A review of the treatment methods for cartilage defects

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Keywords
Cartilage defects, cartilage repair, animal models, treatment methods

Summary
The purpose of this article is to provide a broad review of the literature related to the treatment of cartilage defects and degenerated cartilage in animals with some inferences to the treatment in humans. Methods range from the insertion of osteochondral tissue or cells to the application of radio frequency or insertion of scaffolds and growth factors alone or in combination. Debridement, microfracture, radio frequency, and chondrocyte implantation are all methods normally utilized when treating smaller articular cartilage defects. Scaffolds and mosaicplasty are examples of methods to treat larger defects. This review will cover all major treatment methods currently used to treat articular cartilage defects.

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Vet Comp Orthop Traumatol 2012; 25: 263–272
doi:10.3415/VCOT-11-05-0070
Received: May 5, 2011
Accepted: January 12, 2012
Pre-published online: January 27, 2012

Introduction

Articular cartilage endures repetitive cyclic loading for the lifetime of an animal or human, yet it has poor intrinsic ability for healing due to its isolation from vessels and nerve supply (1). Once degeneration begins or a defect forms, the bordering intact cartilage starts to degenerate and has the potential to destroy opposing intact cartilage, resulting in progressive osteoarthritis (1, 2).

Methods of treatment range from the insertion of osteochondral tissue or cells to the application of radio frequency energy (RFE) or insertion of scaffolds and growth factors alone or in combination. Some methods have been shown to be problematic when treating cartilage defects; for example RFE has been implicated as a potential cause of glenohumeral chondrolysis in humans (3–6). Debridement, microfracture, RFE, and chondrocyte implantation are all methods normally utilized for smaller articular cartilage defects. Scaffolds and mosaicplasty are examples of methods designed to treat larger defects. Some treatment methods such as debridement and mosaicplasty have been intensely studied and the results of these studies are reported in the literature (7–13). Other techniques are undergoing active and current development, or are in need of further investigation, such as the insertion of xenografts or the addition of growth factors. Many growth factors have been investigated with the goal of using them for insertion into defects with and without the addition of cell implantation (14–19). This review provides an updated analysis of the literature related to the range of treatment methods used for repair of cartilage defects in animals with some inferences to the treatment in humans. Although current methods for articular cartilage defects are promising, no treatment has resulted in complete restoration of the hyaline cartilage and the subchondral bone (20).

Lavage

Arthroscopic lavage is a treatment used to alleviate joint pain by irrigating the joint during arthroscopy (21). Excessive growth of irritated synovial membrane buckles into fronds, which may become inflamed and release destructive enzymes and cytokines (such as interleukin-1 and 2, and tumour necrosis factor-α) into the joint space, causing joint swelling and pain. Removing this excess material via lavage usually resolves knee inflammation or pain. Fu et al. used a rabbit model to evaluate the effects of joint lavage (22). Compared to the control knees, both the breakdown of articular cartilage and the inflammation of synovium were less in the lavaged knees. Synovial fluid volume decreased significantly and proteoglycan content in the cartilage matrix was higher in the treatment group than in the control joints without lavage (22).

Many studies have also evaluated the effectiveness of joint lavage in human patients (23, 24). Chang et al. reported a significant improvement in pain at three months post-lavage, which was sustained up to 12 months (23). Edelson et al. in 1995 described the results of 23 patients in which a total of 29 knees underwent joint lavage with Ringer's solution for the complaint of symptomatic osteoarthritis (24). At one year, the mean pain rating improved from 64 to 89 and mean function rating improved from 62 to 82 using the scoring system developed by The Knee Society[a]. Seventeen of 21 patients evaluated at two years had a good or excellent result (24).

Two studies have compared joint lavage versus needle aspiration for the treatment of inflammatory arthritis in humans (25, 26). Van Oosterhout et al. found joint lavage to have three times less risk of recurrence of symptomatic arthritis compared with needle aspiration after 12 months (26). Tanaka et al. compared joint lavage

[a] The Knee Society: http://www.kneesociety.org/web/index.html

using 1, 3, or 5 L of saline with joint aspiration (25). Patients with knee arthritis of more than six months duration and with a Larsen grade 2 or less were more responsive to joint lavage using 3L or 5L than with 1L of needle aspiration (25).

Reichenbach et al. compared lavage treatment from seven previously reported studies (27–34). Three of the studies examined arthroscopic lavage, two looked at non-arthroscopic joint lavage, and the last two were for tidal irrigation (28–32, 35). Reichenbach found that these studies provided little evidence that joint lavage resulted in pain relief at three months post-treatment, or that it resulted in any improvement of function. Tidal irrigation seemed to have the greatest positive effect when followed by non-arthroscopic lavage with arthroscopic lavage having the least effect on improvement (27).

Lavage is commonly used to alleviate joint pain in lower-demand joints and has been shown to be successful in treating the early stages of osteoarthritis. The procedure does not induce repair of articular cartilage; therefore, the procedure offers relief in the short-term and typically is not intended to provide long-term relief.

Radio frequency energy

Radio frequency energy application is a technique used to melt and remove fibrillated tissue and produce a smooth articular surface. In addition, the melted and sealed articular surface may prevent cartilage wear debris from being released into joints to cause inflammation. An electrosurgical generator is connected to either a bipolar (bRFE) or a monopolar (mRFE) wand that is moved across the irregular and roughened articular surface with or without direct contact depending on the device used (36). Radio frequency energy was first investigated for thermal chondroplasty in 1996–1997 (37–39). The principle of RFE heating with a monopolar probe utilizes an alternating current between the application probe and the grounding plate. This ionic current density produces molecular friction in tissue that results in tissue heating. Frictional or resistive heating of tissue around the probe tip is the primary source of heat, rather than the probe itself (40). When used arthroscopically, the mRFE current path may pass from the probe through the cartilage surface and subchondral bone to the grounding plate on the skin, or from the probe through the irrigation solution to the joint capsule and then to the grounding plate. In bRFE heating, the alternating electric current passes from the RFE generator through the connecting cable, through the probe, through the positive electrode to the negative electrode, where both positive and negative electrodes are in the probe tip. The conduction path of the bRFE is within the irrigation fluid, resulting in vaporization of the physiological saline in the joint. Therefore, the tissue effects with bRFE are typically secondary to thermal and ionic modification of the tissue.

Compared to laser thermal chondroplasty, RFE is inexpensive, safe for operating room personnel, and a simple surgical tool that may be delivered arthroscopically with different application probes that offer flexibility to surgeons (41). Currently, opinions regarding the use of RFE treatment for articular cartilage are wide-ranging and contradictory.

Lu et al. in 2000 evaluated mRFE on articular cartilage and concluded that the effects of mRFE were detrimental (38). Monopolar RFE caused immediate chondrocyte death that progressed to full-thickness death after two weeks with concomitant detrimental effects to cartilage proteoglycan concentration that progressed over time. In 2001 and 2002, both Lu et al. and Edwards et al. evaluated the effects of bRFE compared to mRFE and reported the depth of chondrocyte death to be greater for bRFE systems than mRFE, with the cell death extending to the subchondral bone in many instances (42, 43). Although bRFE resulted in greater depth of chondrocyte death, Lu et al. proposed that both mRFE and bRFE should be used cautiously during thermal chondroplasty, because the devices may result in thermal injury to chondrocytes causing their death (38, 43–45).

In 2008, Edwards et al. compared mRFE, bRFE, and mechanical debridement in a partial thickness defect in a pony model (46). Monopolar RFE treated cartilage showed 50% lower stiffness than that of normal healthy cartilage, but had the highest stiffness value compared with bRFE, mechanical debridement, and control (46). Spahn et al. also evaluated the use of both mechanical debridement and bRFE in a human model, and reported that compared with mechanical debridement, bRFE appeared to be the superior method for achieving a good midterm result (47). The contradictions in these two studies that compared bRFE with mechanical debridement could be attributed to the type of model used, the device used for RFE treatment, and length of study.

In vitro and *in vivo* human case reports have reported detrimental effects to the cartilage after RFE treatment, similar to the above animal model studies. These studies concluded that RFE treatment and temperature may be associated with glenohumeral chondrolysis in a small percentage of patients (3–6, 48). In 2005, Caffey et al. reported similar results in a study comparing the effects of five different mRFE and bRFE probes on human cartilage and observed that the probes produced significant cellular death with some probes causing cell death that penetrated to the subchondral bone (48). The development of chondrolysis following the application of thermal energy in human patients has been reported (3–5). It has been suggested that physicians should reconsider the use of postoperative infusion of local anaesthetic drugs with RFE due to the association with glenohumeral chondrolysis (6).

The use of non-ablative RFE is reported to result in less chondrocyte necrosis than ablation RFE (49). The ablation methods were mRFE and bRFE that deliver RFE through a direct electrode-to-tissue contact. The non-ablation method delivers RFE through a bipolar mechanism initiated from a monopolar generator via a protected tip that prevents electrode-to-tissue contact.

To date, studies evaluating thermal chondroplasty using RFE have focused on three major areas: 1) the determination of postoperative clinical results relating to safety and cartilage stabilization over time; 2) the comparison between mechanical debridement and RFE thermal chondroplasty stabilizing the further degradation of chondral lesions; and 3) the determination

of the RFE stimulating effect if any, on chondrocyte proliferation and propagation. We believe that RFE safety studies must be completed before significant application of RFE for chondroplasty is considered.

Microfracture

Microfracture is a technique where the subchondral plate is perforated allowing access to the marrow elements and the potential for the formation of a blood clot to form in the chondral defect. The blood clot provides a scaffold containing growth factors and cytokines. Progenitor cells and bone marrow mesenchymal stem cells, entering an avascular cartilage defect differentiate into fibrocartilage-producing cells, and fill the defect. The blood clot usually induces healing by forming fibrous or fibrocartilaginous repair tissue (50). Microfractures are also sometimes implemented in the surrounding subchondral bone to induce repair tissue formation and attachment.

Studies have found microfracture treatment to be beneficial, leading to increased volume of repair tissue, type II collagen content, and clinical functionality. Frisbie et al. in 1999 performed the microfracture technique on full-thickness defects in the radial carpal bone and medial femoral condyle of 10 horses with ages ranging from two to five years (13). A greater volume of repair tissue filled the treated defects (74%) compared to only 45% in non-treated control defects. There was an increased percentage of type II collagen in the treated defects (13). These results are consistent with a study performed by Frisbie et al. in 2006 that found an increase in overall repair tissue in treated defects at both four and 12 months postoperatively (51).

On the other hand, microfracture has also been found to be less than effective. Custers et al. in 2009 investigated the treatment of cartilage defects with the insertion of defect-sized implants and compared this treatment with microfracture using a goat model (8). Significantly more degeneration, less glycosaminoglycan content, lower synthetic activity, and increased glycosaminoglycan release from medial tibial plateau cartilage occurred in the defects treated with microfracture compared to the implant group ($p < 0.05$) (8).

Microfracture has also been evaluated in human patients. Steadman et al. in 2001 assessed the microfracture technique in humans and concluded that the technique allowed for access to biological modulators and mesenchymal stem cells that had the ability to differentiate into cartilage-like cells and produce a durable repair cartilage which aided in chondral repair (12).

The microfracture technique appears to be useful in cases with larger lesions in low demand areas or smaller regions in high demand areas. Removal of the calcified layer in defects provides optimal attachment of repair tissue. The microfracture technique has benefited horses and humans, indicating its importance in repair of defects in larger species. This technique could be aided in the future by the use of growth factors and mesenchymal stem cells to minimize degeneration in repair sites (52).

Mosaicplasty

Mosaicplasty is normally used to treat full-thickness defects and involves the removal of one or multiple cylindrical plugs of osteochondral tissue from the articular cartilage of non-weight bearing regions. The autogenic plugs are then inserted into the full-thickness defect (21). Mosaicplasty has been studied in many models, with the most commonly treated defect being in the medial femoral condyle (7, 10, 11, 53–55).

Mosaicplasty has shown promising results in animal models. Results seen include the following: an increase in glycosaminoglycan, type II collagen, and repair tissue concentration; an increase in integration of repair tissue with native cartilage; and high viability of repair cells. Bodo et al. transplanted grafts in 11 horses, and reported the bony portions of the grafts to be well integrated with the recipient sites of horses at six and 12 months after surgery (53). Thereafter, Burks et al. in 2006 reported similar results in sheep with improved bonding of the graft to adjacent cartilage compared to an empty defect at six months (7). Prior to that, Lane et al. placed plugs into the central portion of the medial femoral condyle in six goats. He reported high cellular viability in the transplanted grafts, an increase in glycosaminoglycan synthesis indicating continued repair activity, and a six- to seven-fold greater stiffness for the experimental tissue compared with contralateral control tissue (10). Palierne et al. evaluated the one-month morphological appearance of autogenous osteochondral grafting in dogs with stifle osteochondrosis, and reported that histopathological analysis performed one month after surgery confirmed partial integration of the grafts and osteochondral survival (56).

Mosaicplasty has also been shown to be detrimental in the treatment of defects. Hurtig et al. in 2001 used grafts from the femoropatellar joint and transplanted them to the third carpal bone in six horses (57). It was reported that the cell viability in the grafts significantly decreased, and the levels of glycosaminoglycans were significantly decreased in the grafts compared with the donor sites at nine months post-implantation (57). Following that, Whiteside et al. applied the mosaicplasty technique to pigs and reported a decrease in graft fixation strength (58).

Mosaicplasty has also been implemented in the treatment of articular cartilage defects in humans. Hangody et al. in 2003 evaluated 831 cases of mosaicplasty in humans from 1992–2002 (59). Upon evaluating the cases using clinical scores, 92% of patients with femoral condylar implantations, 87% with tibial resurfacings, 79% with patellar and/or trochlear mosaicplasties, and 94% with talar procedures demonstrated good-to-excellent results (59). A study by Hangody et al. evaluated 36 cases of talar implantation that included a three to seven year follow-up (60). Out of the 36 cases, 28 had excellent results, six were good, and two were moderate according to the Hannover scoring system (60).

Mosaicplasty previously was used for smaller cartilage defects. This is because the healthy graft tissue can only be taken from a limited area of the same joint. Mosaicplasty is currently now also used for larger articular cartilage defects. In such cases, mosaicplasty seems to be beneficial in treating cartilage defects in both animals and humans due to the extensive repair ability.

Allografts

If a cartilage defect is too large for treatment using an autograft, then an allograft may be considered. Compared to autograft, allograft has advantages such as avoiding donor site morbidity, reducing surgical time, smaller incisions required, and availability of larger grafts. The allograft can be shaped to fit the exact contour of the defect and then press-fitted into place. Implantation of allografts includes taking osteochondral tissue, chondrocytes or other cells, or cartilage from a donor and transplanting it into a different individual of the same species (61). Cells are removed by small needle-biopsy and expanded *in vitro* whereas plugs are harvested using a trephine or drill to generate a construct that is implanted into the same species (62, 63).

The use of allografts for repaired cartilage defects was effective in horses and rabbits (62, 64). Osteochondral allografts harvested from metatarsophalangeal joints were press-fitted into the medial and lateral metatarsal condyles of six horses with four sham-operated horses (62). Most grafts had 90% or more coverage with hyaline-like cartilage at 25 weeks post-implantation with good graft incorporation as determined by histological and microradiographic analysis. Boopalan et al. in 2006 transplanted allogenic chondrocytes from knee joint cartilage to focal articular cartilage defects of rabbits and assessed the healing of the defects 12 weeks after implantation (64). There was a significantly increased amount of newly formed repair tissue with good integration with the surrounding articular cartilage (64).

Mainil-Varlet et al. in 2001 treated full-thickness articular defects in the patellar groove of the femoral condyle of pigs, and did not find allograft implantation beneficial (65). The reduced thickness, cellularity, and safranin-O staining indicated inadequate repair of the defect (65).

Allograft transplantation has been studied widely in humans (66, 67). Bugbee et al. in 1999 evaluated the allograft procedure in 61 patients with cartilage defects (66). After a two year evaluation, 48 of the 61 patients undergoing allograft transplantation on one surface were rated good or excellent. Of the 30 cases undergoing bipolar allografting, a success rate of 53% was reported. After 10 years, 11 of the 15 cases, bipolar and unipolar, were rated good or excellent (66). Gross et al. in 2008 also evaluated human allograft transplantation and examined histological features of 35 allografts retrieved at the time of subsequent graft revision, osteotomy, or total knee arthroplasty. Lack of chondrocyte viability and loss of matrix cationic staining were histological features of early graft failures (67). Nonunion was evident due to fibrovascular tissue between the graft and host tissue within one year of implantation (67).

The allograft procedure is commonly used for larger articular cartilage defects. Allograft treatment shows promise in animals, but longer term studies need to be carried out. Allograft treatment does seem to be successful in humans and could be used in patients seeking long-term treatment.

Xenografts

Xenografts can be obtained more easily than allografts and involve the use of organs, tissues, or cells derived from a different species than the one being treated. Chondrocytes are grown in culture and transplanted into articular cartilage defects similar to autografts and allografts (68). Partial- and full-thickness defect models have been used principally in the lateral and medial femoral condyles or patellar fossa of the knee (68–70).

A few studies found xenograft treatment to be beneficial in animal models. Ramallal et al. placed xenogeneic chondrocytes from the femoral condyle of pigs into partial chondral defects in the lateral femoral condyle of rabbits and evaluated the grafts at 24 weeks post-implantation (68). The investigators noted good integration between the synthesized cartilage and the surrounding native cartilage, with the repair tissue yielding a smooth surface. Yagihashi et al. noted hyaline-like cartilage in the peripheral region of the graft at six weeks post-implantation of the demineralized dentin matrix of bovine origin in the full-thickness defects in the patellar fossa of the femur in rabbits (70).

Many studies found xenograft treatment to be unfavourable in treating articular cartilage defects. Van Susante et al. in 1999 used xenogeneic rabbit chondrocytes suspended in fibrin glue to treat full-thickness defects in the medial femoral condyle of goats and assessed the xenografts up to 52 weeks after surgery (71). The investigators reported that there was no significant difference between the xenograft treatment group and the control at 52 weeks. Pei et al. evaluated the transplantation of xenograft pig cartilage into osteochondral defects in the medial femoral condyles of rabbits for a duration of six months post-implantation (72). The xenograft treatment group displayed tissue loss compared to untreated defects that were filled with fibrocartilaginous tissue.

The differences between the mentioned studies on xenograft implantation are most likely due to the duration of the study and animal model. The studies that reported overall good results were short-term and in lower-order animal models while the unfavourable results were from longer-term studies in higher-order animal models. It is possible that xenografts cause a delayed immune rejection when treating articular cartilage defects.

Autologous chondrocyte implantation

The autologous chondrocyte implantation (ACI) procedure, first introduced by Brittberg and coworkers, has been the most widely used surgical procedure (73). This procedure aims to provide complete hyaline repair tissues for articular cartilage repair. Autologous chondrocyte implantation is a cell-based therapy that involves transplantation of autogenous cells into articular cartilage defects. The autologous articular chondrocytes are harvested from a minor load-bearing area and expanded before implanting into the defect under a periosteal flap (74).

Many studies have reported favourable results after applying ACI treatment to cartilage defects. Trzeciak et al in 2006 performed ACI in full-thickness defects in the distal femur of rabbits (75). At 12 weeks, microscopic analysis showed repair tissue consisting of morphological features similar to mature hyaline cartilage with a

smooth surface and uniform thickness. Dell'Accio et al. used goats to evaluate ACI for full-thickness defects of the lateral femoral condyle (76). The investigators reported that at 14 weeks after surgery, collagen fibres with a disposition similar to that of hyaline cartilage were present as evaluated by phase-contrast microscopy. High proteoglycan expression in repair tissue was also reported. Min et al. in 2007 reported regenerative tissue with high proteoglycan expression that resembled hyaline cartilage in the periphery of the implantation site of the defects in a dog model at four weeks after ACI implantation (77). Litzke et al. performed ACI in full-thickness defects in the minor load-boarding area on the lateral talus of the talocrural joint in horses (74). The investigators reported strong to moderate expression of hyaline cartilage after two years, and reported expression of type II collagen in deep areas of 80% of the defects compared with reduced or no expression in untreated defects (74). Kamarul et al. implanted autologous chondrocytes into full-thickness defects in the medial femoral condyle of rabbits and reported homogeneous distribution of type II collagen similar to surrounding normal cartilage at three months after surgery (78).

The findings of another study contradicted the previous studies and reported a trend toward decreased hyaline cartilage at 18 months post-implantation in a dog model (79). The investigators also reported an increased amount of fibrous tissue from 12 to 18 months post-implantation.

Autologous chondrocyte implantation treatment also has been prevalent in human patients. Peterson et al. in 2000 evaluated ACI of the first 94 of 101 patients treated in Sweden (1987–1999) (80). Fifty-three patients showed good repair tissue fill, good adherence to underlying bone, seamless integration with adjacent cartilage, and hardness close to that of the adjacent tissue. Peterson et al. in 2010 evaluated ACI by using questionnaires filled out by 224 patients 10–20 years post-implantation (81). Seventy-four percent of these patients reported their status as better or the same as the previous status while 26% reported they were worse. Patients with bipolar lesions were reported to have a worse final outcome than patients with multiple unipolar lesions (81).

Autologous chondrocyte implantation is commonly used for smaller articular cartilage defects, with monopolar or bipolar lesions. Most animal studies reported favourable results after using the ACI treatment with high prevalence of hyaline-like cartilage repair tissue, high expression of type II collagen and proteoglycans, with improved bonding to the native cartilage. Autologous chondrocyte implantation performed on humans resulted in similar results with good repair tissue fill and seamless integration with native cartilage. Autologous chondrocyte implantation treatment is beneficial to both human and animal patients and should be considered a viable option when repairing articular cartilage defects, although the technique needs to be simplified.

Cells within the collagen membrane

Recent technological improvements have aimed to overcome the intrinsic technical disadvantages of ACI by using cartilage tissue engineering grafts developed with three-dimensional scaffolds or matrices that contain autologous chondrocytes for cartilage regeneration. Specifically, a stable three-dimensional matrix which provides the hyaline-like phenotype of the chondrocytes, in conjunction with seeding more efficiently at the site of implantation, should promote integration between the neo-cartilage and the surrounding host articular cartilage (82). With this technique, autogenic or allogenic cells are seeded onto a collagen membrane (83). One proprietary technique, Matrix-induced Autologous Chondrocyte Implant (MACI®[b]), involves the transplantation of autologous chondrocytes obtained arthroscopically, cultured over several weeks, and then impregnated on an absorbable collagen I/III membrane. The membrane can be fixed to the cartilage with fibrin, glue, pins, or sutures. A periosteal membrane layer is not placed over the implant.

[b] Genzyme Europe BV, Naarden, The Netherlands

Many studies that implanted a collagen membrane seeded with cells have reported favourable results in the repair of articular cartilage defects (84–86). Yanai et al. placed mesenchymal stem cells harvested from the intercondylar notch of the distal femur and cultured in a collagen gel into large full-thickness articular cartilage defects of the tibial plateau in rabbits (86). At 12 weeks post-surgery, hyaline-like cartilage was observed immediately below the superficial zone, and there was significantly better matrix morphology in the cell-seeded membrane group compared with the membrane implantation only group (86). Chiang et al. in 2005 reported results similar to Yanai et al. with significantly greater hyaline-like cartilage in the transplanted group after six months post-implantation in a pig model (84). In 2005, De Franceschi et al. implanted autologous chondrocytes seeded on a type I collagen scaffold into full-thickness defects in the weight-bearing surface of the medial femoral condyle of rabbits and assessed the treatment at six and 12 months post-implantation (85). The investigators reported a significantly higher presence of type II collagen and proteoglycan production in the chondrocyte seeded scaffold group compared to control.

In contrast, other studies did not find collagen membrane treatment to be beneficial in all aspects of defect repair. Willers et al. used rabbits as a model to implant inoculated autologous chondrocytes onto a type I/III collagen scaffold into medial condylar defects (87). Willers et al. reported a reduced amount of proteoglycan and reduced thickness in the repair tissue compared with adjacent cartilage at 12 weeks (87). Lee et al. used a type II collagen scaffold cultured for four weeks prior to implantation and seeded with autologous chondrocytes in defects of the trochlear groove in dogs (83). The investigators reported a compressive stiffness of the repair tissue to be 20-fold lower than that of native articular cartilage at 15 weeks after surgery. The repair tissue was only partially integrated with adjacent cartilage and consisted of mainly fibrocartilage (83). In 2008, Jones et al. reported poor integration and poor architectural restoration at 12 weeks after implantation, and biomechanical properties of the repair tissue re-

mained inferior compared with native cartilage in a sheep model (88).

Collagen membrane treatment has also been assessed in human patients. In 2007, Zheng et al. implanted a scaffold of ACI seeded onto a type I/III collagen membrane in 56 humans (89). The investigators reported that the chondrocytes appeared well-integrated into the matrix and maintained the chondrocyte phenotype as evidenced by aggrecan, type II collagen, and S-100 expression from 21 days to 24 months after surgery. Formation of cartilage-like tissue was seen as early as 21 days (89). Crawford et al. implanted autogenous chondrocytes seeded into a three-dimensional type I collagen scaffold into eight patients with full-thickness cartilage injury (90). Pain scores were significantly lower than baseline at 12 and 24 months after implantation using a visual analog scale (90).

Although some studies reported adverse results about this technique, most animal and human patient studies have shown favourable results in the repair of cartilage defects after implantation of a collagen membrane seeded with cells. The prevalence of hyaline-like cartilage and type II collagen as repair tissue signifies the benefits of repair with collagen treatment. This treatment may be considered a valuable option when treating articular cartilage defects.

Cells within synthetics

Instead of seeding cells within a collagen membrane, other synthetic materials have been investigated as potential scaffolds including polyglycolic acid or polylactic acid (91). These polymeric scaffolds have proven to be biocompatible, biodegradable, permeable, reproducible, mechanically stable, non-cytotoxic, and capable of serving as a temporary support (92). The chondrocytes are cultured and seeded *in vitro* onto the synthetics. A few studies have evaluated this technique using horse, rabbit, and pig animal models for the treatment of cartilage defects (91, 93–95).

Studies have implanted cells seeded onto a polyglycolic scaffold into cartilage defects and reported favourable outcomes. Zhou et al. implanted autologous mesenchymal stem cells embedded in a polyglycolic acid-hydroxyapatite scaffold into full-thickness cartilage defects in the intercondylar fossa of the femur in rabbits (95). The repair tissue consisted of hyaline cartilage and complete subchondral bone formation was seen at 16 weeks post-implantation. Prior to that, Liu et al. placed autologous chondrocytes from the patellar groove of the inferior femur segment with polyglycolic acid into full-thickness defects in pigs (94). Histological examination at 24 weeks in this study demonstrated typical hyaline cartilage structure with good interface healing as well as underlying cancellous bone. The biomechanical properties of the repair tissue improved over time and were significantly better compared to control (94). Barnewitz et al. embedded autologous chondrocytes into polyglactin/polydioxanone scaffolds which were then transplanted into full-thickness defects in the distal condyle of the third metacarpus in a horse model (93). The content of both glycosaminoglycans and hydroxyproline in the repair tissue of treated and control defects were comparable at 12 months post-surgery (93).

In contrast to the above studies, one study noted unfavourable results after synthetic membrane treatment. Dounchis et al. implanted a composite graft of autogeneic perichondrial cells and polylactic acid into medial femoral condylar defects in rabbits, and reported suboptimal concentrations of glycosaminoglycan in the neocartilage matrix in a rabbit model at 12 months after surgery, and the repair tissue had a depressed surface with the histological appearance of the repair tissue poorer than that of normal articular cartilage (91). The differences in the studies could be attributed to the implantation of a perichondrial cell compared to autogenic chondrocytes and the type of synthetic membrane used.

To compare different synthetic membranes, Knecht et al. mechanically tested the fixation stability of four commonly used biomaterials (polyglycolic acid [PGA], poly-L-lactic acid [PLLA], collagen membranes, and gel-like matrix material) for ACI attached by four different fixation techniques (unfixed, fibrin glue, chondral suture, and transosseous suture) *in situ* (96). The investigators reported the PGA-scaffold could withstand the highest load before failure compared to the other biomaterials (96).

Due to the success in animal models, human studies have been performed implanting synthetic membranes into defects. Minenna et al. in 2005 reported a study of 32 human patients comparing the use of a polylactide and polyglycolide copolymer graft in conjunction with an open flap debridement procedure to open flap debridement alone (97). At six months post-implantation of the graft, clinical attachment was significantly greater in the defects receiving the copolymer graft than debridement alone. At 12 months, there were not any significant differences in any of the clinical parameters (clinical attachment level, recession depth, and probing depth) observed between the groups (97).

Animal studies have shown the value of implanting synthetic membranes consisting of polyglycolic acid and autogenic cells into articular cartilage defects compared to other synthetic membranes (91, 98). In the study evaluating this procedure in humans, no clear advantage was shown at 12 months and this could be attributed to the fact that no autogenic cells were embedded within the synthetic membrane.

Scaffolds

Common to all attempts at tissue engineering for cartilage repair is to deliver the repair material to the injury site and ensuring that it stay in place long enough to effect the desired repair. This issue may be solved by using scaffolds as vehicles. Biphasic scaffolds contain an osseous phase and a chondral phase so that the scaffold can integrate with both the bone and cartilage surrounding the defect (99). Many combinations have been employed for each phase. There are two principal types of scaffolds, scaffolds seeded with autologous or allogenic cells, and scaffolds augmented with growth factors with or without cells.

Scaffolds with Cells

Beta (β)-tricalcium phosphate (TCP) has been used in several biphasic scaffolds with

mainly favourable results (99–102). Guo et al. used a sheep model to place autologous mesenchymal stem cells into bioceramic scaffolds of TCP implanted into the weight-bearing area of the medial femoral condyle (100). At 24 weeks, the repair tissue consisted of hyaline tissue which was almost indistinguishable from the surrounding normal cartilage. The glycosaminoglycan content was significantly higher in defects treated with the cell-seeded TCP scaffolds compared to cell-free scaffolds or defects left untreated (100). Jiang et al. performed a study placing a biphasic scaffold of autologous chondrocytes with poly(D,L)-lactide-co-glycolide as the chondral phase and TCP as the osseous phase into full-thickness femoral condylar defects in mini-pigs (99). The experimental group received higher mean scores in surface morphology, matrix, cell distribution, and cell viability than the control (99). Tanaka et al. placed allogenic chondrocytes in collagen gel overlying a resorbable TCP block in the intercondylar groove of the distal femur in rabbits (102). At eight weeks, repair tissue filled at least 85% of each defect and consisted of hyaline-like cartilage. Most of the TCP was replaced by bone with a small amount remaining in the underlying cartilage at 12 weeks post-implantation (102).

Shao et al. used a different scaffold that consisted of medical-grade polycaprolactone (mPCL) as the bone phase and fibrin glue as the cartilage phase (103). Both phases were seeded with bone-marrow derived allogenic mesenchymal cells from the iliac crest and placed into a medial femoral condylar defect in rabbits. The investigators reported the majority of six-month specimens revealed poor remodelling and fissured integration with host cartilage (103).

Another scaffold consists of allogenic chondrocytes seeded on cancellous bone matrix gelatin which is employed by Song et al. in 2006 in the treatment of defects in the medial femoral condyles of rabbits (104). At 24 weeks post-implantation, proteoglycan and type II collagen were detected in the matrix of repair tissue. The chondrocytes and cartilage matrix in repair tissue were almost identical to those in normal articular cartilage (104).

Another category of a scaffold is a composite seeded with cells (105, 106). Ito et al. transplanted scaffolds consisting of autogenic chondrocytes from the humeral head embedded in atelocollagen gel and seeded on an atelocollagen sponge/PLLA mesh composite for mechanical strength (105). After 12 weeks, the defects were repaired with hyaline-like cartilage and type II collagen with well organized subchondral bone formation (105). Ito et al. also transplanted autogenic chondrocytes embedded in atelocollagen gel, but the cells were seeded on top of an interconnected porous calcium hydroxyapatite ceramic compared to the atelocollagen sponge/PLLA mesh composite as previously performed (105, 106). The investigators reported that at 12 weeks, 90% of the graft areas showed cartilage-like tissue with good subchondral bone formation (106).

Cells have been implanted in various scaffolds including β-TCP, medical-grade polycaprolactone, bone matrix gelatin, and composites. Scaffolds with β-TCP, bone matrix gelatin, or composites have shown favourable results with quality repair tissue. In contrast, medical-grade polycaprolactone resulted in unfavourable results with poor remodelling, which could be attributed to the low sample size. More long-term studies with larger sample sizes should be investigated before the application of the technique in human patients.

Scaffolds with growth factors

For cartilage repair and regeneration, mesenchymal stem cells have to differentiate into chondrocytes for the correct extracellular matrix generation. To ensure chondrogenic differentiation, the mesenchymal stem cells will have to be able to attract and respond to the correct biological signals for tissue regeneration and repair. Growth factors have functions to regulate chondrocytes and cartilage development. These growth factors can be delivered to the required specific site by incorporating these molecules into a scaffold for controlled release to the exact site or by the use of gene therapy. Growth factors have been used to stimulate bone and cartilage growth typically using either autogenic or allogenic chondrocytes. The chondrocytes are isolated and then cultured and genetically modified *in vitro* (15).

A commonly used growth factor in scaffolds to treat articular cartilage defects is transforming growth factor-β (TGF-β), which has been reported to show favourable results. Wayne et al. placed a construct composed of polylactic acid-alginate amalgam seeded with autologous mesenchymal stem cells, and stimulated *in vitro* with TGF-β, into the femoral chondyles of a dog model (17). Cell-seeded experimental defects showed more cartilage-like matrix quality, cell distribution, and proteoglycan staining than control defects (17). Zhou et al. also used a construct consisting of autologous mesenchymal stem cells and dexamethasone seeded onto polylactic acid-coated polyglycolic acid scaffold stimulated with TGF-β, and the construct was placed in a pig model (18). Eleven of the 16 defects were completely repaired by hyaline cartilage and cancellous bone with high glycosaminoglycan content in the repair tissue at six months. Aggrecan gene expression and type II collagen was significantly enhanced in the treated defects (18).

Another commonly used growth factor is the insulin-like growth factor-1 (IGF-1). Articular cartilage defects treated with IGF-1 showed mixed results. Goodrich et al. implanted allogenic chondrocytes from the femoropatellar joints of neonatal foals that were incubated with IGF-1 into the lateral trochlear ridge of a femoropatellar joint defect of horses (15). The experimental defects had greater tissue filling and higher levels of type II collagen at eight months post-implantation in the experimental repair tissue compared with control defects (15). Strauss et al. used allogenic chondrocytes that were stimulated by gene transfer with IGF-1 and then placed into full-thickness lateral trochlear ridge defects of horses (19). The proteoglycan content and the equilibrium modulus were significantly increased for the experimental defects. Fortier et al. implanted allogenic chondrocytes supplemented with IFG-1 (0 µg, 12.5 µg, 25 µg) in an *in vitro* study (14). The dosage of 25 µg of IGF-1 increased the glycosaminoglycan content and synthesis the most in comparison to the lower dose or no IGF-1 (14).

A third growth factor is bone morphogenetic protein-7 (BMP-7) (107, 108). Hidaka et al. transplanted allogenic chondrocytes modified by gene transfer with BMP-7 into articular cartilage defects in the femoropatellar joints of 10 horses (107). There was an approximately two- to 2.5-fold decrease in dynamic modulus of the repair tissue compared to normal cartilage at eight months (107).

Recombinant human basic fibroblast growth factor (rh-bFGF) also has been investigated by Siebert et al. in 2003 (109). The investigators transplanted grafts bathed in phosphate buffered sulfate containing 50 µg of rh-bFGF into the femoral condyle of sheep. The quality of the repair was less than excellent since there was a 28% difference in the cartilage thickness between the transplanted plug and the recipient cartilage which resulted in a primary offset in the subchondral plate (109).

Growth factors are commonly used in experimental animal studies including TGF-β, IGF-1, and BMP-7. Transforming growth factor-β showed the most promising results in repair of articular cartilage defects and should be implemented in human studies. Overall the use of growth factors is growing rapidly and has the potential of surpassing other methods in treating articular cartilage defects.

Summary

Articular cartilage defects may be treated using any of the treatment methods discussed in this article. In general, smaller articular cartilage defects are treated using debridement, microfracture, radio frequency energy, or chondrocyte implantation, whereas the other methods, such as scaffolds and mosaicplasty, are normally used for larger articular cartilage defects.

Lavage, radio frequency energy, microfracture, mosaicplasty, allografts, and chondrocyte implantation, including MACI®, have all been studied in humans. Xenografts and scaffolds with growth factors and cells are still in the experimental phase and have not been used in treating human cartilage defects. More clinical trials must be conducted before these treatment methods can be made available for human applications.

Acknowledgements

The authors thank Mary Thurber for the preliminary literature research.

Conflict of interest

None declared.

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