Chapter 18
Pure Cartilage-Based Repair Modalities of Focal Cartilage Lesions

Tamas Bardos

Abstract Focal cartilage lesions in diarthrodial joints have a limited capacity to heal, and repair techniques used at present are still unable to provide a universal solution. Osteochondral auto- and allografts are accepted and successful methods for the treatment of these lesions, but occasionally the osseal incorporation is delayed or insufficient and graft integration might be unsuccessful. Failure at this level generates a large osseos crater and the consequences can prove challenging.

Until just a few years ago, it was a generally accepted dogma that when cartilage is detached from the subchondral bone it would fail to reintegrate to its bed and its surrounding cartilage. Recently, innovative approaches have been established to repair cartilage defects using pure cartilage-based implants, and so far they seem to have had considerable success.

One of the available options is to use autologous minced cartilage in a single-stage procedure. Cartilage tissue is obtained from the less-weight-bearing surface of the affected joint and the sample is processed *in situ* resulting in a cartilage fragment-loaded scaffold that can be applied to the lesion of the weight-bearing area. Another system repairs with cadaveric juvenile articular hyaline cartilage cut into 1 mm^3-cartilage cubes and using fibrin glue as vehicle the tissue particles are evenly distributed on the defected articular surface. Both methods are relatively new and therefore lacking long-term follow up, but the short-term results seem encouraging.

An additional concept for cartilage-based repair is when pure cartilage allograft is peeled from the subchondral bone, and instead of mincing the tissue it is repeatedly incised on its basilar surface rendering the rigid cartilage graft into a rather pliable graft. Since the superficial layer is preserved the graft is similar to any scaffold used in cartilage repair, and it can be secured to the lesion site using sutures and

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fibrin glue. Although this method is in the experimental phase, a short term clinical trial has proved it to be safe.

In this chapter we will briefly describe the physiology of cartilage integration; summarize the basis and the potential pitfalls of these methods; and provide a review of the available data on the clinical outcomes.

Keywords Focal lesion • Pure cartilage • Cartilage allograft • Cartilage fragmentation

Key Points

- Recently novel cartilage repair methods have emerged, which are based on processed pure cartilage tissue placed on the focal chondral lesion.
- Cartilage Autograft Implantation System (CAIS) uses minced autologous hyaline cartilage from lessweight-bearing surfaces and secures it to the lesion site with resorbable mesh and anchors. This method is in the clinical trial phase.
- DeNovo NT system operates with minced juvenile hyaline cartilage allograft that is delivered to the lesion site with fibrin glue and it exploits the high growth capacity of the young cartilage cells. This technique is already in clinical use.
- If a larger pure cartilage piece is peeled off from its osseal base and is multiply incised on one surface, the graft appears to have good potential to repair focal lesions by adhering to the recipient subchondral bone. This approach is only in the pre-clinical phase.
- It was a generally accepted view amongst orthopeadic surgeons that once cartilage tissue is delaminated from the subchondral bone it is destined to degenerate. In view of these new cartilage repair methods this theory might need some adjustments.

18.1 Introduction

Articular cartilage lesion is still considered a difficult problem due to its poor regenerative potential [1, 2]. Many distinct cartilage repair modalities are available but none of them offer a universal solution for the various types of lesions. The most frequently used surgical solutions employ the reparative capacity of the subchondral bone (chondral debridement, marrow stimulation) or provide restoration of the articular surface by transplantation of cartilage either on a cellular level (ACI with or without matrix) or as part of an osteochondral graft (autologous or allogeneic). More recently a new concept has come to light. It is postulated that cartilage tissue alone could be transplanted to the site of the lesion and it would eventually integrate

to the lytic site providing a durable hyaline or hyaline-like coverage for the affected area [3].

The reason why cartilage cannot re-integrate to the osseal bone has been investigated. Both the cartilage matrix and surviving chondrocytes may play a role in the failure to integration to the subchondral bone. Many factors have been held responsible for this phenomenon, such as impaired collagen network cross linking [4, 5] or proteoglycan components (lubricin) in the synovial fluid [6] preventing integration. Today it is still not clear why articular cartilage has such poor vertical and lateral integration, but gap formation between host and graft cartilage tissue is hypothesized to be very significant in the long term survival of any repair tissue [7, 8]. In earlier studies articular cartilage was demonstrated to have limited capacity to heal to the subchondral bone once detached [9, 10], therefore the idea of transplanting pure cartilage onto the subchondral bone would have been considered unorthodox- to say the least. In the last few years this long-standing dogma has been challenged and it appears that the concept of cartilage as an indifferent and passive part of the reintegration process is to be re-evaluated. Many studies showed that cartilage cells can be rather motile and can move through the extracellular matrix [11, 12] once adequate signals are present. Cutting the cartilage tissue has been shown to induce cell death in the adjacent zone of cartilage [13]. On the other hand, cartilage cells show good motility after cutting (mincing) and evade the original cartilage tissue [14]. The result of the evasion is neocartilage formation which varies depending on the zone (superficial vs. deep) and the age of the cartilage (young vs. adult) [14].

While autologous chondrocyte implantation has been a promising repair technique its drawbacks prevent it from a broader acceptance: the need of a 2-stage surgery, significant expenses of laboratory culturing, cumbersome arrangements for adequate quality insurance and transportation. To explore other possible techniques, research groups started to investigate the potential of pure hyaline cartilage-based repair modalities. The concept of mincing tissue laid onto the defect site is not entirely new. In the early 90's Stone et al. implanted a paste of minced autologous osteochondral tissue onto the defect sites following microfracture [15]. In their concept the lesion had to be properly debrided and the mesenchymal stem cells were stimulated by fracturing the subchondral plate; the scaffold for these cells was a "putty" derived from osteochondral autografts from the intercondylar notch (8 mm trephine – 1.5 cm long cylinder) that was crushed into a paste and impacted onto the fractured subchondral boneplate of the defect – not to fill but rather to cover the lesion and the penetrations of the bone [15]. In the 2- to 12-year follow-up of 136 procedures Stone et al. showed a relatively small portion of failures (14.4 %) especially considering the stage and size of the lesions (all grade IV lesions with average size of 28.6 cm^2) [16]. The 65 follow-up biopsies showed mostly fibrocartilage with or without GAG, and only 18 of the 65 biopsies showed areas of hyaline cartilage; yet overall 82 % of patients reported improved pain scores.

The need for a single-stage procedure from the surgeons, patients and insurance companies and the encouraging data of the morselized tissue grafting led to new investigations and resulted in new cartilage repair procedures.

18.2 Cartilage Autograft Implantation System (CAIS™)

Cartilage Autograft Implantation System (CAIS) is one of the new repair procedures for the treatment of cartilage lesions in the knee. It uses autologous cartilage obtained from the less-weight-bearing surface of the affected joint; the sample is processed *in situ* resulting in a cartilage fragment-loaded scaffold that can be applied to the lesion of the weight-bearing area. In contrast with the earlier osteochondral morselized grafting method in this approach the pure cartilage graft is delivered on a non-bleeding chondral defect thus the repair is likely to be driven by the chondrocytes rather than the mesenchymal stem cells from the bone marrow.

A minimum of 200 mg cartilage tissue (approximately two 13 × 5 mm pieces) is harvested from the non weight-bearing surfaces (intercondylar notch or trochlear ridge), similarly to the first step of ACI. Using a disposable device (CAIS Harvester and Dispenser, DePuy Mitek, Raynham, MA) the harvested cartilage sample is minced into 1–2 mm particles and using surgical vacuum and irrigation fluid the minced cartilage is evenly dispersed onto a scaffold. The scaffold is made from an absorbable copolymer foam of 35 %polycaprolactone (PCL) and 65 % polyglycolic acid (PGA), that is augmented with a polydioxanone(PDO) mesh (DePuy Mitek, Raynham, MA). The mesh provides the mechanical strength for the graft to be easily handled during implantation. Fibrin glue is used to keep the pieces on the foam; to ensure that the prepared graft is secured on the defect site firmly, two or more biodegradable staple anchors are used to affix the graft (side with the cartilage particle facing the osseal base) (Fig. 18.1). The staple anchors (DePuy Mitek, Raynham, MA) consist of a PDO strap and a PGA tip, and were shown in a cadaver knee study to hold scaffolds in place even after 10,000 cycles of CPM [18].

Large animal studies using goats and horses proved CAIS feasible and safe [17, 19]. In the equine experiment 15 mm full thickness cartilage defects of the trochlea were treated in 2- to 5-year old horses and various techniques were used for repair: scaffold only, CAIS, modified-ACI or left empty [17]. The gross examination of the repair tissues showed significantly firmer tissue in the CAIS and the ACI groups. The total histology scores were significantly better in modified-ACI- or CAIS-treated defects than in the empty or PDS scaffold-treated groups.

Based on the preclinical results a randomized clinical trial has been commenced to determine the safety and efficacy of CAIS compared to microfracture in reducing pain and improving function at 24 months. The study is designed to enroll a rather large number of patients (over 300). Patients are included with 1–2 focal chondral lesions that are less than 6 mm in depth with the affected area between 1 and 10 cm^2. The major exclusion criteria are bilateral disease, advanced radiological OA, >5° of malalignment and bipolar (kissing) lesions.

Two-year follow-up data of a prospective clinical safety trial has already been published [20]. In this study 29 patients were randomized to the CAIS treatment (20) or to the microfracture active control (9) group. In addition to knee-specific outcome data (IKDC and KOOS) MRI was performed at 3 weeks, 6, 12 and 24 months.

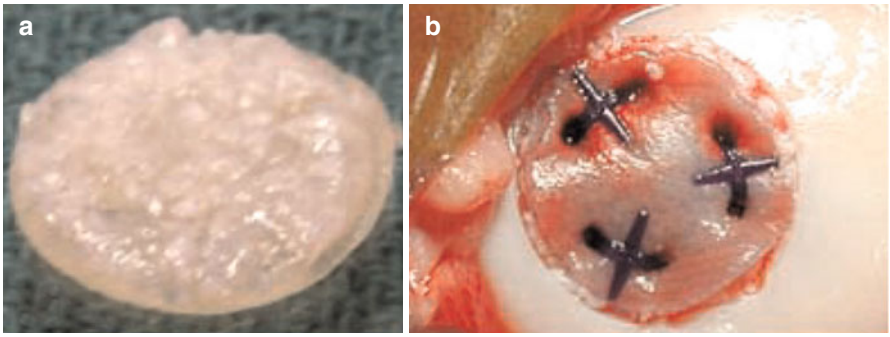

Fig. 18.1 CAIS in equine model. Morselized cartilage on top of the scaffold before implantation (**a**). Graft after implantation to the trochlea using three resorbable staples (with scaffold side up) (**b**) (Picture modified reproduction from Frisbie et al. [17])

The surgical procedure was carried out using a similar method to that described above. The rehabilitation protocol was adjusted to the site of the lesion (condylar or trochlear lesion) using the basic principle of non-weight-bearing for 2 weeks and 50 % weight-bearing until week 6 on the repaired area.

Complete blinding was not possible due to the different nature of the two procedures (microfracture – wholly arthroscopic, CAIS – mini arthrotomy). MRI showed comparable results in both groups with 76–100 % fill of the repair sites in nearly all lesions by 24 months (Fig. 18.2). There was no significant difference in terms of the subchondral cyst formation or the graft integration, but the intralesional osteophytes were significantly more common in the microfractured group at 6 and 12 months. The Short Form 36 (SF-36) score did not show significant differences between the two groups, but the knee-specific outcomes (IKDC and KOOS) showed significantly higher scores for the CAIS-treated group at 24 months. Although the study is limited by the small sample size and the lack of total blinding, the authors conclude that CAIS is well tolerated among the patients, and it is a safe and feasible treatment technique for focal chondral lesion in the knee [20]. Short term follow-up results of larger patient cohorts are expected in the next few years.

18.3 DeNovo® NT Natural Tissue Graft

DeNovo NT (Zimmer, Warsaw, IN / ISTO, St Louis, MO) is a distinct technique to repair focal chondral defects, but it shows some similarities with CAIS. DeNovo NT repairs the focal cartilage lesions with particulated juvenile articular hyaline cartilage allograft. The tissue is cut into 1 mm^3-cartilage cubes and using fibrin glue as a vehicle the tissue particles are evenly distributed on the defected articular surface.

Previous animal studies have showed that mature articular cartilage pieces can remodel and form adequate cartilage repair tissues in rabbits, goats and horses [17,

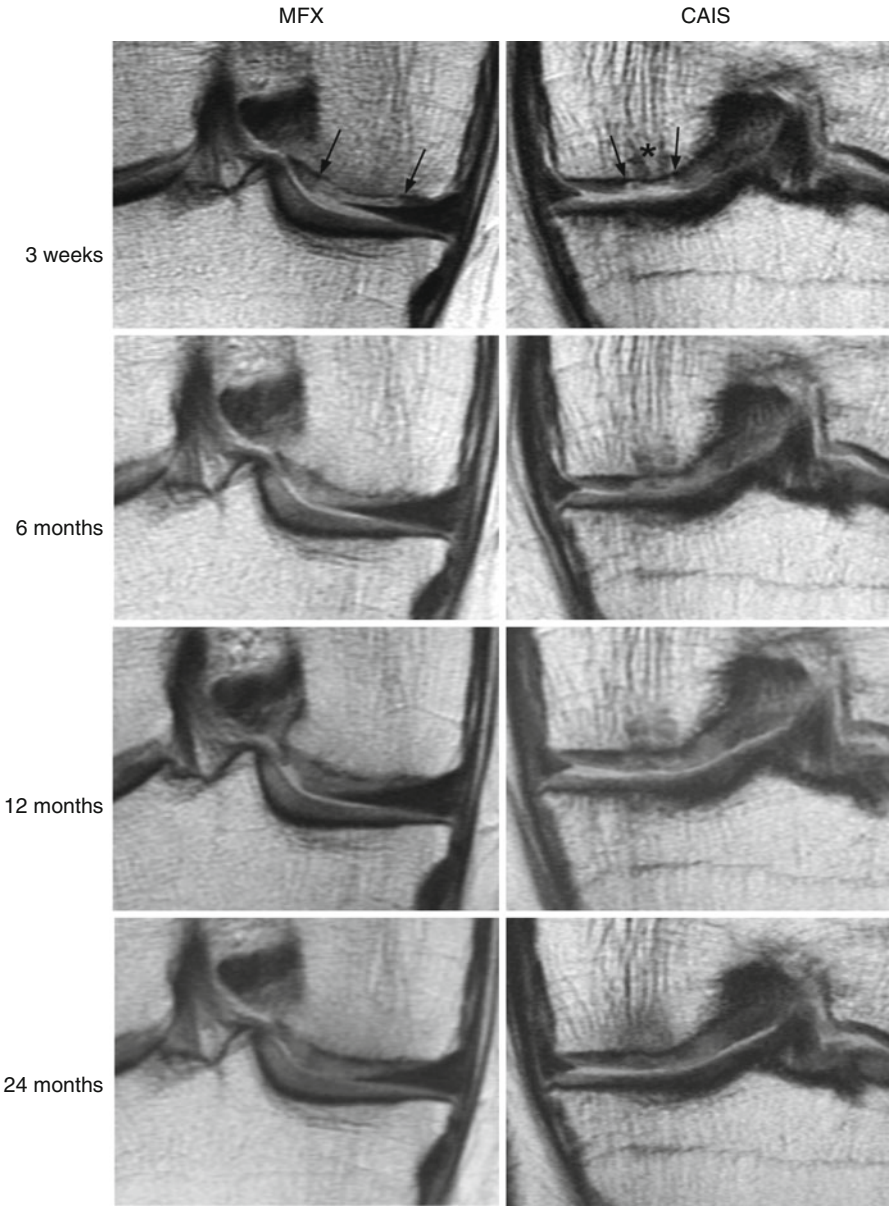

Fig. 18.2 Magnetic resonance images of two representative patients treated with microfracture (*MFX*) or Cartilage Autograft Implantation System (*CAIS*) in coronal view at 3 weeks, 6-, 12- and 24 months. The two low intensity structures (next to *) in CAIS at 3 weeks represent the staples (which gradually absorbed) (Picture modified reproduction from Cole et al. [20])

19, 21]. When juvenile and adult cartilage have been compared in terms of cell proliferation, potential to generate neocartilage, and production of GAG – juvenile cartilage was found to be dramatically better and the results in all aspect were

superior in the groups using juvenile cartilage [14, 22, 23]. Also, injured immature cartilage has a good healing potential compared to that of an adult [2], which is often explained by the higher cell density in the juvenile cartilage [24]. Unpublished data on equine trochlear lesion repaired with human particulated juvenile cartilage showed no necrotic changes in the subchondral bone, with full thickness continuous layer of cartilage repair tissue after 6 months, with better appearance than the control fibrin glue repaired defects (Frisbie et al. 2007, data on file at ISTO Technology, Inc.). Based on these results DeNovo NT was introduced to the market as a novel cartilage repair kit in 2007.

During the production of DeNovo NT graft pure cartilage tissue is harvested from fresh cadaveric juvenile (<13 years old excluding stillbirth and fetal donors) femoral condyles, and the tissue pieces are manually minced under aseptic conditions (Good Tissue Practice, ISTO Tech Inc.) without enzymatic digestion. In accordance with the FDA guidance (21 CFR Part 1271 subpart C and Guidance for Industry), strict viral and bacterial screening is completed using a similar method to other fresh osteochondral allografts. The single donor-derived minced sample is aliquoted and sealed with medium in blister packs and is to be used within 52 days after packaging.

As DeNovo NT graft is "minimally manipulated tissue", the product does not require premarketing approval from the FDA, and so post-launch clinical studies are conducted. The special requirements for donor eligibility have been speculated to limit the supply but following an early period of relative shortage of donor tissues the company now claims to have a good supply of donor tissues and to deliver the product without major interruption. DeNovo NT has been used for cartilage repair in various joints like knee, ankle, elbow, shoulder and hip.

The surgical technique in the knee is straightforward: after confirmatory arthroscopy the defect is approached via limited arthrotomy. The lesion is prepared with ring curette by removing the affected cartilage, forming vertical shoulder around the defect (Fig. 18.3). The congruent replica of the lesion is prepared using thin aluminum foil. Depending on the size of the lesion (each package is used for 2.5 cm^2) the appropriate amount of cartilage particles are evenly distributed on the foil mold and immobilized using fibrin glue. After setting, the construct (fibrin glue patch containing the cartilage particles) is removed from the foil in one piece and secured on the defect site using fibrin glue. The repair construct should be recessed relative to the surrounding cartilage to avoid dislodging (so far reported only in one case- Zimmer Orthobiologics, Inc. internal data). The postoperative rehabilitation protocol is identical to that used in similar repair techniques (e.g., following CAIS, see above).

Notwithstanding the rapidly increasing popularity of this technique, the available DeNovo NT clinical studies are limited. One case study reported an arthroscopic repair of a posteromedial talar osteochondral lesion using DeNovo NT, and found that the procedure is well tolerated, the patient returned to full activity within 6 months and remained free of pain at 24 months [26]. Another case study found this technique to be clinically successful for patellar cartilage defect and the 2 years MRI demonstrated good fill of the defect [27].

An additional case study series of four patients who completed the 24 months follow-up period has also just recently been published [25]. Five focal lesions with an average size of 2.7 cm^2 were treated using DeNovo NT. At 24 months all four

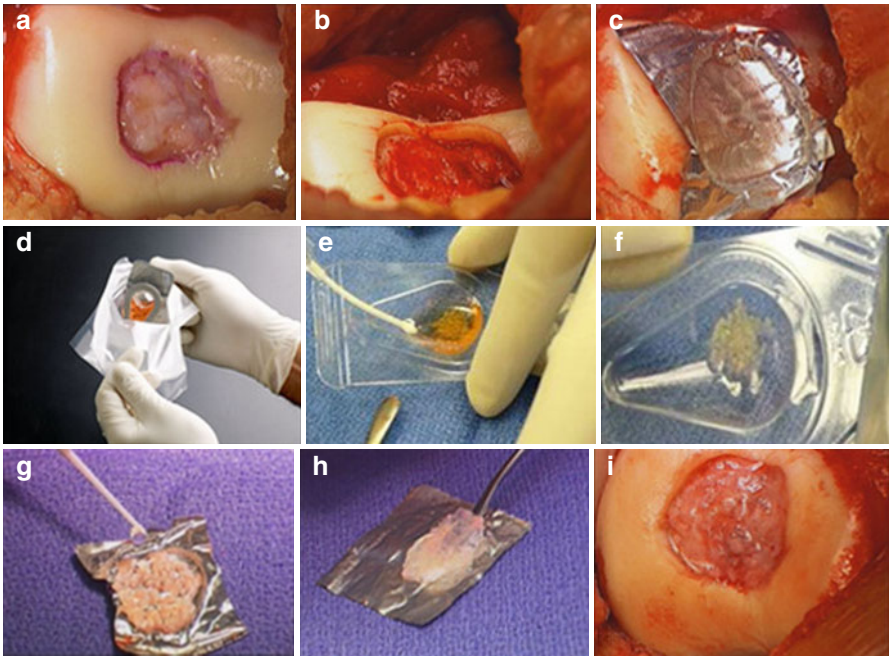

Fig. 18.3 Clinical steps of DeNovo NT technique. The cartilage defect (**a**) is debrided (**b**) and the sterile foil is pressed to form a replica (**c**). The blister pack of DeNovo NT is opened (**d**) and the culture medium is aspirated (**e**). The particulated cartilage (**f**) is distributed evenly in the foil and fibrin glue is allowed to solidify (**g**). The graft is carefully removed from its mold (**h**) and secured to the defect site using fibrin glue (**i**) (Picture reproduced from Farr et al. [25])

patients showed improvements in KOOS and IKDC scores as well as in VAS pain scores. MRI showed good filling of the defects (Fig. 18.4), however, due to the low number of patients the interpretation is tempered.

The DeNovo NT technique is suggested to have several advantages. As it is a single-stage cartilage repair technique, there is no need to compromise the subchondral bone, therefore it doesn't "burn bridges", no autologous tissue needs to be harvested and the juvenile tissue has great proliferative potential. As of today more than 2,500 DeNovo NT implantations were performed, and it is claimed that soon it may be used for cartilage repair more often than ACI. Although the results are very promising, further clinical data will have to be collected and analyzed in the next few years allowing better insight into this technique.

18.4 Processed Chondro-Graft

The central dogma of orthopedics, i.e., once cartilage is separated from its osseal base, it cannot grow back – seems to weaken with the emerging results of CAIS and DeNovo NT. Yet the question, whether pure cartilage peeled off the subchondral

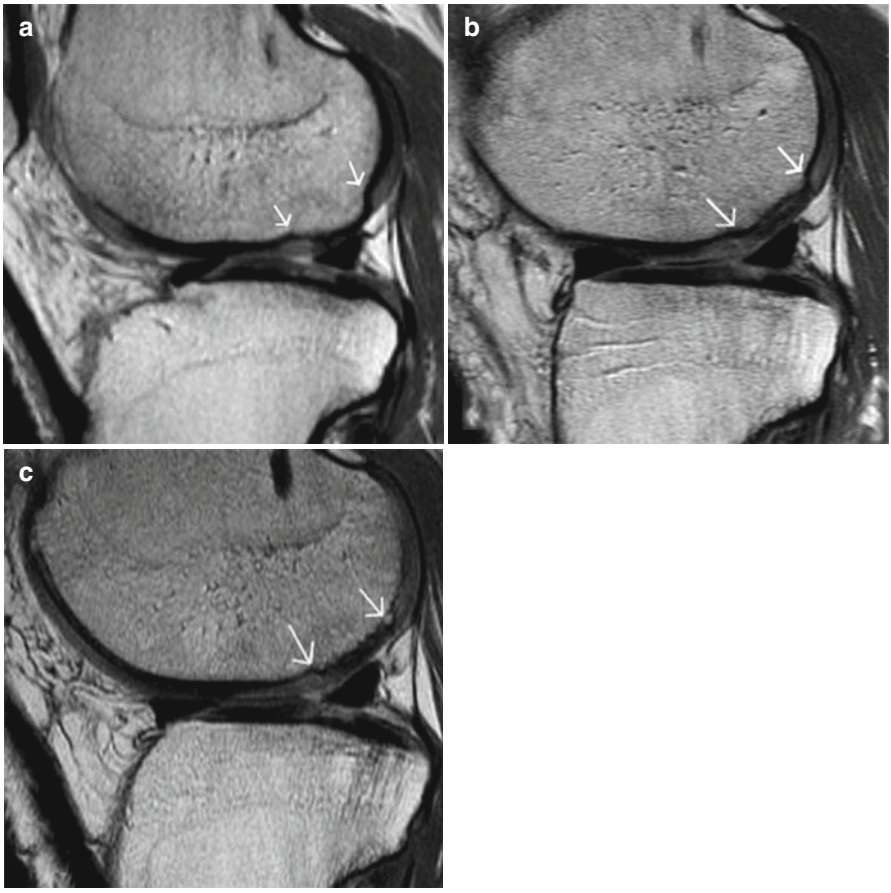

Fig. 18.4 Magnetic resonance images (sagittal plane) of a representative patient with focal chondral lesion of the knee treated with DeNovo NT technique: preoperative (**a**), at 12-months (**b**) and at 24 months (**c**). Arrows mark the margins of the lesion. (Picture reproduced from Farr et al. [25])

bone (the "absolute shell graft") could ever be used for repairing cartilage defects is still unanswered.

Processed chondrograft is a technique that lies somewhere between the large osteochondral shell allograft and the minced cartilage allograft implantation. Occasionally it is also called the "hedgehog graft" after its appearance (when the incised cartilage is turned "inside-out"). The basic steps of this technique are the harvesting of the pure cartilage allograft from an adult cadaveric knee joint (large intact piece peeled from the femoral condyle), the multiple incision of the deep zone of the cartilage graft (Fig. 18.5) to improve handling and healing characteristics, and the implantation via mini arthrotomy.

For graft harvesting the cadaveric knee joints are prepared under aseptic conditions. The condylar surfaces are used as donor sites. Approximately 2.5×4 cm grafts are harvested by peeling the cartilage off of the subchondral bone. Calcified

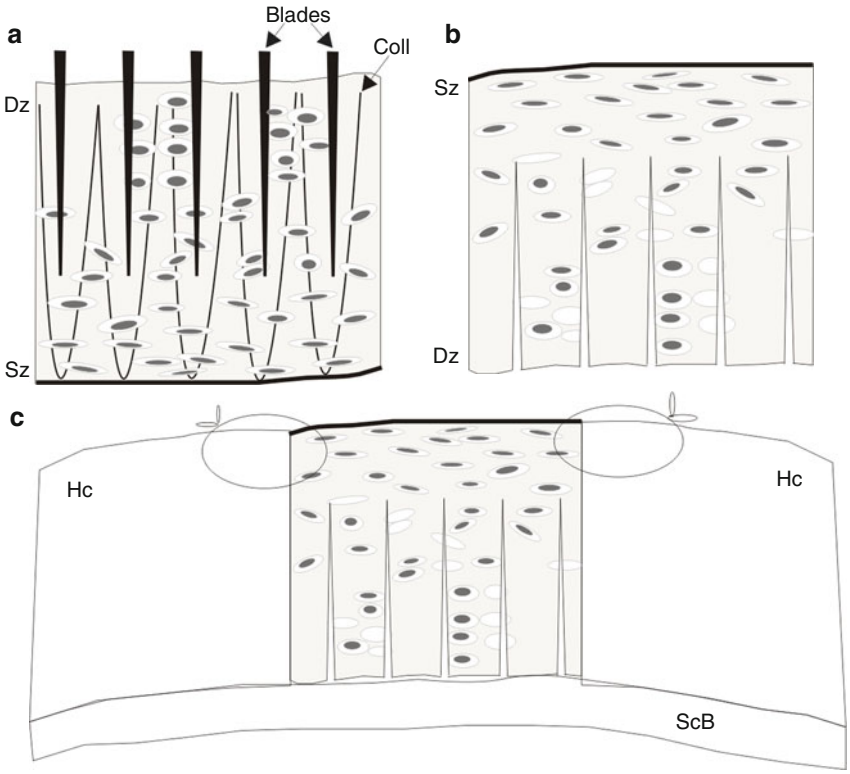

Fig. 18.5 The basic concept of processed cartilage allograft. (**a**) Articular cartilage specimen multiply incised through the deep zone (*Dz*). Note that the collagen fibers (*Coll*) run parallel with the incisions in this zone. Graft before (**b**) and after (**c**) implantation. (*ScB* subchondral bone, *Hc* healthy hyaline cartilage, *Sz* superficial zone) (Picture reproduced from Bardos et al. [3])

cartilage remnants are meticulously removed from the graft after harvesting. The graft is kept moist throughout the whole process (to prevent cell death in the superficial zone of the graft) and stored in medium until used (within 35 days).

During surgery a specific incisor is used to create parallel incisions in the deep zone of the graft limiting the incision depth to 600 μm from the superficial zone, therefore preserving the arcading collagen network in the superficial zone and providing the pliable graft with good tensile strength. The incisions convert the graft into a pliable, well accommodating tissue that can be firmly positioned and fixed to the cartilage site but the incisions also significantly increase the surface area for attachment. The incisions can be performed in two or more different directions, creating larger surface for cell invasion/evasion at the integration site. The graft must be recessed relative to the contiguous host cartilage surface and it is secured to the defect site using 6.0 PDF stitches and Fibrin Glue (Fig. 18.6).

Recently we showed in a porcine model that fresh pure cartilage allograft incised through the deep zone has a good healing potential to the subchondral bone [3]. The

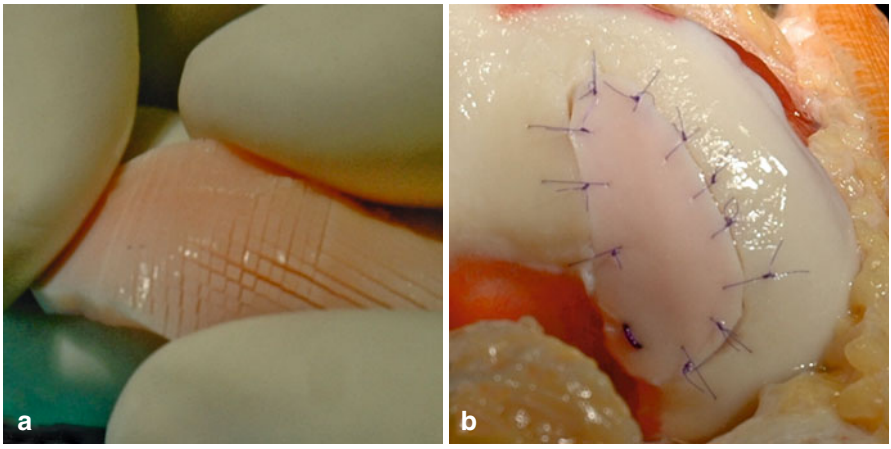

Fig. 18.6 (**a**) Hedgehog appearance of the basal surface of a processed cartilage allograft before implantation. (**b**) Intraoperative picture of the graft after securing with stitches, trans-osseal knot and fibrin glue

study showed that the grafts had good primary stability and the grafts were held in place at 6 weeks even though the securing stitches were reabsorbed by then. The basal incisions were visible with histology at 6 weeks postoperatively without any obvious tissue formation within the incisions (almost only virtual space), nevertheless at 6 months the former incisions were not detectable anymore (unpublished data from the author). Lateral integration was incomplete in most grafts, and the quality of the subchondral bone appeared somewhat irregular (less trabecula in the subchondral bone, with slightly thicker appearance than at the recipient site). However, the microscopic assessment showed good preservation of the graft with hyaline cartilage on the recipient site.

A small clinical trial has been introduced to assess the repair potential of processed chondrograft in human knee joints. Seven patients with eight focal chondral lesions were enrolled into the study. The average size of the chondral defects was 3.9 cm^2 (2.0–5.4 cm^2). The lesions were accessed via a small arthrotomy and prepared for the graft implantation with thorough debridement of the lesion down to the underlying subchondral plate. Fresh human chondral allografts (obtained from knee joints, containing no bony component, stored at 4 °C) were tailored to match the shape of the lesion, incised on the formerly osseous side and secured with stitches and fibrin glue as described above. Postoperative rehabilitation was similar to the previous methods. At an average of 18 months follow up no adverse reaction was reported; patients did not experience any sudden deterioration in the joint functions (e.g., loose body sensation, joint locking, or sharp pain). The patients were satisfied with the outcome and the SF-36 health survey revealed significant increase (the mean combined SF-36 scores increased from 57 ± 19 at baseline to 85 ± 13 at the latest examination, $p < 0.001$). The knee functions improved in all patients (Lysholm's knee score from 62 ± 18 preoperatively to 74 ± 14 postoperatively,

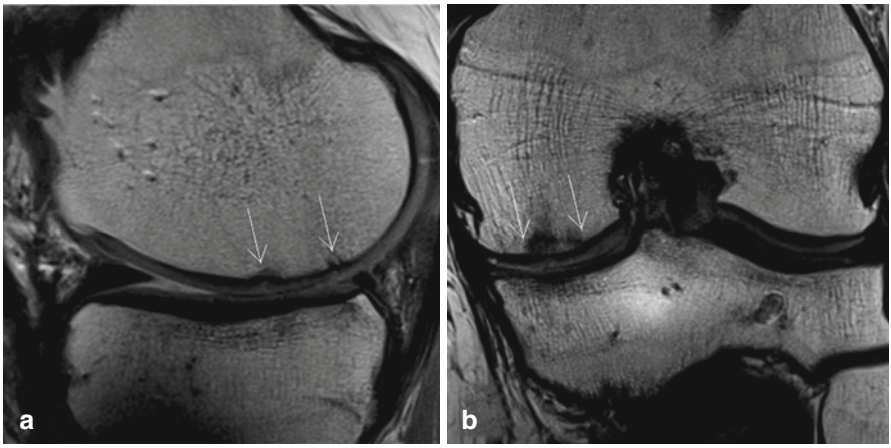

Fig. 18.7 Magnetic resonance images in sagittal (**a**) and coronal plane (**b**) of a representative patient 12 months after focal defect repair of the medial femoral condyle using processed allograft (hedgehog). Please note that the patient does not correspond with the pictures shown in Fig. 18.6

$p < 0.05$). At 12 months MRI suggested possible partial delamination of the chondral graft (fluid signal beneath the graft) in only one patient.

In the other patients MRI proved good osteochondral integration without any sign of degeneration or rejection of the cartilage graft (Fig. 18.7). The grafts demonstrated good congruency with the host condyle, and the cartilage signal was isointense to that of the host area with only mild subchondral edema. It appears that processed chondrograft has capacity to integrate to the subchondral bone following surface augmentation, and the straightforward technique seems to be safe and feasible as well. Additional long term clinical investigations must be carried out to assess the possible role of processed pure cartilage allografts in cartilage repair.

18.5 Conclusion

The new concept in cartilage repair- that pure cartilage tissue following mincing or incisions could be used in a single-stage procedure – is very promising and opens a whole new field for research and investigations. The results of any cartilage repair technique can only be judged years following the initial treatment. Maturation of the cartilage tissue, vascular invasion from the subchondral bone and transformation into fibrous cartilage are still feared possible long term outcomes in all these techniques, but the data available in the literature to date is very encouraging, and the attractiveness of a single stage procedure with off-the-shelf or readily-available repair kits are difficult to resist for any cartilage surgeon when providing similar or better results compared to existing techniques. These techniques may have potential and if the outcome meets the expectations, they may become repair techniques in the future.

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