NOVEL CARTILAGE REPAIR STRATEGIES – THE AMIC TECHNIQUE

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Injuries to articular cartilage are one of the most challenging pathologies of musculoskeletal medicine due to the poor intrinsic healing capacities of damaged cartilage. Autologous Matrix Induced Chondrogenesis (AMIC) is an innovative treatment for localized full-thickness cartilage defects combining the well-known microfracturing with a collagen I/III scaffold. The current article reviews the treatment modalities utilized in cartilage repair procedures, focusing on the role of AMIC in clinical practice today and it´s way from "bench to bedside".

The limited intrinsic healing potential of damaged articular cartilage is a well-known problem in orthopedic surgery (1). Cartilage degeneration may be accompanied by pain, immobility, stiffness, loss of quality of life and can potentially lead to severe osteoarthritis in the long term. A plethora of emerging treatments and associated surgical techniques have been described to improve cartilage repair techniques. The treatment should aim at alleviating pain and restoring functionality in first place eventually leading to the formation of an entirely new articulating surface that essentially duplicates the original articular cartilage in its structure, composition and function.

Supporting the intrinsic repair mechanism is achieved by initiating the recruitment of chondrogenic progenitor cells (e.g. MSCs) from the bone marrow by penetration of the subchondral bone by drilling or microfracturing (2). Currently, microfracturing is the most common used cartilage repair procedure in cartilage defects (3) often resulting in fibrocartilaginous repair tissue. Chondrogenic progenitor cells migrate in the fibrin network of the blood clot (4). However, this fibrin clot is fragile and not mechanically stable to withstand tangential forces (5). Therefore, an implanted exogenous scaffold (e.g. a collagen matrix) is sought to improve the mechanical stability of the clot and may ideally provide a proper stimulus for chondrogenic differentiation and hence cartilage repair. Autologous Matrix-Induced Chondrogenesis (AMIC®) combines microfracturing with a collagen I/III matrix (Chondro-Gide®, Geistlich Pharma AG, Wolhusen, Switzerland). The AMIC procedure provides 2 major advantages; on the one hand it is a one-step procedure with no need of cartilage harvesting potentially leading to donor site morbidity and on the other hand it is cost-effective with no need of in vitro cell expansion (6).

In this article we focus on the pre-clinical rationale of the AMIC technique and it´s surgical procedure, before summarizing first clinical results of this enhanced microfracturing technique.

Pre-clinical Rationale

Mesenchymal stem cells (MSCs) possess the ability to proliferate extensively in culture,

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Fig. 1. ***(A - C)*** *Intraoperative findings of an open AMIC procedure (18 yrs. female, cartilage defect at the patella). Perforations into the subchondral bone with a sharp canula (Fig. 3A). Application of fibrin glue (Baxter-Immuno, Heidelberg, Germany) (Fig. 3B). The collagen I/III matrix (Geistlich Pharma AG, Wolhusen, Switzerland) is applied (Fig. 3C).*

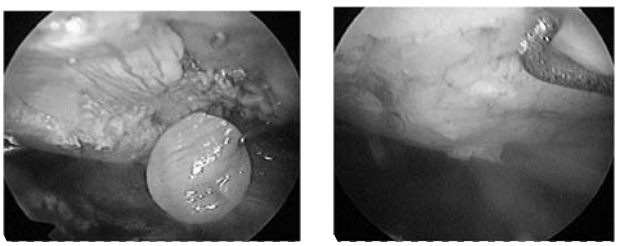

Fig. 2. ***(A – B)*** *Intraoperative findings of an all-arthroscopic AMIC technique (32 y.o. male, cartilage defect at the patella). After debridement of the cartilage defect numerous perforations of the subchondral lamina are performed. Circular overlapping patches of Chondro-Gide are placed in the defect area with Pean clamps (Fig. 2A). The matrix covered area is sealed with fibrin glue (Baxter-Immuno, Heidelberg, Germany) and stability of the implant is checked by arthroscopy (Fig. 2B).*

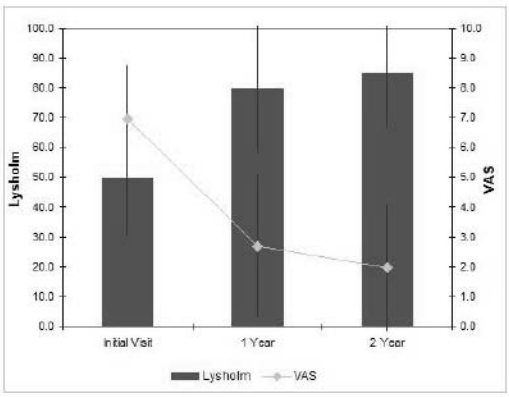

Fig. 3. *Results of the AMIC Registry: 1 and 2year follow of clinical outcome after AMIC evaluated by the Lysholm and VAS score (n=57). Scores are presented as medians.*

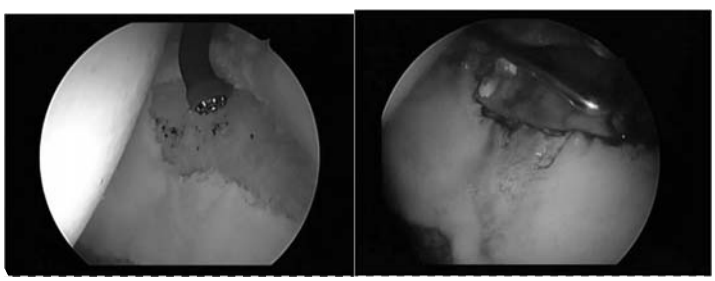

Fig. 4. ***(A-B)*** *Intraoperative findings of an all-arthroscopic AMIC technique at the hip (cartilage defect at the femoral head). After debridement of the cartilage defect (Fig. 4A) the matrix, which was trimmed to defect size, is placed in the cartilage defect (Fig. 4B).*

and chondrocytes derived from them have been observed to maintain a stable phenotype compared to chondrocytes derived from primary cultures. In addition, adult chondrocytes show a restricted proliferation capacity in culture resulting in a limited number of cells, almost insufficient for regenerative strategies (7).

The AMIC technique allows to access intrinsic cartilage repair resources of the bone marrow. Indeed, Kramer et al. were reproducibly able to detect the rapid appearance of human MS cells in the collagenous matrix (7).

Dickhut et al. analyzed whether a collagen type I/III carrier and fibrin glue (FG) combined to a biphasic construct supports chondrogenesis of MSCs *in vitro* allowing the local release of bioactive transforming growth factor-beta1 (TGF-b1) (8). In conclusion, this study demonstrated that a biphasic carrier made of these two biomaterials supports chondrogenic *in vitro* differentiation of human MSCs. Besides this it was shown that FG as a clinically applied biomaterial is suitable as a TGF-b delivery system.

In an animal model the potential effect of matrix assisted MSC transplantation for articular cartilage regeneration 8 weeks postoperatively was investigated by Jung et al (9). Cell distribution was more homogeneous in MSC compared to membrane-only group, where cells were found mainly near the subchondral zone. The authors concluded that autologous matrix assisted MSC transplantation significantly increased the histomorphological repair tissue quality during early articular cartilage defect repair and resulted in higher GAG/collagen type II-positive cross-sectional areas of the regenerated tissue.

In an ovine model with a follow-up period of 12 months, the average thickness of the repair tissue was significantly greater when a scaffold was used, especially a collagen I/III membrane (10). No differences were detected when comparing cell-free and cell-laden collagen membrane biomechanically and histologically.

In conclusion, *in vitro* studies show that the AMIC technique leads to the accessibility of the intrinsic cartilage repair resources represented by MS cells in bone marrow. Animal studies showed an enhanced defect filling and higher quality repair tissue when a collagen matrix was used.

Surgical technique

The AMIC technique was first developed for the knee joint. Therefore we will focus on the knee to describe the open and arthroscopic approach.

The open procedure is a standardized surgical technique and was described before (11). After exposure of the defect area (mini-arthrotomy), degenerative and attached cartilage is completely removed. Microfracturing is performed for instance via perforations of the subchondral bone with a sharp canula (Fig. 1A) and application of fibrin glue (Baxter-Immuno, Heidelberg) is done (Fig. 1B). The defect is covered with a collagen I/III matrix (Geistlich Pharma AG, Wolhusen, Switzerland) that was prior trimmed to fit to the cartilage lesion by adaption to an appropriate template(Fig. 1C). The knee joint is held in an extended position for 5 minutes before the joint is flexed 10 times to test the stability and position of the matrix.

In arthroscopic assisted AMIC, the implantation of the matrix is performed under dry, arthroscopic conditions, as previously described (12). Circles patches of Chondro-Gide are placed in the prepared defect area with Pean clamps (Fig. 2A). The patches overlap. According to the original technique, the porous surface of the matrix is facing the bone surface. Fibrin glue is applied and its excess is removed from the surrounding soft tissue, and left to set for 5 min. Then, 10 knee movements (consisting of flexion and extension) are performed to check the stability of the implanted matrix (Fig. 2B).

Clinical studies

AMIC has been established and performed in the knee since 2004. Over the past few years there is an increasing interest and experience for its application in the hip and ankle joints also. Below, we present the joint by joint clinical results to give an overview of AMIC in clinical practice today.

Knee joint

The AMIC technique was first described in 2005 by Behrens et al. and is at present widely used (13-14). So far, no data from a randomized controlled trial have been published investigating the performance of AMIC compared to other cartilage repair procedures. A couple of case series showed good to excellent results up to long-term follow-up.

In a study to evaluate the quality of the repair tissue obtained from biopsies harvested during second-look arthroscopy after arthroscopic AMIC augmented with bone marrow concentrate, 5 second-look core biopsies were harvested at 12 months. The clinical and histological data suggest that a nearly normal arthroscopic appearance and a satisfactory repair tissue was achieved, which was possibly still maturing at then (15).

In 1 of our series, 32 chondral lesions in 27 patients were treated with AMIC (11). These patients were

evaluated for up to 5 years after the intervention. The mean defect size of the chondral lesions was 4.2 cm^2. 87% of the patients studied were subjectively highly satisfied with the results after surgery. Significant improvement of all clinical scores was observed 12 months after AMIC, and further improvement was found up to 24 months postoperatively. MRI analysis showed moderate to complete filling with a normal to incidentally hyperintense signal in most cases. Results did not show a clinical impact of patient's age at the time of operation, body mass index and number of previous operations. In contrast, males showed significant higher values in the IKDC score compared to their female counterparts, although the reason remains unclear.

In a recent study we evaluated the data of the AMIC Registry, an internet-based tool to longitudinally track changes in function and symptoms by the Lysholm score and VAS (16).

The results of 57 cases with a follow-up period of 2 years were presented. The majority of patients were satisfied with the postoperative outcome, reporting a significant decrease of pain (mean VAS preop=7.0; 1year postop=2.7; 2years postop=2.0). Significant improvement of the mean Lysholm score was observed at 1 year after AMIC and further increased values were noted up to 2 years postoperatively (preop=50.1, 1year postop=79.9, 2year postop=85.2) (Fig 3).

Another retrospective evaluation of clinical and radiographic outcomes of patients treated with AMIC for chondral and osteochondral full-thickness cartilage defects of the knee was performed with a mean follow-up of 29 months (17). Significant improvements in clinical outcome scores (IKDC, Lysholm, Tegner, and VAS pain score) were noted. Patients were generally satisfied with their results. MRI evaluation showed that tissue filling was present but generally not complete or homogenous.

Emerging techniques have the potential to complement the "first generation" AMIC technique as described by Behrens et al. which is based on microfracture (13), for instance the addition of concentrated bone marrow from the iliac crest. A study of de Girolamo et al. suggests a difference in mesenchymal stem cells (MSCs) harvested after microfracturing to MSCs derived primarily from the iliac crest (18). It is observed that the MSCs from the microfractured areas demonstrate a different more irregular pattern compared to those harvested from the iliac crest.

In comparison to microfractures, drilling does not seem to have such a deleterious effect on the subchondral bone matrix as was formerly speculated but instead leads to better access to the bone-marrow stroma in the rabbit model (19). Following these new findings, the AMIC technique in the knee was modified and drilling instead of microfractures used to penetrate the subchondral layer (20-21). An arthroscopic approach of the AMIC technique was published by Piontek et al. (12). Compared to open surgery, the described arthroscopic technique may offer advantages including minimal soft tissue trauma and minimal blood loss.

In conclusion, AMIC in the knee has been reported to be an effective and safe method of treating symptomatic full-thickness chondral defects of the knee in appropriately selected cases.

Ankle joint

Chondral defects of the talus are common and remain a challenging therapeutic task to orthopedic surgeons. Several surgical techniques are available for treatment. Good early results are reported; however, literature is limited to case series and case reports and long-term outcome is unknown (22).

AMIC at the talus was first described in 2008; good clinical results were initially reported as an open procedure (23). In 2011 Simon et al. published the description of an arthroscopic AMIC technique having all the advantages of arthroscopy and with no need for osteotomy of the medial malleolus (24).

In a case series of 72 osteochondral lesions at the talus (Outerbridge III-IV) an increase of the AOFAS score improved from 47.3 to 88.3. The follow-up MRI demonstrated good cartilage regeneration without joint effusion (25).

Hip joint

Chondropathies of the acetabulum and the femoral head are a frequent cause of pain and functional limitation (26). AMIC was previously performed as an open procedure, raising the same issues associated with all arthrotomies, such as the risk of infection and a prolonged recovery time. These could be minimized by performing the

procedure arthroscopically (Fig. 4A-B). Compared with the knee, the hip has more soft tissue coverage and more bony constraint, making hip arthroscopy and open approaches more technically complex and invasive than those for the knee. AMIC as an open procedure by surgical hip dislocation has been described by Leunig et al. (27).

A fully arthroscopic approach of AMIC at the hip has been recently published (28). In a randomized case series both groups, AMIC and microfracture showed a significant increase of the HSS (Harris Hip Score) at 1year follow-up, but a deterioration of the HHS results was notable in the microfracture group, while in the AMIC group improvements could be maintained over time (3). No significant differences were seen in another series comparing arthroscopic AMIC and ACI in acetabular cartilage defects (29).

In another report, the potential etiology of the rare parafoveal femoral head lesions seen in 3 of 6 patients and their treatment with AMIC was described (30).

In conclusion, the AMIC technique is technically feasible for the hip joint in an open or all-arthroscopic procedure. Preliminary findings after AMIC for femoroacetabular cartilage lesions are promising, but further studies are necessary to elucidate this fact.

CONCLUSION

AMIC is an innovative treatment that made its way from “bench to bedside” and is today a well-established surgical procedure for articular cartilage defect therapy in the knee, hip and ankle joint. Clinical studies prove a significant decrease of pain and increase of the functional outcome scores after AMIC.

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