Müller-Rath et al. [1] were the first to report a new **collagen type I**, which they extracted from the **tails of rats**. It is used as the source material for the CaReS® product by Arthro Kinetics, Austria, as well as the products by Amedrix GmbH, which are assessed in this clinical evaluation. In this paper, the authors examined the difference of different cell densities of the chondrocytes combined on the proliferation factor of these cells.

The same work group [2] implanted human cartilage preparations with artificially created defects in nude mice. These defects were previously covered with conventional ACI or the above-mentioned **collagen gel**. After six weeks, the preparations were explanted and examined histologically and immunohistochemically. Immature scar tissue with a low production of collagen type II was identified. The redifferentiation of chondrocytes also remained incomplete.

Schneider and Andereya reported 2003 [3] first results of a prospective randomized comparative study between traditional ACT and the CaReS®-/MACI technology (**collagen type I**).
20 patients were associated to one of the above-mentioned treatment groups using the matched pair method. The defect size in the CaReS® group was by average 5.78 cm² and in the ACT group by average 6.63cm². In both groups, an improvement of the IKDC score by an average of 13 points could be observed after 6 months. Surgery durations were very significantly shorter in the CaReS® group, and the ACT group had significantly more and longer lasting swelling and contusion formation even after the 12th week.

The workgroup cited above **¡Error! No se encuentra el origen de la referencia.** examined in a prospective study, to what extent the matrix-based chondrocyte transplantation with the above mentioned **3D collagen** (CaReS®) was able to achieve improvements in the ICRS and IKDC scores in 22 patients with chondral or osteochondral femoral defects. Results two years after surgery: 14 patients were treated with the collagen gel for a a focal femoral solely chondral lesion. In 8 cases, the bone of the subchondral bearing had to be reconstructed due to OCD. Defect size on average was 6 cm². In all cases, the matrix could be glued to the defect with fibrin without problem. The average surgery duration was 69 min, the length of the surgical access 8.2 cm. No complications specific to this kind of surgery were observed. Over the post-operative course, there was a significant improvement in the subjective / objective IKDC as well as in the functional score and the overall assessment after 3 and 6 months until the end of the study duration. At this point in time, a follow-up examination of 13 patients was performed. 84.6 % of the patients assessed the success of the method as excellent or good at the follow-up.

Andereya et al. **¡Error! No se encuentra el origen de la referencia.** treated 14 patients suffering from patello-femoral cartilage damage (chondropathia retropatellaris) with the matrix-based ACT used CaReS®. In these patients (13 retropatellar, 1 trochlear), isolated femoro-patellar cartilage damage was treated by autologous chondrocyte transplantation (ACT) with a **collagen cell carrier**. The size of the cartilage defects was 1.7 - 8.4 cm². The ICRS-IKDC scores and the Brittberg score showed a significant improvement over the period of observation. The assessment of the objective IKDC and ICRS function scores improved from 0/14 or 2/14 (14.3%) pre-operative to 11/14 (78.6%) in the categories A/B or I/II after two years. 11 (78.6 %) patients rated the result after two years very good/good. The subjective IKDC score improved from 32.4 +/- 8.4 pre-operative to 67.8 +/- 27.4 after two years. See also table 1.

Table 1: Change of clinical parameters within two years after MACI

	Before surgery	**36 months after surgery**
Objective IKDC score	0/14 (0 %)	11/14 (78.6 %)
Objective ICRS score	2/14 (14.3 %)	11/12 (78.6 %)

Subjective IKDC score	32.4 (+/-8.4)	67.8 (+/-27.4)
Brittberg score	0	78.6 %

Maus et al. [6] also used the combination from autologous bone transplantation and MACI with the CaReS® implants by Arthro Kinetics (**Kollagen Typ I**) for the treatment of osteochondral defects in 13 knees. The average defect size was 8.1 (2.8 - 13.5) cm^2. The subjective and objective IKDC, Brittberg and ICRS scores significantly increased in the observation time of 36 months. In Brittberg score, 83.4 % of the patients categorized their treatment result as good or excellent (see table 2).

Table 2: Change of clinical parameters within three years after MACI

	Before surgery	**36 months after surgery**
Objective IKDC score	0/13 (0 %)	11/12 (91.7 %)
Objective ICRS score	0/13 (0 %)	11/12 (91.7 %)
Subjective IKDC score	38.4 (+/-12.7)	66.1 (+/-17.0)
Brittberg score	0	83.4%

Acellular collagen implants including Amedrix GmbH products

CaReS®-1S is an acellular collagen type I gel implant which is used for the treatment of localized focal cartilage defects in the knee joint. It was approved as a medical device in 2010 and implanted in 15 patients (9 women and 6 men) between July 2008 and February 2009 **¡Error! No se encuentra el origen de la referencia.**. This "prospective clinical study for the determination of the effectiveness of an acellular collagen type I implant for filling localized focal defects" was performed due to an ethics committee vote from April 10, 2008 by the University Hospital Marburg.
Using fibrin glue (Tissucol by Baxter), defects of an average size of 0.62 +/- 0.19 cm^2 were treated.
Inclusion criteria were among others an intact cartilage shoulder, intact surrounding cartilage and the corresponding joint surface, free movement of the joint, grade of defect acc. to Outerbrigde III and IV, osteochondritis dissecans and a defect size < 11 mm diameter (defect not prepared). The average patient age was 26 years (15 to 40 years). MRT was done after 6 weeks as well as after 6 and 12 months. As early as after 6 weeks, all patients regained full weight-bearing capacity free of pain as well as free knee mobility 8 weeks after surgery **¡Error! No se encuentra el origen de la referencia.**. There were no adverse effects or complications in context with the product.
After a year, regular implant localization could be determined in 13 patients, as well as timely regeneration of the defects with an IKDC score of about 70, which was directly comparable to the IKDC score of the transplants populated with cells (CaReS®). Partial filling of the defect of one patient was determined after 6 weeks and after 6 months. In the case of another patient, the implant could not be located in the MRT examination after 6 weeks. Thus, the defect was considered empty. In the examination after 6 months and after 1 year however, a complete filling could be detected. In addition, the IKDC score and the Tegner activity score were determined and compared to the data of the CaReS® transplant populated with cells. A significant increase in both score values was already evident after 6 months. Schofer et al conclude that the implant CaReS®-1S of Arthro Kinetics, Austrua has an excellent tolerability and stably remains in the defect even without using autologous cartilage cells. Clinical results show that it is comparable to cell-based CaReS® transplants.

Another case study, for application to the ankle joint, was also published on the homepage of Arthro Kinetics, Austria. 2012, defective areas in the ankle joint were treated with the product CaReS®-1S in 5 patients. Implantation was done at the open joint after osteotomy. On the basis of the American Orthopedic Foot and Ankle Society score (AOFAS), a significant improvement of the score values "pain" and "function" could be determined after 2, 3, 6 and 12 months, compared to preoperative values.
The concluding result by Bichmann [8] is that implantation of CaReS®-1S is a new alternative for the treatment of cartilage defects in the ankle joint.

In February 2013, the first results of the multi-center study on CaReS®-1S were published on the homepage of Arthro Kinetics, compiled in a presentation [9]. Between 2011 and 2013, a total of 37 patients were included in the study. The results of the follow-up examinations 24 months after surgery are already available for 2 patients. Arthro Kinetics has chosen the same study design as for CaReS® **¡Error! No se encuentra el origen de la referencia.** and thus has reference values. The initial IKDC score values were even worse with CaReS®-1S. Considerably better scores were already determined after 3 months, with another improvement after 24 months (33.1 preoperative compared to 72.6 postoperative). The unknown author concludes that the CaReS®-1S method is suitable for successful treatment of different, even large, cartilage defects (defect size in the study up to 8 cm^2).

The product by Amedrix GmbH, ChondroFiller^{liquid}, is a collagen gel as well, which can be accurately injected into defects thanks to its way of application, making it possible to completely fill the entire defect. This way, the cells of the surrounding tissue can migrate into the collagen structure (**collagen type I**) to synthesize collagen type II there. The matrix introduced can be converted into autologous tissue.

Ability to migrate of the chondrocytes

About two years later, the work group of Gavenis et al. [10] were able to show the ability to migrate of chondrocytes *in vivo*: As a preliminary test, a cell-free **collagen type I** gel plug with a diameter of 1 cm^2 was cast in a petri dish with collagen gel populated with cells in a concentration of 2 x 10^5 chondrocytes per milliliter and cultivated *in vitro* for 6 weeks. As expected, migration of the chondrocytes into the cell-free collagen plug could be observed and the plug was homogeneously interspersed with chondrocytes as early as after four weeks.
In parallel, defects in human osteochondral blocks were filled with **cell-free collagen** and subsequently cultivated in a nude mouse. After six weeks, a macroscopically excellent cartilaginous repair tissue formed. However, the collagen in this *in vivo* model was not completely interspersed with chondrocytes after 6 weeks. The attachment of the collagen with the surrounding cartilage on the other hand was excellent and the immunohistochemical staining evidence of a strong production of collagen type II in the pericellular space with a simultaneous reduction in collagen type I.

Results after a study time of 52 weeks were described by Schneider et al. in 2011 [11]. Using Goettingen minipigs as test subjects, this work group was able to show that the cell-free collagen piece (**collagen type I from rat tail tendons, 4.8 mg/mL**) yields the same results after a year (collagen type II production, cell morphology and O'Driscoll score) as a collagen gel populated with cells. In addition, repair tissue of adequate high quality could be detected in both treatment groups after this period of time.
In total, 18 minipigs were observed over a period of 6, 12 and 52 weeks (6 animals per date). Three defects were applied to the hind leg of each animal, with two defects being treated (with cell-free collagen gel or collagen gel populated with cells) and the third defect remaining untreated. As early as after 6 weeks, a high cell count could be determined in the gel that

was cell-free before. The cell morphology corresponded to the appearance typical of chondrocytes.
At all scheduled dates, all areas treated with collagen (cell-free or populated with cells) showed a complete filling of the defect zone as well as a smooth surface. After a year, a completely developed hyaline tissue could be determined in the defects treated with collagen, whereas the untreated defect showed fibrous tissue, which was shrunken after 1 year.
This study shows that the use of previously cell-free collagen gel reduces the number of surgical interventions (removal of a biopsy for cell cultivation and transplantation of the collagen matrix populated with cells) needed to one intervention, as the same results could be achieved after a year.

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