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Matrix-associated autologous chondrocyte transplantation/implantation (MACT/MACI)—5-year follow-up

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Abstract

Matrix-associated autologous chondrocyte transplantation/implantation (MACT/MACI) is a new operation procedure using a cell seeded collagen matrix for the treatement of localized full-thickness cartilage defects. A prospective clinical investigation was carried out in order to clarify whether this proves suitable and confirms objective and subjective clinical improvement over a period of up to 5 years after operation.

Thirty-eight patients with localised cartilage defects were treated with MACT. Within the context of clinical follow-up, these patients were evaluated for up to 5 years after the intervention. Four different scores (Meyers score, Tegner–Lysholm activity score, Lysholm–Gillquist score, ICRS score) as well as the results of six arthroscopies and biopsies obtained from four patients formed the basis of this study. For 15 patients, 5 or more years had elapsed since the operation at the time this study was completed. It was possible to obtain results 5 years postoperatively from 11 (73.3%) of these 15 patients. Overall, we included 25 patients into the evaluation with a 2-year or longer postoperative period.

Five years after transplantation 8 out of 11 patients rated the function of their knee as much better or better than before. Three of the four scores showed significant improvement compared to the preoperative value. One score, the Tegner–Lysholm score showed improvement, which, however, did not prove to be significant.

The significantly improved results on three scores after 5 years suggest that MACT represents a suitable but cost-intensive alternative in the treatment of local cartilage defects in the knee.

Keywords: Knee; Cartilage repair; MACT; MACI; Autologous chondrocyte transplantation; Matrix

1. Introduction

Cartilage defects and subsequent osteoarthritis entail pain and loss of mobility for the patients due to limitation of movement, leading to substantial lowering of their quality of life.

Different approaches and considerations exist regarding therapeutic possibilities, from which numerous forms of treatment have been developed to date [1–4].

Based on the idea to use the patient's own chondrocytes for regeneration of the defect area, Brittberg et al. treated large and deep cartilage defects with autologous chondrocyte implantation plus periosteum flap (ACI), first published in 1994 [5]. Over the past years, some problems linked with ACI have become apparent. It is known that chondrocytes in two-dimensional cell cultures alter their phenotype and dedifferentiate to fibroblast cells that no longer possess the capacity to produce collagen type II and proteoglycans [6]. In addition, the ACI technique is associated with a frequent occurrence of postoperative periost hypertrophy [7,8].

With the intention to respond to those difficulties and to enhance the redifferentiation of chondrocytes various scaffold used as carriers for chondrocyte implantation are under investigation [8,9].

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A new therapeutic procedure to overcome the problems mentioned above was developed at the Orthopaedic Department of the Medical University of Lübeck [10]. In 1998, we performed the first transplantation using a porcine collagen I/III matrix (Chondro-Gide®, Geistlich Biomaterials, Wolhusen, Switzerland) in place of ACI. Instead of periosteum flap, this was utilized as substrate for the so-called matrix-associated autologous chondrocyte transplantation (MACT, MACI®, Verigen Transplantation Service, Copenhagen, Denmark).

An uncontrolled prospective clinical investigation was carried out in order to clarify whether MACT proves suitable to treat cartilage defects and confirms objective and subjective clinical improvement over a period of up to 5 years after operation.

2. Materials and methods

Patients were selected for the MACT technique after conservative measures and imaging procedures confirmed cartilage damage requiring arthroscopy. Inclusion criteria were patients between 18 and 60 with localized cartilage defects. Exclusion criteria were inflammable arthritis, total meniscectomy, knee instability, an inoperable valgus or varus deformity, patelladysplasia or massive overweight (BMI>35). All patients gave informed consent and treatment was approved by our local ethic committee on May 6th, 1998 (file number 98/056).

After inspection of the defect area, with localised cartilage defects of grades III to IV according to Outerbridge [11], 200 to 300 mg of full thickness cartilage was extracted from non-weight-bearing areas (trochlea/notch area). Together with autologous patient serum, it was sent to Verigen Transplantation Service (VTS, Copenhagen, Denmark) in a transport container. Chondrocytes were isolated from the biopsy specimen by means of enzymatic digestion of the surrounding matrix. The chondrocytes were cultured subsequently for 4 weeks before being seeded (about 1 million cells/cm^2) on the rough side of the porcine collagen I/III matrix (Chondro-Gide®, Geistlich Biomaterials, Wollhusen, Switzerland). The loaded matrix was then cultured with autologous serum for the remaining 3 days. There was an overall chondrocyte proliferation from a mean of 0.3×10^6 to 16.3×10^6 at extraction. In a second operative procedure, the chondrocyte-loaded matrix was transplanted into the defect area. Following arthrotomy, debridement of the defect area down to the subchondral bone was carried out. Afterwards, using a foil template reflecting size and geometry of the defect, the Chondro-Gide® matrix loaded with chondrocytes was cut to size and fitted into the defect with the cell-loaded surface facing the subchondral bone.

Four different scores formed the basis for evaluation of the therapeutic success: the Meyer score, the Tegner–Lysholm score [12], the Lyshom–Gilquist score [13] and the ICRS score, representing the IKDC evaluation endorsed by the International Cartilage Repair Society (ICRS, www.cartilage.org). Postoperative findings that resulted from follow-up examinations conducted at 3, 6, 12, 18, 24, 36 and 60 months were documented and compared with the preoperative findings. Statistical tests were performed using the Wilcoxon test and the Kruskal–Wallis test. During the 5-year postoperative evaluation phase, diagnostic re-arthroscopy was indicated for six patients. Biopsies could be obtained for four patients at 12 months or later after MACT for histological analysis (methods described by Kurz et al. [14]).

3. Results

From November 1998 to March 2001, 38 patients were treated with MACT. These knee patients were monitored during the period from November 1998 to June 2004. Overall, we were able to obtain valid preoperative and postoperative investigational results for 34 out of 38 patients (see Table 1). All of the results presented here are based on 25 patients with a minimum of 2-year follow-up postoperatively. For 15 patients, 5 or more years had elapsed since the operation at the time this study was completed. It was possible to obtain results 5 years postoperatively from 11 of these patients.

The mean follow-up period was 34.5 months (min: 6 months, max: 60 months). 19 patients were female, 19 male. Their mean age was 35 years (min: 18 years, max: 58 years) (Table 1).

For the majority of 16 patients (42.1%), the defects were predominantly located at the medial condyle. Ten patients (26.3%) were diagnosed with an isolated defect in the retropatellar area. With an incidence of three (7.9%), damage solely to the lateral condyle was the least common. A further nine patients (23.6%) had multiple lesions. Defect size varied between a total of 0.64 cm^2 and 17.75 cm^2, taken into account that the surface areas of the multiple lesions were added cumulatively. The mean value was 4.08 cm^2.

Twenty-five patients had previous surgery to their knee prior to undergoing MACT. Thirteen patients (36.11%) had already been operated once; 12 patients (33.3%) had already had two or more interventions. These included diagnostic arthroscopy, debridement and lavage, microfracture, lateral release, reconstruction of the anterior crucial ligament, high tibia osteotomy (HTO), partial meniscectomy and osteo/chondroplasty (see Table 2).

In the subjective rating after 5 years, 8 out of 11 patients stated that their knee was “much better” or “better” than before the operation. The Meyer score, compared with the preoperative value, showed significant improvement after 5 years ($p=0.007$, $n=11$) (Fig. 1). The Lysholm–Gilquist score also showed a significant improvement 5 years postoperatively ($p=0.04$, $n=11$) compared to the initial value before the operation (Fig. 2) and the ICRS score was significantly improved 5 years postoperatively as well ($p=0.03$, $n=11$) (Fig. 3).

In contrast, no significant improvement could be seen in the Tegner–Lysholm score 5 years postoperatively ($p=0.41$, $n=11$) (Fig. 4). In order to determine the influence of patient age at the time of operation on the results, the patients were divided into three subgroups: patients aged between 18 and 32 years, patients from 33 to 46 years and patients between 47 and 60 years. Looking at the score results, none of the four scores showed a significant difference (Meyer score $p=0.97$, Tegner–Lysholm score $p=0.81$, Lysholm–Gilquist score $p=0.59$, ICRS score $p=0.51$).

There were no significant differences between male and female (Meyer score $p=0.15$, Tegner–Lysholm score $p=0.07$, Lysholm–Gilquist score $p=0.16$, ICRS score $p=0.27$).

The localisation of the defect (medial femur condyle, lateral femur condyle, patellar or multiple lesions) did not influence the result (Meyer score $p=0.58$, Tegner–Lysholm score $p=0.25$, Lysholm–Gilquist score $p=0.25$, ICRS score $p=0.81$).

Table 1
Overview: patients characteristics and results

No.	Age	Gender	Defect localisation	Defect size (cm^2)	Etiology	Previous knee surgery	Meyer preoperative ($n=34$)	Tegner–Lysholm preoperative ($n=34$)	Lysholm–Gilquist preoperative ($n=34$)	ICRS preoperative ($n=34$)	Meyer postoperative at final follow-up ($n=34$)	Tegner–Lysholm postoperative at final follow-up ($n=34$)	Lysholm–Gilquist postoperative at final follow-up ($n=34$)	ICRS postoperative at final follow-up ($n=34$)	Follow-up (months)
1	48	Female	Medial femoral condyle	3	Unknown	0	18	8	100	88	18	3	100	80.4	60
2	58	Female	Retropatallar	3.75	Unknown	0	9	3	49	29.3	18	4	97	83.9	60
3	35	Male	Medial femoral condyle	1.5	Trauma	0	9	2	63	40.3	18	4	87	80.4	60
4	19	Male	Lateral femoral condyle	7	Unknown	1	17	7	100	97.8	12	2	28		6
5	52	Female	Medial femoral condyle	2.55	Daily activities	1	9	2	27	23.9	9	1	55	31	60
6	51	Female	Medial femoral condyle	1.92	Trauma	1	9	2	20	38	13	3	61	42.3	12
7	27	Female	Retropatallar	1.95	Daily activities	1	15	3	75	58.6	17	5	94	73.6	60
8	19	Female	Retropatallar	1.8	Unknown	1	15	6	88	71.7	18	4	91	83.9	60
9	40	Male	Medial femoral condyle	3	Unknown	>3	9	3	42	32.6	17	5	94	55.1	60
10	37	Male	Multiple lesions	3.8	Unknown	0	10	3	42	19.6	11	4	63		6
11	41	Male	Multiple lesions	5	Unknown		0								0
12	43	Female	Medial femoral condyle	2	Unknown	0	7	1	46	28.2	8	1	35	23	60
13	35	Male	Multiple lesions	17.75	Unknown	3	10	3	61	42.3	16	5	89	69.8	60
14	44	Female	Multiple lesions	2	Daily activities	1	8	1	38	22.8	18	2	41	35.6	60
15	51	Female	Medial femoral condyle	3	Unknown	1	12	3	80	61.9	17	4	67	54	60
16	36	Male	Retropatallar	1.5	Unknown	>3	11	1	54	32.6	10	2	32	26	24
17	43	Male	Multiple lesions	11.75	Daily activities	2	9	3	41	28.2	13	2	50	34.4	24
18	39	Female	Multiple lesions	3	Daily activities	0	6	0	45	18.4	13	3	71	49.4	24
19	42	Male	Medial femoral condyle	8.75	OCD	1	14	3	63	46.6	18	5	100	87	24
20	35	Male	Multiple lesions	7.85	Trauma	1	12	0	10	35.8	17	3	81	65.4	24
21	43	Male	Medial femoral condyle	2.25	Trauma	0	13	3	83	41.3	18	6	93	80.4	24
22	35	Male	Medial femoral condyle	4.4	Unknown	0	17	4	50	70.6					0
23	19	Female	Lateral femoral condyle	7.5	Unknown	1	15	7	50	53.2	9	1	27	18.5	36
24	28	Female	Retropatallar	2.55	OCD	0	13	2	64	34.5	18	5	97	74.7	24
25	18	Female	Medial femoral condyle	1.08	Unknown	1	16	7	81	72.8	17	8	90	85	24
26	20	Female	Retropatallar	0.64											0
27	23	Female	Retropatallar	2.88	Trauma	1	12	5	68	68.4	18	8	85	88.5	24
28	36	Male	Medial femoral condyle	4.5	Trauma	0	17	3	55	50	13	2	92	40.3	24
29	36	Male	Medial femoral condyle	1.8	Unknown	2	17	6	90	64.1	17	3	94	65.5	24
30	34	Female	Retropatallar	2.6	Unknown	2	9	2	32	51	14	3	65	40.3	24
31	30	Female	Multiple lesions	5.79	Unknown	2	16	2	72	32.6	13	3	71	44.6	24
32	44	Male	Lateral femoral condyle	4.5			14	3	54	48.9	18	5	100	78.2	12
33	34	Female	Multiple lesions	3.45	Trauma	>3	11	3	20	23.9	8	1	27	32.6	12
34	38	Male	Medial femoral condyle	1.1	Daily activities	1	10	2	36	34.7	17	4	79	62	12
35	41	Male	Medial femoral condyle	7.5	Unknown	>3	7	4	21	38	9	2	22		6
36	28	Male	Medial femoral condyle	1.5	OCD	>3	13	3	67	48.9	17	5	71	54	18
37	18	Male	Retropatallar												0
38	21	Female	Retropatallar	4											0

Table 2
Previous surgery

Previous procedures on the knee	Number of patients
Debridement, lavage and/or microfracture	31
Partial meniscectomy	11
Diagnostic arthroscopy	3
HTO	2
ACL reconstruction	2
Osteo/chondroplasty	2
Lateral retinacular release	2

The defect size in the individual groups (group I: defect size >0–3 cm^2, group II: >3–6 cm^2, group III: >6–18 cm^2) did not differ significantly in the scores (Meyer score $p=0.58$, Tegner–Lysholm score $p=0.25$, Lysholm–Gilquist score $p=0.81$, ICRS score $p=0.36$).

In order to investigate whether the score results were dependent on the number of previous operations, the patients were divided into two subgroups (no previous operation and previous operation). The score values proved to be independent of whether or not the patients had previously been operated (Meyers score $p=0.36$, Tegner–Lysholm score $p=0.73$, Lysholm–Gilquist score $p=0.35$, ICRS score $p=0.67$).

Utilising the 2000 IKDC (International Knee Documentation Classification) Knee Examination Form, the knees of the patients were examined for alignment, patella position, patella dislocation, range of motion, swelling, ligament instabilities and crepitations. For the assessment, the examination findings were divided into four groups according to the worst individual result. Grade A means that the knee is normal; grade B stands for a nearly normal knee, grade C for an abnormal knee and grade D for a severely abnormal knee. Compared to the preoperative value, there was a clear left shift of the bars during the clinical follow-up period (see Fig. 5). This indicates clinical improvement of the knee after the MACT.

During the arthroscopies, one patient in the fourth postoperative month showed detachment of the transplant in terms of a transplant failure. Arthroscopy in another patient in the seventh postoperative month showed a softer transplant region, but already satisfactory integration into the surrounding tissue at the edges of the defect. As a clinical impression from probing the hardness of the regenerated cartilage appeared to increase with postoperative duration. Arthroscopies of the other four patients after 12, 19, 24 and 27 months with defects of the medial condyle in three cases and multiple lesions in one case showed tissue that corresponds to the genuine cartilage, as well as good integration into the adjacent areas. However, the consistency of the surrounding healthy hyaline cartilage was never achieved. Hypertrophy, calcification or ossification of the transplant was not observed in any case.

Using the ICRS Visual Histological Assessment Scale score, histological examination of four biopsies at least 12 months and later after implantation showed a smooth, continuous surface of the regenerative tissue in three patients; in one, the tissue appeared discontinuous with irregularities. In three biopsy specimens, the matrix itself proved to be fibrocartilaginous and in one to be fibrous connective tissue. One histology sample showed a mixed arrangement of chondrones and clusters; in another, there were not only clusters but also unorganised cells, positioned separately. On the other hand, two preparations exhibited completely unorganised cells separated from another. Predominantly living cells were found in all four histology samples. There was increased remodelling of subchondral bony tissue in all four preparations. The zone of mineralised cartilage turned out to be abnormal, or rather, in abnormal position in all four biopsy specimens. For summary, the four histology samples examined showed no hyaline cartilage; in only one case were isogenic cell groups, surrounded by interterritorial matrix was partly visible in separate chondrones (Fig. 6). There seemed to be no correlation with the clinical outcomes in the four cases; unfortunately, a more

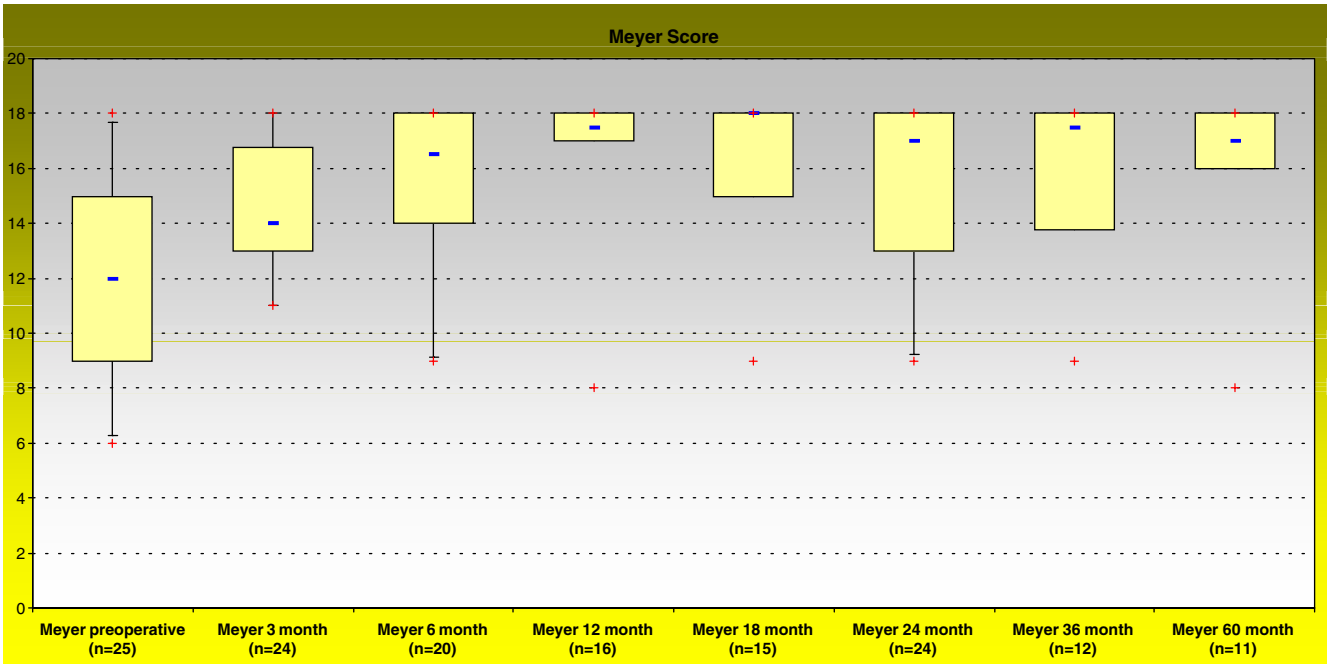

Fig. 1. Box and whisker plot of the Meyer score.

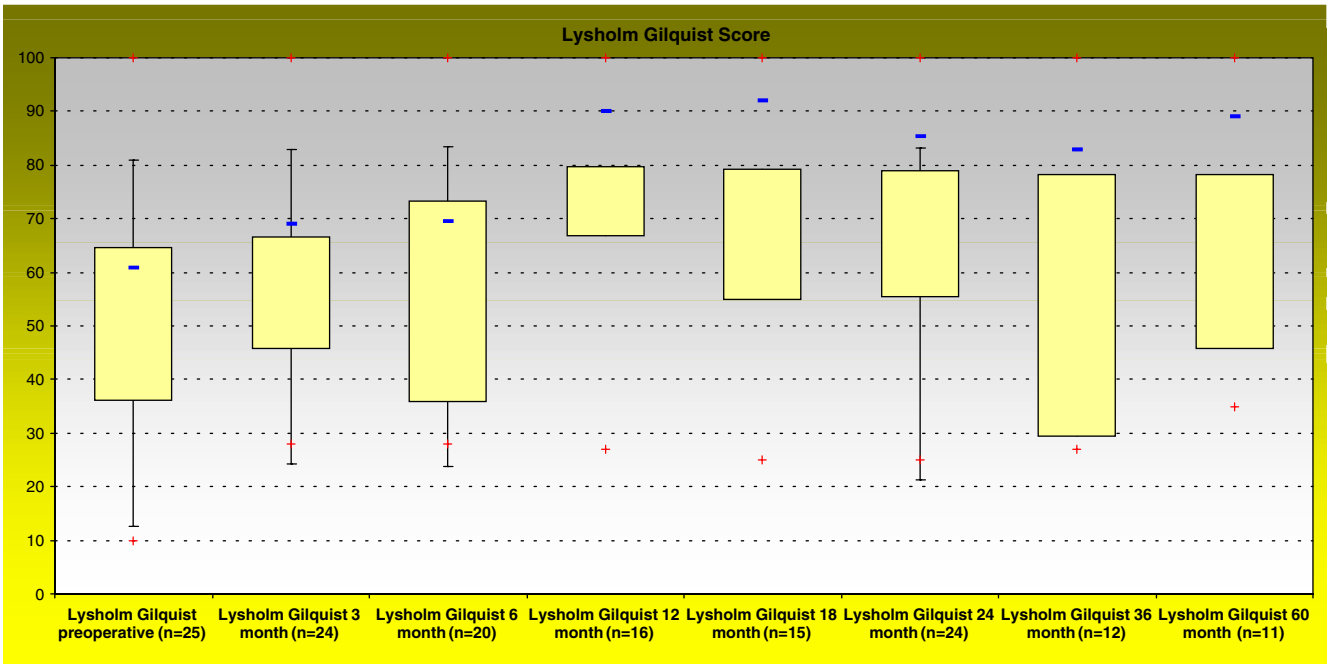

Fig. 2. Box and whisker plot of the Lysholm–Gilquist score.

precise statistical analysis would not be valid with such a small number of cases.

4. Discussion

This is the first uncontrolled clinical study presenting mid-term results from matrix-associated autologous chondrocyte transplantation (MACT) of up to 60 months; thus, the required 24 months to obtain the final regenerate quality was fulfilled [15–17].

Patient satisfaction was found somewhat less after 5 years compared to other publications. Authors reporting results after ACI claimed patient satisfaction of up to 95% after 2 years [18].

Mid-term, all ACI studies showed significant improvement in each of the often different scoring methods employed [19–24]. Various authors of studies of osteo-

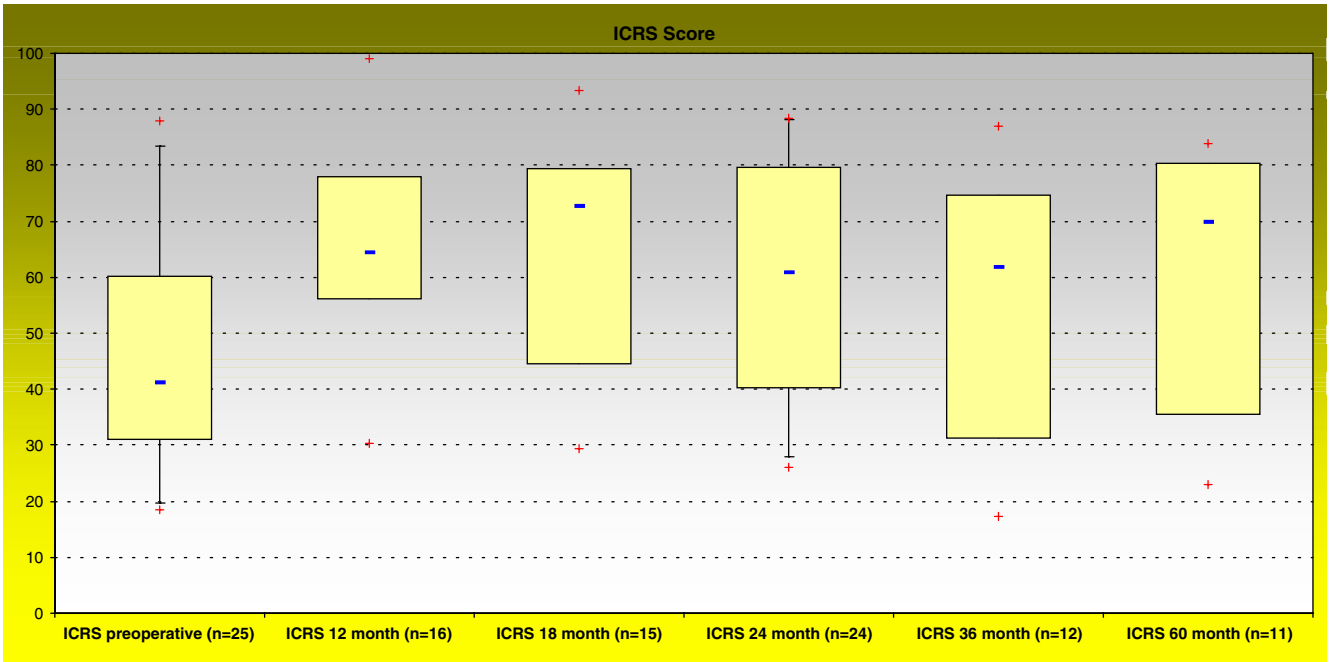

Fig. 3. Box and whisker plot of the ICRS score.

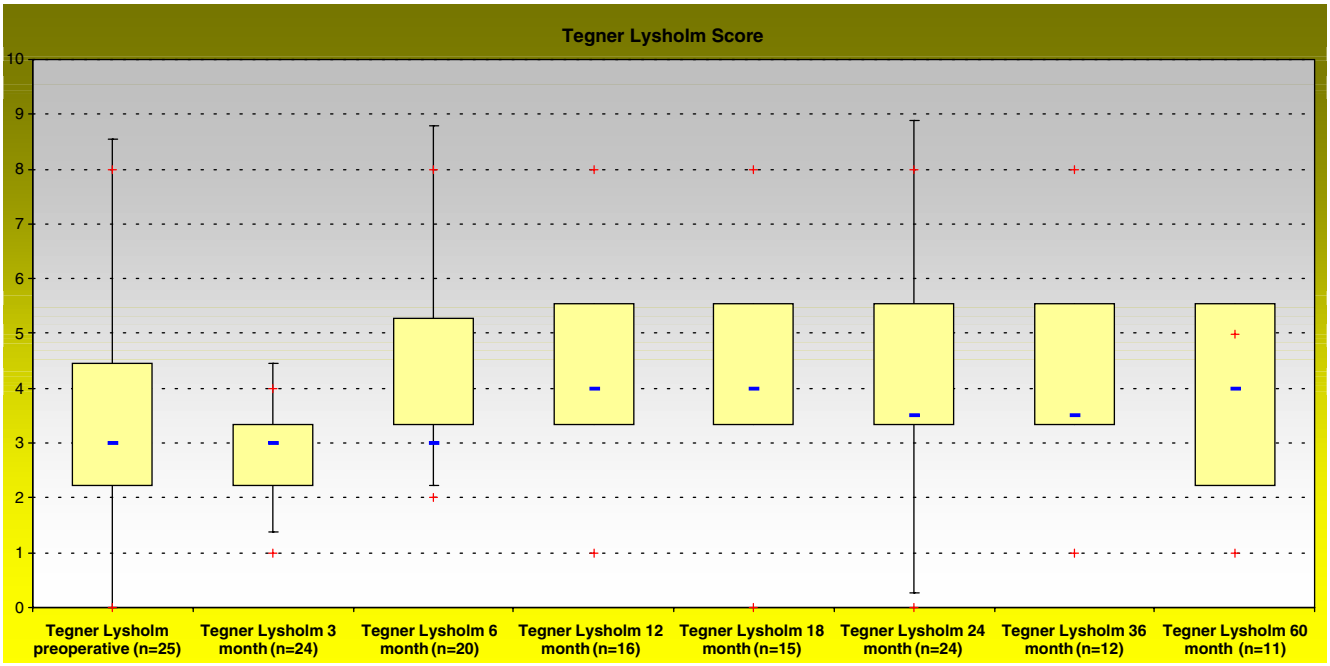

Fig. 4. Box and whisker plot of the Tegner–Lysholm score.

chondral transplantation procedures could report mid-term successes, demonstrated by the large increases in the scores [5,25–28]. One study of perichondrium transplantation conducted by Bruns and Behrens showed predominantly positive mid-term results also for this procedure [29]. Bone marrow stimulation techniques in a comparative study by Knutsen produced better results than ACI [30]. Fu et al. stated poorer results for debridement compared to ACI after 3 years [31]. Debridement and lavage only could not substantiate good mid-term or long-term results in any comparative study.

Unfortunately, no other MACT studies with mid-term results have been published to date.

Unlike described in the literature, we could not show a correlation between clinical results and patient age, defect size, defect localisation and number of previous operations

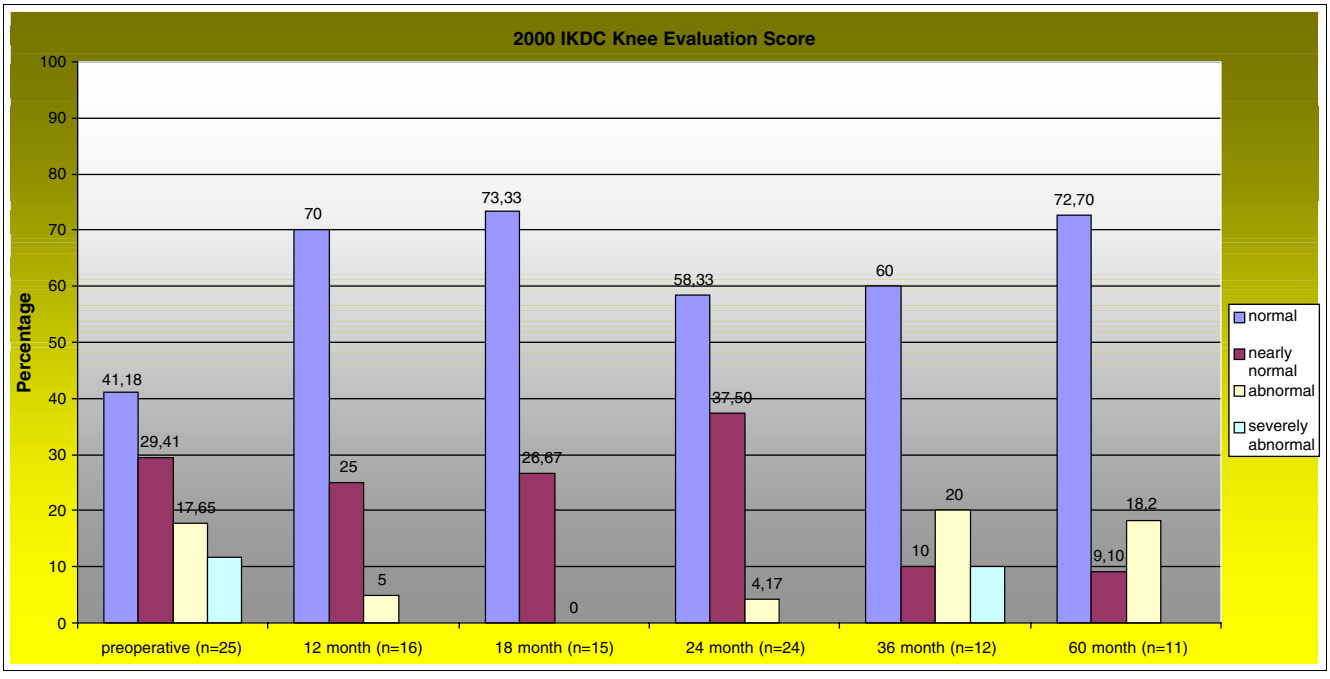

Fig. 5. Clinical evaluation of the knee.

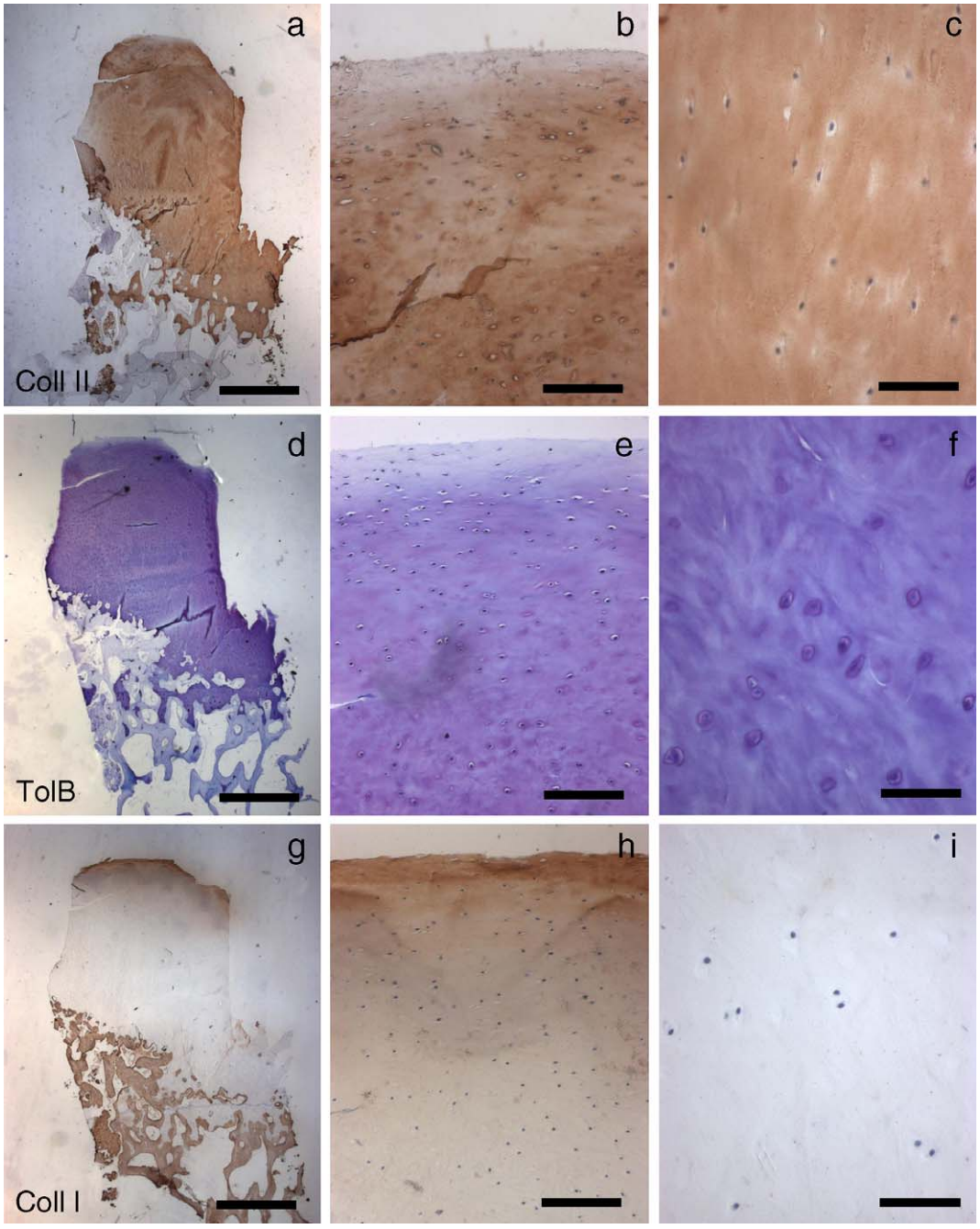

Fig. 6. Histological evaluation of a biopsy 2 years after treatment using toluidine blue staining (TolB, d–f) and immunohistochemical staining of collagen types II and I [Coll II (a–c) and Coll I (g–i)]. The left column shows overviews including bone tissue facing down (bar=1.1 mm), the middle column shows the surface area with stronger Coll I and less cartilage-specific staining at the top (bar=140 μm), and the right column shows tissue in deeper zones where Coll I staining is almost missing (bar=70 μm).

at the time of operation. This could be due to the small number of patients in the different groups possibly. Defect localization as being a decisive criterion for successful results was represented in several publications about ACI [23,29,32,33]. Minas determined that previous operations, such as a realignment osteotomy, limit the indication for ACI [33]. Henderson and La recently presented that subchondral bone overgrowth as one criteria of larger defect areas showed no significant difference in radiological and clinical follow-up compared to the control group [34]. On the other hand, success of mosaicplasty or OATS was shown to be dependent on defect size [15]. In the transplantation of periosteum and perichondrium, O'Driscoll et al. determined a strong correlation of outcome to patient age [35]. Therefore, it may be generalized, the indication for operation may be constructively applied to the results of this study within the boundaries described by the AG-ACI and Tissue Engineering [36] without further limitation.

Our arthroscopic evaluation of the defect areas showed increasing hardness of the regenerated cartilage with time. However, the consistency of the surrounding hyaline cartilage as a clinical impression from probing could not be achieved. This also correlates with the results described in the literature, not only for the MACT [37,38] but also for ACI [22,23,39].

Several authors described good regeneration of the joint surface with the osteochondral procedure [5,24,27] and Homminga et al. described good regeneration at the outset, also for periosteum and perichondrium transplantation [40]. Transplant hypertrophy described in ACI studies [19,22] could not be found in our investigation with MACT, which supports the results by Haddo et al. [7]. No evidence of ossification could be seen, which, although consistent with the results of ACI follow-ups [22], is known to be a serious problem in the case of transplantation of periosteum or perichondrium [35].

Histological examinations of the biopsies taken from four patients 1 year or longer after the intervention showed predominantly living cells in all specimen preparations. Those cells were to be found separate and in an unorganised manner in 50% of the specimen, surrounded by a fibrocartilaginous matrix in 75% and even by a fibrous matrix in 25% of the cases.

This deviates from the previously described results described by other authors. Histological examination of core biopsies taken from 20 patients stated eight to be hyaline, five hyaline-like, four to be fibrocartilage and another three mixed fibrohyaline cartilage [23]. Brittberg et al. found hyaline-like cartilage in 11 of 15 specimen preparations (73.3%) [4]. There was at least partly hyaline-like cartilage in 39% of the cases described by Knutsen et al., as opposed to the 43% of the 32 biopsies examined showing predominantly fibrocartilaginous connective tissue [4].

We could not detect a correlation between histological findings and clinical outcome based on the scores. However, the significance and consequently the validity of our findings are limited by the numbers of histologies taken and present rather a trend. To conclude this study of 25 patients, MACT confirmed objective and subjective clinical improvement over a period of up to 5 years after operation. MACT proved suitable to treat cartilage defects in the context of this study.

The MACT/ACI represents a very cost-intensive procedure and to date it is covered by private insurance in individual cases only. Therefore, we have not performed any MACT since 2001. This economic aspect shows that future therapeutic approaches will have to undergo cost/benefit evaluations before being brought into the market. Since 2003, we use the porcine collagen I/III-matrix (Chondro-Gide®) in combination with microfracture to use bone marrow derived mesenchymal stem cells and accommodate chondrogenic differentiation of these (autologous matrix induces chondrogenesis, AMIC) [41].

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