good results in the age group > 47 years.
- Anders et al. 2013, RCT                            LOE 2  RoB mod.
  *Summary:* No age influences seen on the repair between micro-fracture alone or augmented microfracture. Mean age 37 (21–50).
- Shive et al. 2015, RCT                             LOE 1  RoB low
  *Summary:* Gel augmentation patients had significantly better MRI results compared to only microfracture patients but the mirctofrac-ture group was significantly older; mean age 40.0 ± 10.0 vs 34.3 ± 9.7 years; p = 0.03.
- Di Martino et al. 2015, case series                LOE 4  RoB high
  *Summary:* A significant difference was shown between patients younger versus older than 40 years, with younger patients having a significant better clinical improvement.
- Brittberg et al.1994, case series                  LOE 4  RoB high
- De Windt et al. 2012, case series                  LOE 4  RoB high
  *Summary:* Carbon as scaffolds for treatment of early localized OA gives significant pain relief up to 4 years follow-up.

LOE = Level of evidence (1–4)
RCT = Randomized controlled trial
RoB = Risk of bias (low, moderate, high)

## Bone marrow stimulation of degenerative and/or osteoarthritic joints (Table 1)

The chondrogeneic potency of bone marrow-derived mesen-chymal stem cells of elderly patients is clearly inferior, which could negatively affect the treatment outcome of bone marrow stimulation techniques when used in older patients. Further-more, if these patients' joints are not only affected by age but are also in a diseased state, the reparative capacity will be fur-ther reduced (Smeriglio et al. 2015).

A recent review summarized the primary indications for bone marrow stimulation (BMS) with either microfracture or drilling (Gomoll et al. 2012). Briefly, BMS is indicated for the treatment of full-thickness defects in articular cartilage without significant bone involvement and measuring less than or equal to 2–4 $cm^2$. The review also noted that an elevated BMI (30 or over), defects larger than 2–4 $cm^2$, patellofemoral compartment/tibial plateau defects, and a patient age of 35–45 years or more, are associated with worse outcomes (Gomoll 2012).

The most frequently used BMS technique is microfracture. Only a few studies have looked at microfracture outcomes in patients aged 45 years and older, without any reference to the joints being diseased (Miller et al. 2004, Bae et al. 2013). In these studies, it was clear that younger age was beneficial for a successful outcome (Miller et al. 2004, Bae et al. 2013).

Furthermore, reports on patients with established OA treated by BMS are few. A minimum 10-year follow-up survival anal-ysis on microfracture in osteoarthritic knees showed that only 40% of the surviving patients underwent total knee arthro-plasty (TKA) (Bae et al. 2013). These findings suggest that the size of the initial OA lesion (improved outcomes in lesions < 2 $cm^2$ in their study) is the most important factor in determining the survival of microfractured OA knees—defining survival as time before TKA is performed (Bae et al. 2013).

In another study carried out on 81 middle-aged patients with a mean age of 49 years who had undergone arthroscopic microfracture for isolated osteoarthritic cartilage defects, out-come scores improved significantly without any significant association between the improvement in score and a patient's age or sex (Miller et al. 2004). The study, however, revealed complications in one fifth of the patients, including the need for lysis of adhesions, the need for revision surgery, and the need for subsequent TKA.

The use of marrow stimulation as a treatment for large car-tilage defects in osteoarthritic knees has also been explored (Sakata et al. 2013). Marrow stimulation resulted in reduced knee pain in the short term. However, varus leg alignment gradually progressed and TKA was required in many patients. It is important to note that the grade of cartilage repair was not improved. Marrow stimulation resulted in insufficient car-tilage regeneration on medial femoral condyles. The reason for failure might be explained by the fact that failed marrow stimulation of articular cartilage defects in patients with early osteoarthritis is characterized by fibrocartilaginous repair (Kaul et al. 2012). A failure could also be due to malalign-ment that has not been corrected at the time of surgery, as shown in a retrospective study of 106 patients (Sterett et al. 2010). A knee survivorship of 91% was found at 7 years after a combination of high tibial osteotomy and microfracture, and 12 patients (11%) had been revised with arthroplasty.

In summary, BMS, mainly performed as microfracture, is an extensively studied procedure for the treatment of isolated traumatic cartilage defects. However, the applicability and outcomes of the procedure in OA patients have not been rigor-ously studied, and the few studies that have been published

have shown results that are generally worse in older patients with OA.

### Bone marrow-augmented techniques for degenerative and/or osteoarthritic joints (Table 1)

Various single-stage scaffold-based cartilage repair techniques exist today that can improve clinical outcomes after treatment of isolated cartilage defects. Scaffolds used in cartilage repair can be based on components of the cartilage matrix such as collagen or hyaluronan (van Osch et al. 2009, Gomoll 2012), proteins and natural polymers (such as fibrin, agarose, alginate, and chitosan) (Bonzani et al. 2006), or synthetic polyesters (such as polylactic acid, polyglycolic acid, polylactide-coglycolide, polyethylene oxide, and polypropylene oxide) (Kon et al. 2015). Chondral scaffolds are either composed of a single material (monophasic scaffold) or are layered structures to better reconstruct the biphasic architecture of the osteochondral unit (cartilage and bone). The matrices currently used most frequently for cartilage repair consist of collagen (Gille et al. 2013).

There have been few studies involving the repair of degenerative cartilage lesions using cell-based techniques (de Windt et al. 2013). Since cell-free scaffolds have been developed only recently, even fewer clinical studies have been published, mostly with short-term follow-up and a limited number of patients with degenerative joints.

Scaffold-enhanced microfracture is a treatment principle for focal full-thickness cartilage defects, combining microfracture with a protective cover of a collagen or polymer scaffold. If a collagen scaffold is used, the principle is also designated autologous matrix-induced chondrogenesis (AMIC) (Gille et al. 2013). With the use of microfractures, chondrogenic cells (MSCs) migrate into the fibrin network of the blood clot. However, the fibrin clot is not very stable (Benthien and Behrens 2010, 2015). An implanted covering scaffold (e.g. a collagen matrix) can possibly improve the mechanical stability of endogenous cells from the bone marrow. A study from an AMIC company registry included 57 patients in 3 age groups: 17–32 years, 33–46 years, and over 46 years. It was found that all 3 age groups had significant improvements in outcome scores at 2-year follow-up. It was also shown that there was a tendency for less improvement in patients over 47 years of age (Gille et al. 2013).

In another study, 38 patients (mean age 37 years, mean defect size 3.4 cm2) were randomized and treated either with microfracture alone, with sutured AMIC, or with glued AMIC (Anders et al. 2013). Considerable improvements were seen in all groups, but without statistically significant differences between the groups (Anders et al. 2013).

Cartilage-stimulating hydrogels have been developed, and one such scaffold is a chitosan-based biomaterial developed to form a stable clot in the cartilage lesion after microfracture (Shive et al. 2015). This product has been tested in a randomized study and compared to microfracture alone. Blinded MRI analysis demonstrated that hydrogel-treated patients showed a statistically significantly greater treatment effect for lesion filling over 5 years compared to microfracture alone. It is important to highlight that these patients with microfracture alone were significantly older than those in the gel group (mean age 40 years as opposed to 34.3 years) (Shive et al. 2015). Other hydrogels for cartilage repair exist but so far only used clinically too short and those gels have not yet been tried in elderly.

Osteochondral scaffolds are designed to induce healing of combined bone and cartilage lesions. One scaffold (Maioregen; Fin-Ceramica, Faenza, Italy) is a porous 3-dimensional tri-layer hydroxyapatite-collagen composite structure that mimics the osteochondral anatomy (Delcogliano et al. 2014). It has been used in a study for treatment of early OA (Di Martino et al. 2015), in which 23 patients were prospectively evaluated for up to 2 years. The etiology of the chondral or osteochondral defect was rated as micro-traumatic or degenerative in 18 cases, and traumatic in 5 cases. All the patients improved in a statistically significant manner clinically in all the scores that were used. Patients less than 40 years of age had statistically significant better clinical improvements than those who were older.

Woven meshworks of carbon fiber filaments (used as carbon pads and rods) have been used for more than 25 years to treat a spectrum of cartilage damage ranging from focal defects to widespread degenerative lesions and early OA. In a carbon fiber study on 37 patients with an average age of 39 (25–53) years and an average follow-up of 48 (33–63) months, the outcomes were assessed with 4 scoring systems (Brittberg et al. 1994b). 30 of the 36 patients who could be observed were rated as good or excellent. The most striking result was good pain relief. In another study (de Windt et al. 2012), carbon fiber implants were used for salvage cases with degenerative joints treated arthroscopically, and there were statistically significant clinical improvements at 3 years after surgery.

In summary, several single-stage scaffold-based cartilage repair techniques exist today that can improve clinical outcomes after treatment of isolated cartilage defects. Only limited data are available regarding the application of these techniques specifically for the treatment of early OA or cartilage lesions in older patients.

### Autologous chondrocyte implantation as treatment for degenerative and/or osteoarthritic joints (Table 2)

Autologous chondrocyte implantation (ACI) was introduced in the late 1980s as the first manipulated cell-based treatment for cartilage defects of the knee (Brittberg et al. 1994a).

There have been numerous reports on ACI treatment of various patient subpopulations, but most reports have been on non-OA joints. Today, there are long-term results covering up to 20 years with first-generation ACI (Peterson et al. 2010, Brix et al. 2014, Niemeyer et al. 2014, Knutsen et al. 2016). In 2016, there have been 14 RCTs where different generations of autologous chondrocyte-mediated repair (ACI genera-

Table 2. Autologous chondrocyte implantations (ACI)

| | | |
|---|---|---|
| **ACI (1st Generation)** | | |
| • Brittberg et al. 1994, case series | LOE 4 | RoB high |
| **Long-term follow-ups with ACI** | | |
| • Peterson et al. 2010 case series | LOE 4 | RoB high |
| • Brix et al. 2014 case series | LOE 4 | RoB high |
| • Niemeyer et al. 2014 case series | LOE 4 | RoB high |
| **RCT with different ACI generations** | | |
| **– 1st and 2nd generation ACI** | | |
| • Horas et al. 2003, RCT | LOE 2 | RoB mod. |
| • Bentley et al. 2003, RCT | LOE 2 | RoB mod. |
| • Dozin et al. 2005, RCT | LOE 2 | RoB mod. |
| • Knutsen et al. 2004, 2007, 2016, RCT | LOE 1 | RoB mod. |
| • Lim et al. 2012 RCT | LOE 2 | RoB mod. |
| • Vanlauwe et al. 2011, RCT | LOE 1 | RoB low |
| **– 3rd generation ACI** | | |
| • Visna et al.2004, RCT | LOE 2 | RoB mod. |
| • Basad et al. 2010, RCT | LOE 1 | RoB Low |
| • Crawford et al. 2012, RCT | LOE 2 | RoB mod. |
| • Saris et al. 2014, RCT | LOE 1 | RoB low |
| • Akgun et al. 2015, RCT | LOE 2 | RoB low |
| • Clavé et al. 2016, RCT | LOE 1 | RoB mod. |
| **– 4th generation ACI (cartilage fragments)** | | |
| • Cole et al. 2011, RCT | LOE 2 | RoB mod. |
| • Spalding et al. 2011, RCT | LOE 2 | RoB mod. |
| **Autologous chondrocyte implantation as treatment for degenerative and/or osteoarthritic joints** | | |
| • Ossendorf et al 2007, case series | LOE 4 | RoB high |
| • Kreuz et al. 2009, case series | LOE 4 | RoB high |
| *Summary:* Overall improvements in patients affected by early osteoarthritis treated with polymer-based autologous cartilage implants. Results were sustained over 4 years follow up and significant improvement in symptoms and good defect filling on MRI were seen. | | |
| • Minas et al. 2010, case series | LOE 4 | RoB high |
| • Rosenberger et al. 2008, case series | LOE 4 | RoB high |
| *Summary:* Large early OA knees were treated with significant outcome improvements and with failure rates between 8–14% (knees turned into joint arthroplasties after up to 11 years follow up). | | |
| • Filardo et al. 2012, case series | LOE 4 | RoB high |
| *Summary:* Patients with degenerative lesions were treated and statistically significant improvements were observed in all the scores at mid-term follow-up. However, these scores were lower and failures more frequently than previously reported in non-arthritic populations. | | |
| • Bauer et. 2012, case series | LOE 4 | RoB high |
| *Summary:* There were significant improvements in all five KOOS domains. Four were significantly maintained to 5 years. | | |

LOE, RCT, and RoB, see Table 1

tions1–4) have been compared with other techniques (Horas et al. 2003, Bentley et al. 2003, Visna et al. 2004, Knutsen et al. 2004, 2007, 2016, Dozin et al. 2005, Basad et al. 2010, Vanlauwe et al. 2011, Cole et al. 2011, Spalding et al. 2011, Lim et al. 2012, Crawford et al. 2012, Saris et al. 2014, Akgun et al. 2015, Clavé et al. 2016).

While there continues to be no indication for cartilage repair in severe OA with complete loss of joint space, favorable results have been obtained with ACI in early OA when all articular comorbidities involved were recognized and addressed (Minas 2003, Minas et al. 2010, Filardo et al. 2012).

Although the disturbed homeostasis presents a challenging environment, studies have provided evidence that even degenerative pathology may benefit from regenerative techniques. In a clinical pilot study, cell-based implants were placed in human osteoarthritic joints and showed signs of healing, thus demonstrating that regenerative processes are not completely inhibited by the degenerative environment (Hollander et al. 2006). Furthermore, it has been shown that chondrocytes obtained from arthritic knees still exhibit good proliferative potential and are able to re-differentiate and produce extracellular matrix when re-introduced into a three-dimensional pellet model (Tallheden et al. 2005). Cavallo et al. (2010) confirmed these findings, showing that a hyaluronan-based scaffold might favor the activation of anabolic factors, and the same research group reported that the addition of chondrocytes to a scaffold produced better repair tissue than scaffold alone in an animal model of osteoarthritis (Desando et al. 2012).

The literature also has findings that are promising for the treatment of degenerative lesions. Overall improvements have been noted in patients affected by early osteoarthritis who were treated with polymer-based autologous cartilage implants (Ossendorf et al. 2007). These results have been confirmed by another study that found stable results 4 years after implantation of focal degenerative lesions, with significant improvement in symptoms and good defect filling on MRI (Kreuz et al. 2009).

There are long-term first-generation ACI results for the treatment of early OA, in 153 patients with a mean age of 38 years who were followed for up to 11 years (Minas et al. 2010). On average, 2.1 defects were treated per knee with a defect size of 4.9 cm$^2$ and a total area per knee of 10 cm$^2$. It was noted that 12 joints were revised with arthroplasty; the remaining patients experienced 50–75% improvement in WOMAC subscale, and patient satisfaction exceeded 90%. The same group also reported on their outcomes of ACI in 56 patients over 45 years of age, a group that can be considered to represent early OA rather than acute focal defects. These patients (average age 48 years; average follow-up 4.7 years) with an average defect size of 4.7 cm$^2$ and a total treated area of 9.8 cm$^2$ had a total of 8 patients with failures, 6 patients being worker's compensation patients (Rosenberger et al. 2008).

For patients with degenerative cartilage lesions (but not established OA) treated with arthroscopic hyaluronic scaffold ACI, statistically significant improvement was found in all the scores at medium-term follow-up (Filardo et al. 2012). These scores were lower, however, and failures were observed more frequently than what had been reported previously in non-arthritic populations (Kon et al. 2011).

Cartilage defects rarely exist in isolation, especially in patients with early OA. Thus, special consideration must be given to the identification and treatment of concurrent pathologies, such as malalignment. Unloading as part of ACI treat-

ment has been investigated, with a statistically significant clinical improvement being noted in 18 patients with medial knee OA (mean age 47 years) who received matrix-induced ACI and concurrent high tibial osteotomy (Bauer et al. 2012).

In summary, ACI can be considered for the treatment of cartilage defects in the setting of early OA in younger patients. Different generations of ACI techniques have been studied both in long-term follow-ups and in several randomized trials (level 1–2, most of them with a moderate RoB; see Table 2), showing that chondrocyte implantation may give improvement in patients with traumatic local cartilage defects. In this section on ACI treatment of degenerative joints, the studies presented have investigated outcomes with a level of evidence limited to case series—accordingly with a high risk of bias. Reported outcomes showed improved pain and function, and also a high degree of satisfaction in the majority of patients. However, patients with local defects in a degenerative/early OA joint should be counselled that this procedure will not provide a normal knee and should be seen as a bridging intervention to probably delay arthroplasty.

### Allografts for degenerative and/or osteoarthritic joints (Table 3)

Very large chondral and osteochondral defects have traditionally been treated with osteochondral allograft transplantation. Young patients with severe joint trauma can develop a degenerative joint that, if the patient was older, would be treated with a prosthetic joint replacement. For such young to middle-aged patients afflicted by degenerative joint disease, osteochondral allograft transplantation may be an alternative. However, because biologically subtle immunological responses may occur within the joint, the long-term consequences of which have yet to be fully characterized, the allografts do not last forever (failure can occur both within the bone and in the cartilage). Fresh and cryopreserved allografts are available options for these patients. Patients with opposing (bipolar) joint lesions (Meric et al. 2015), uncorrectable malalignment, or advanced osteoarthritis—and those over 40—tend to have less favorable outcomes.

**Fresh stored osteochondral allograft**

In comparison to autograft tissue, osteochondral allografts (OCAs) have no donor site morbidity and OCA reports have demonstrated good long-term outcomes (Gross et al. 2005, Raz et al. 2014). In addition, OCA can be used to treat large and uncontained lesions. However, disadvantages of OCA are the possibility of disease transmission, unknown long-term immune response, and limited availability.

Pioneering work on allografts was done in Canada (Gross et al. 1975) and in the USA (Locht et al. 1984, Garrett 1986, Meyers et al. 1989, Convery et al. 1991). These reports were case series with LOE 4 and high RoBs involving patients with degenerative, traumatic large defects. Long-term follow-up has shown 95% survivorship of OCA at 5 years and 85%

**Table 3. Osteochondral allografts**

**Longterm results with osteochondral allografts**
- Gross et al. 2005, prospective cohort study      LOE 2   RoB mod.
- Raz et al. 2014, case series      LOE 4   RoB high
  *Summary:* Survival analysis revealed 95% survival at 5 years and 59% at 25 years. Patients with surviving grafts had good function, with a mean modified HSS score of 86 at 15 years or more following the allograft transplant surgery. Late osteoarthritic degeneration on radiographs was associatedwith lower HSS scores and poorer clinical outcomes.

**Allografts for degenerative and/or osteoarthritic joints**
**– Fresh stored osteochondral allograft**
- Jamali et al. 2005, case series      LOE 4   RoB high
  S*ummary:* Fresh osteochondral allografting is a salvage procedure for the young, active patient with severe degenerative articular cartilage disease of the patellofemoral joint.
- Getgood et al. 2015, case series      LOE 4   RoB high
  *Summary:* Concomitant osteochondral allografts + meniscal allografts were performed. The underlying diagnosis was trauma (tibial plateau fracture) in 33 % with osteoarthritis predominating in 54 % of cases. A trend towards a worse outcome was observed with bipolar tibio-femoral grafts in the setting of OA.
**– Particulated osteochondral allograft (PJAC)**
  *Summary:* There are no reports on the use of PJAC on aging, degenerative joints.
**– Cryopreserved osteochondral allograft**
  *Summary:* No clinical report on the treatment ofdegenerative cartilage exist but the technique is interesting for an early OA treatment related to a potential delivery of growth factors to the diseased environment.

LOE, RCT, and RoB, see Table 1

survivorship at 10 years in 60 patients with femoral condylar lesions, and survivorship rates of 95%, 80%, and 65% at 5, 10, and 15 years, respectively, in 65 patients treated with tibial plateau lesions (Gross et al. 2005). A recent long-term follow-up found similar results in 58 patients (Raz et al. 2014).

Reports exist also on 48 patients who received simultaneous meniscal allograft transplantation (MAT) and osteochondral allografts (OCA) between 1983 and 2011 (Getgood et al. 2015). The main underlying diagnoses were trauma in one third and osteoarthritis in one half of the cases. The overall success rate of concomitant meniscal allografts and OCA was comparable with results reported for either procedure in isolation. A trend of worse outcomes was observed with bipolar tibial-femoral grafts in the setting of OA. The 5-year survivorship was 78% and 73% for MAT and OCA, respectively, and 69% and 68% at 10 years (Getgood et al. 2015).

**Particulate osteochondral allograft**

The implantation of fragments of juvenile allograft cartilage is termed particulate juvenile allograft cartilage (PJAC) (DeNovo NT Natural Tissue Graft; Zimmer Inc., Warsaw, IN) (Tompkins et al. 2014). The tissue is juvenile allograft articular cartilage (with donors being less than 13 years of age) that is cut into approximately 1- to 2-mm cubes. PJAC is applied in a monolayer and secured in the defect with fibrin glue,

which has been prepared for use with cell implants (cleared base and vertical walls) (Farr et al. 2014). In the USA, PJAC falls under the same human tissue regulatory pathway as fresh stored OCA (HCT/P 361). As this does not require a Biological License Application (BLA) based on a randomized controlled trial, none are planned.

There have been no reports on the use of PJAC in ageing, degenerative joints.

## Cryopreserved osteochondral allograft

As fresh tissue is difficult to manage logistically, the alternative possibility of using frozen osteochondral allograft was enticing (Malinin et al. 1994). Unfortunately, the freezing process had resulted in chondrocyte lysis, and the absence of chondrocytes in turn caused gradual deterioration of the extracellular matrix.

With new developments in tissue processing, there is a recent technique that reportedly maintains chondrocyte viability at approximately 70%, which may give an adequate cell number to maintain the matrix (Cook et al. 2014). This proprietary tissue cryopreservation technique differs from past attempts: all bone, apart from a few microns, is removed and the resulting cartilage is then perforated. This treatment may aid in better dispersion of cryopreservatives and allow molding of the graft into complex topology while not requiring bone removal when there is no bony lesion/defect (note that OCA removes normal bone if there are no bony defects). Theoretically, the CPAC (cryopreserved perforated allogeneic cartilage) could deliver cells (similar to PJAC) and a variety of growth factors, both of which may influence marrow, cartilage, and synovial recruited mesenchymal stem cells (e.g. TGF-β1: for promotion of chondrogeneic differentiation and regulation of type-II collagen expression; BMP-2, 4, 7: for induction of chondrogenesis by MSCs and stimulation of ECM production by chondrocytes; bFGF: for proliferation of chondrocytes; and IGF-1: for induction of ECM synthesis) (Geraghty et al. 2015). A proprietary in-house study showed defect filling in an animal model, and there is one case report in the literature (Hoffman et al. 2015).

CPAC falls under the same FDA exclusion as PJAC and OCA, and therefore does not require a BLA. There have been no clinical reports on the treatment of degenerative cartilage with CPAC. However, the technique is interesting for an early OA treatment related to a potential growth factor delivery through the perforated structure of CPAC to a diseased environment. (Geraghty et al. 2015).

In summary, the indications for the different types of allograft transplantations include treatment of large chondral or osteochondral defects and salvage of previously failed cartilage repair. The procedure can also be used for complex biological knee reconstruction, as seen in osteonecrosis, in fracture malunion, and in early posttraumatic osteoarthritis in young patients (Sherman et al. 2014).

## Stem cell treatment for degenerative and/or osteoarthritic joints (Table 4)

The self-renewing ability and pluripotency of stem cells has led to it being keenly explored as an alternative to chondrocytes for cartilage repair. Its superior proliferation rate has made the use of greater cell numbers possible for the treatment of large cartilage defects. The collection of stem cells is usually minimally invasive, and some stem cell treatments are offered as single-stage procedures, which enhances the attractiveness of its usage—alongside the reduced financial burden on patients.

### Bone marrow-derived mesenchymal stem cells

Encouraging results have arisen from the use of bone marrow mesenchymal stem cells (BM-MSCs) for cartilage regeneration. In 2002, successful repair of cartilage defects using expanded BM-MSCs in osteoarthritic patients operated with high tibial osteotomy was reported (Waitangi et al. 2002). Despite the lack of obvious clinical improvements, arthroscopic and histological grading scores were better in the cell-transplanted group than in the cell-free control group (Wakitani et al. 2002). This discovery played a leading role in opening up the possibility of BM-MSCs being used for cartilage repair in ageing joints. Safety of autologous BM-MSC transplantation for cartilage repair has been confirmed by long-term follow-up of 41 patients (Wakitani et al. 2011). The results showed that patients who received the stem cell treatment did not develop tumors or infections even after 11 years of follow-up, which is currently the strongest evidence for the safety of BM-MSC transplantation for articular cartilage repair (Wakitani et al. 2011).

In a comparison between ACI and BM-MSCs, BM-MSC transplantation was found to be as effective as ACI for articular cartilage repair (Nejadnik et al. 2010). A greater improvement in "physical role functioning" was observed in the BM-MSC group over time. Patient age was found to be negatively correlated to the clinical outcome in the ACI-treated group but not in the BM-MSC-treated group, where patients older than 45 years had the same clinical outcomes as younger patients.

A phase-I/II trial (open-label, single-dose, single-arm clinical trial) on 15 patients (mean age 52 years) suffering from grade-II to -III Kellgren-Lawrence OA showed a relevant decrease in pain intensity from the eighth day after injection, and confirmed the safety of MSC treatment for ageing patients, as seen from the low number of adverse events that were reported during the follow-up period (Soler et al. 2016). Interesting results were also reported from a clinical trial involving older patients (mean age 57 years) using BM-MSC treatment (Kim et al. 2013). The improvement was better in patients with large lesions.

Allogeneic BM-MSCs hold great potential for the treatment of knee cartilage defects. 30 patients with chronic knee pain that was unresponsive to non-operative treatments, and with radiological osteoarthritis, were randomized into 2 groups of

**Table 4. Stem cells treatment for degenerative and/or osteoarthritic joints**

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**Autologous bone marrow-derived mesenchymal stem cells**
**– Safety study**
  Yamasaki et al. 2014, RCT          LOE 2   RoB mod.
  *Summary:* patients who received the stem cell treatment did not develop tumours or infections even at 11 years follow-up.

**– Clinical follow-up studies**
• Wakitani et al. 2002, RCT LOE 2 RoB mod.
  *Summary:* Successful repair of cartilage defects using expanded bone marrow mesenchymal cells for 24 patients with mean 63 years age with OA who underwent a high tibial osteotomy.

• Nejadnik et al. 2010, cohort study      LOE 3   RoB mod.
  *Summary:* It was found out that age affected the clinical outcome in chondrocyte implanted group, but not in the bone marrow-MSCs group. Patients older than 45 years in bone marrow-MSCs group had the same results as younger patients.

• Soler et al. 2016, open-label, single-dose,
  single-arm trial                LOE 3   RoB mod.
  *Summary:* The study showed decrease in the intensity of pain in the study patients since day 8 post injection, and confirmed safety of MSCs treatment for aging patients by low adverse events reported during the follow-up period.

• Kim et al. 2015. Cohort study LOE 3 RoB high
  *Summary:* Old patients were treated with significant improvement in pan relief. The improvement was more significant for patients with large lesion size or existence of subchondral cysts.

**Allogeneic bone marrow-derived mesenchymal stem cells**
• Vega et al. 2014, RCT             LOE 2   RoB low
  *Summary:* OA Patients with mean age of 57 were treated by MSCs. The result showed cartilage quality improvements by T2 relaxation measurements and safety was confirmed by no serious adverse event reported.

• Wong et al. 2015, RCT            LOE 2   RoB low
  *Summary:* 56 knees with unicompartmental osteoarthritic knees were treated by microfracture and osteotomy ±mscs. The cell-recipient group showed significantly better clinical scores after 1 year follow-up than control group.

• Enea et al. 2013, case series        LOE 4   RoB high
• Gobbi et al. 2016, prospective cohort study    LOE 2   RoB mod.
  *Summary:* The follow ups showed similar results that bone marrow mscs or bone marrow concentrates could be useful for patients older 45 years, and the outcome was mainly affected by lesion size and number but not age.

**Peripheral blood progenitor cells**
• Saw et al. 2015, therapeutic case series     LOE 4   RoB high
  *Summary:* Repair with stem cells in combination with medial open-wedge HTO for varus deformity correction of the knee joint induced a repair tissue that closely resembled the native articular cartilage.

**Adipose-derived mesenchymal stem cells**
• Koh et al. 2012, therapeutic case-control study LOE 3   RoB high
  *Summary:* Adipose stem cells group showed significantly poorer scores than a control group but the clinical results during the follow-up period were similar and had no significant difference.

• Kim et al. 2014, cohort study         LOE 3   RoB high
  *Summary:* Patient age > 46 years.

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LOE, RCT, and RoB, see Table 1

15 (Vega et al. 2015). 1 group was treated with allogeneic bone marrow MSCs by intra-articular injection. The control group received hyaluronic acid intra-articularly in a single dose. 1

year postoperatively, T2 relaxation measurements showed that MSC treatment had led to improved cartilage quality. The MSC-treated patients showed statistically significant improvement in pain reduction relative to the controls.

The use of high tibial osteotomy (HTO) combined with microfracture with or without BM-MSCs mixed in hyaluronic acid gel (HA) for injection in patients (mean age 51) with varus knee and cartilage defects has also been reported (Wong et al. 2013). At the 1 year follow-up, the cell-recipient group showed statistically significantly better clinical scores than the control group.

Bone marrow concentrate (BMC) implantation has been successfully demonstrated as a single-stage technique for cartilage repair in 9 patients with focal lesions (mean age 48 years) (Enea et al. 2013). The patients were treated with microfracture and BMC scaffold, and 8 of them showed improvement at the 2-year follow-up. The results demonstrated the clinical effectiveness of BMC implantation for cartilage repair, even in this middle-aged group with early signs of cartilage degeneration. In a comparative study, the efficacy of BMC treatment in patients over 45 years of age and in younger patients was studied (Gobbi et al. 2016). BMC was found to be effective for patients over 45, and the outcome was mainly affected by lesion size, not patient age (Gobbi et al. 2016).

**Peripheral blood progenitor cells**

Stem cells can also be induced to enter the peripheral blood through the use of growth factors. In a randomized level-2 study, the use of peripheral blood progenitor cells (PBPCs) and HA gel for the treatment of cartilage defects after arthroscopic subchondral drilling was studied in 50 patients with a mean age of 38 years (Saw et al. 2013). Arthroscopy results confirmed that there was articular cartilage repair, and hyaline-like cartilage tissue repair was observed by histological analysis. The result showed that intra-articular injection of PBPCs and HA is a possible method for articular cartilage repair, and in another paper the same authors also described the method as being usable for knees with varus deformity (Saw et al. 2015).

**Adipose-derived mesenchymal stem cells**

Lipo-aspirates offer a convenient source of cells for cartilage tissue engineering, due to their abundance and potential to differentiate into cartilage. 25 patients diagnosed with knee osteoarthritis (mean age 54 years) underwent arthroscopic debridement and injection of adipose stem cells combined with platelet-rich plasma (PRP) (Koh and Choi 2012). No major adverse events related to the injections were observed during the 12- to 18-month follow-up period. Patients subjected to adipose stem cell treatment showed poorer scores than the control group. However, the clinical results during the follow-up period were similar.

In summary, the use of both autologous and allogeneic bone marrow MSCs has consistently resulted in early pain relief.

Several studies have shown clinical improvements in osteoarthritic patients with large lesion sizes. Despite these encouraging findings, studies with larger numbers of patients are required to confirm the efficacy of MSCs for repair of osteoarthritic cartilage defects.

## General discussion

In this review, there have been many papers studying the effect of different cartilage repair methods on cartilage injuries in middle-aged patients where one can expect a certain degree of degenerative cartilage, but there have not been many papers where the study group had manifest osteoarthritis.

In general, results were less good when using pure bone marrow stimulation, but in some reports the results were less age-dependent when using an augmentation. Regarding the treatment of early degenerative joints with ACI, reported outcomes showed improved pain and function, as well as high satisfaction, in the majority of patients—but the level of evidence was limited to case series with a high risk of bias. The technique with the largest number of degenerative joints treated and the longest follow-up is osteochondral allograft transplantation (OCA). However, the OCA studies and most of the other repair studies that have been reviewed were level-4 studies, with only a few high-level studies. Furthermore, the risk of bias in the studies included has been mostly high. Different forms of stem cell treatment are now being presented, and with direct focus on OA. Several of these papers have reported pain relief in their study groups, but the stem cells were of different origin and it is difficult to compare the studies.

In summary, the applicability and outcomes of these cartilage repair techniques in OA patients have not been rigorously studied, but the few available studies have had results that are generally worse in older patients and those with OA. The main effect of the different treatments has been pain relief.

It is important to understand that cartilage repair techniques have been developed to treat patients with localized cartilage injuries, to reduce joint pain and mechanical disabilities. These techniques should be seen as plug-in techniques inducing a reasonably functional, good-quality repair tissue that can reduce symptoms—and with long durability. A common misunderstanding is that it might be possible to use these cartilage repair methods to resurface a generalized osteoarthritic joint characterized by thinning of cartilage and subchondral cyst development. However, such a tissue engineered product is still a dream scenario.

In early OA, however, local defects exist that may also give pain and mechanical disability. Such defects can be treated with the cartilage repair methods described in this review, but increasing age may influence the results negatively, and the results are based on case series with a high degree of bias. Such patients may not be suitable candidates for joint arthroplasty, and when non-operative treatments such as physiotherapy and weight reduction are not enough, local repair of such defects may be useful.

### The challenge, and translation to the clinic

The treatment of local cartilage injuries in an otherwise healthy joint has been successful in terms of pain relief and functional recovery using a variety of methods in young patients. However, the translation of methods used for local traumatic cartilage defects to joints with an unhealthy cartilage matrix and disturbed joint homeostasis is a difficult task. Still, the local repair methods need to be improved regarding our knowledge of how to induce and control the repair events for different types and locations of lesions.

The weaknesses of all the cartilage repair techniques available to date is that none of them have been able to induce the zonal organization of chondrocytes that is seen in vivo. Such zonal organization must be shown in local cartilage repair before one can use cartilage repair techniques to resurface an osteoarthritic joint (Felka et al. 2016). The choice of type of cell could be crucial. There are multipotent mesenchymal progenitor cells, defined as CD105+/CD166+ cells, in human articular cartilage of all ages (Chang et al. 2011). It is of interest that the fetal mesenchymal progenitor cells have the highest rates of proliferation (measured by cell doubling times and chondrogeneic differentiation) compared to those from adults and elderly patients. Furthermore, spontaneous osteogenic differentiation has been detected only in mesenchymal progenitor cells from elderly patients (Chang et al. 2011). The above findings suggest that committed chondrocytes outperform mesenchymal stem cells, that young chondrocytes outperform old chondrocytes, and that cartilage progenitor cells outperform committed chondrocytes. The most suitable cell type to use when repairing a cartilage defect in an early degenerative joint would then theoretically be allogenic cartilage progenitor cells from young individuals. Further support for this theory comes from a study showing statistically significantly better repair when allogenic young cartilage fragments were mixed with fragments from old donors, compared to the use of only old cartilage fragments when treating cartilage defects in a rabbit model (Bonasia et al. 2015).

Furthermore, there is a sliding scale of cartilage areas to treat—from the local fresh lesions with normal surrounding cartilage to slightly degenerative cartilage to early OA, but still with a substantial amount of cartilage shouldering the traumatized cartilage. With better characterization of the cartilage defects that are treated and well-documented in cartilage registries, we will be able to define when and where an operative attempt could be performed, related to the status of the cartilage and the joint. Monitoring of these patients with serum biomarkers could be of great value for evaluation of the effect of local repair on joint disease processes.

### Future treatment goals

To move our knowledge forward for improvement of treat-

ment possibilities for degenerative joints, we need to:

• Define more precisely the difference between a local traumatic defect, a posttraumatic degenerative lesion, and OA (Jarraya et al. 2016, Dore et al. 2010).

• Determine whether a local cartilage repair may not only reduce pain and disability but also have a disease-modifying effect, slowing down progression to OA (Heir et al. 2010, Ryd et al. 2015).

• Evaluate and compare the use of committed chondrocytes and stem cells of various origins (Sakaguchi et al. 2005, Karlsson et al. 2007, Williams et al. 2010, Marmotti et al. 2014, Nelson et al. 2014).

• Make better use of outcome databases to follow ongoing studies on a global basis, such as ACL- hip and knee prosthesis databases (Gracitelli et al. 2016).

Furthermore, studies of importance that should be done are:

• Prospective long-term studies on the natural course of cartilage lesions of different origins and types.

• Large long-term multicenter RCTs comparing physiotherapy, local biological repairs, and prosthesis implants for early OA.

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