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Autologous implantation of chondrocytes on a solid collagen scaffold: clinical and histological outcomes after two years of follow-up

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Abstract From our overall experience in 56 patients, we here report the treatment with matrix-induced autologous chondrocyte implantation (MACI) of 35 patients suffering from knee cartilage defects measuring about 4 cm^2, and followed for a minimum of 6 months. A total of 36 knees were treated (1 patient on both knees) and clinically observed for 22 months (in some cases for over 39 months), in accordance with a standardised protocol. Subjective parameters (pain, well-being, functional state, symptoms during specific activity) and objective outcomes (IKDC score and Lysholm and Tegner scores) were recorded. One or 2 years after implantation, some biopsies of the regenerated cartilage were histologically evaluated. The subjective parameters (VAS pain score, 2.80±1.49, $p<0.0001$; change vs. basal score, 2.72) promptly normalized after 1 month, as did the objective ones (IKDC score after 6 months, 1.53±0.59, $p<0.0001$; change vs. basal score, 1.78). Similar results were observed after the treatment of a femoropatellar kissing lesion. The three cartilage biopsies that were analysed from different patients showed a tissue positivity to immunohistochemical markers of hyaline cartilage. The conclusions of this preliminary analysis are that the clinical outcome and histological evaluation suggest that MACI is able to relieve pain and restore the functionality of the knee, and that the treatment appears capable of regenerating hyaline cartilage.

Key words Autologous chondrocyte implantation • Clinical follow-up • Histological evaluation • IKDC score • Matrix-induced autologous chondrocyte implantation (MACI)

Introduction

Articular cartilage defects in weight-bearing joints, due to trauma or other conditions, often fail to heal on their own and may be associated with pain, loss of function, disability, and long-term complications such as osteoarthritis. Chondral lesions may naturally occur in osteochondritis dissecans (OCD). Improved diagnostic procedures like magnetic resonance imaging (MRI) and arthroscopy have demonstrated that chondral lesions are quite frequent, even in persons without symptoms: at least 5% of cases of traumatic haemarthrosis [1] are associated with chondral defects, confirmed in 63% of arthroscopies [2]. Some traditional surgical procedures, such as endoarticular washing, shaving and debridement, provide relief from pain, locking and swelling, while there are others, such as Pridie's subchondral perforation and Steadman's microfracture, which can generate cartilage but only of the fibrous type, having biomechanical properties that are inferior to the original hyaline cartilage. Even restoration with osteochondral grafts has its limitations, which often depend on the size and depth of the defects, the dead space between circular grafts and integration of the donor and recipient hyaline cartilage [3].

With the development of autologous chondrocyte implantation (ACI), research by Smith [4], Aston and Bentley [5] and Brittberg et al. [6] has led to a new biotechnological treatment of cartilage defects. The clinical outcome, the histological evidence and, more recently, the results of randomised controlled studies have demonstrated better recovery of the cartilage defects in patients treated with ACI-based techniques, rather than by mosaicplasty [7] and microfracture [8]. Over the last few years, great strides have been made in research on ACI applications and ACI-based surgery, and now a second generation of autologous chondrocyte implantation called MACI (matrix-induced autologous chondrocyte implantation; Verigen) has become available. This technique is based upon the growth of chondrocytes directly on a collagen I-III matrix, and the cells can perfectly differentiate in the matrix three-dimensional environment [7, 9]. At a second surgical procedure, the chondrocyte-loaded matrix's fixed to the defect with fibrin glue, so much so that it is no longer necessary to saturate the periosteal flap to the cartilage, as was the case in the original technique. With the MACI procedure, we have treated patients suffering from chondral lesions, which were sometimes associated with other pathological conditions of the joint. We followed their clinical course by using a standard evaluation protocol. This report summarizes the preliminary results obtained from the treatment of 36 knees that had a follow-up of at least of 6 months.

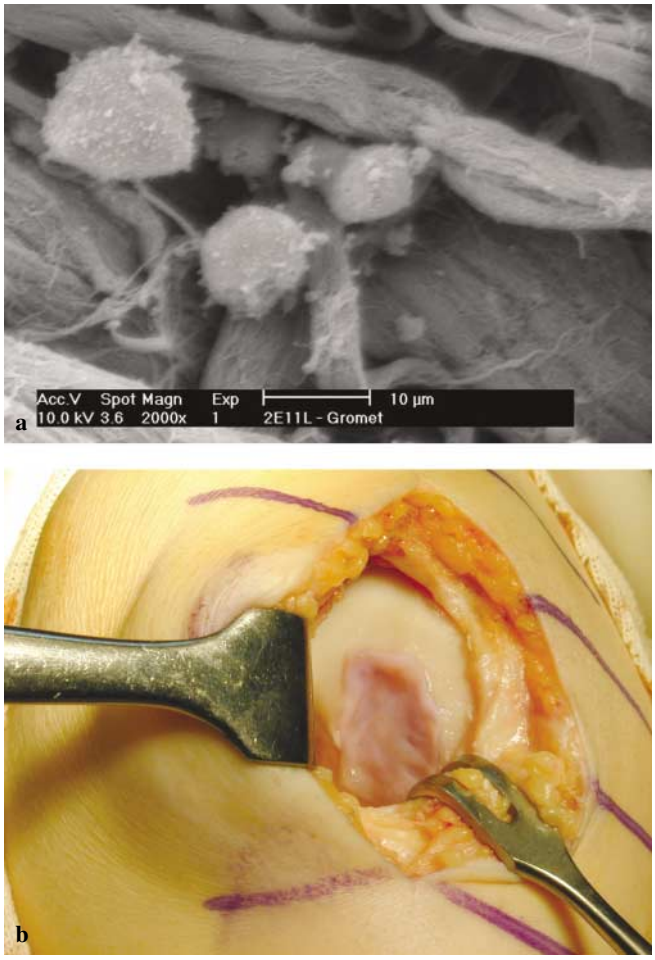

Fig. 1a, b *Matrix-induced autologous chondrocyte implantation (MACI) technique.* **a** Electron microscope image (2000x) shows chondrocytes embedded in the collagen I-III matrix and secreted collagen II fibers. **b** MACI on the chondral lesion after application of fibrin glue

Materials and methods

In accordance with International Cartilage Repair Society (ICRS) guidelines, 56 consecutive patients with chondral knee defects were selected from September 2000 and, after informed consent was obtained, we treated the cartilage defects with MACI. Nineteen of 56 patients had less than 6 months of follow-up and their data are not reported here. Two patients did not adhere to the scheduled visits and so were considered as drop-outs. Thirty-five of 56 patients (23 male, 12 female) adhered to the scheduled visits and consequently were included in this analysis: all the data reported here refer to these 35 patients, aged 33.1±7.9 years (range, 18–51 years). One of them who had bilateral osteochondritis dissecans had both his knees treated. The mean follow-up of these patients was 22 months (range, 6–39 months). Patients were treated according to the ethical standards outlined in the Helsinki Declaration.

Surgery was performed in two stages. Initially, an arthroscopy was carried out and the lesions were evaluated if they were suitable for MACI. At the arthroscopic examination, a slice of cartilage (roughly 200 mg), extending down to the subchondral bone plate, was harvested from a non-weight-bearing area. The biopsy was placed in a nutrient medium and shipped to Verigen Laboratories (Leverkusen, Germany and Kastrupp, Denmark) together with 100 ml of the patient's venous blood. Chondrocytes were enzymatically separated from their matrix, the cells were cultured, loaded on the collagen I-III matrix (Fig. 1a) and then expanded over 3–4 weeks, until a density of 1×10^6 cell/cm^2 was obtained. The seeded membrane (MACI) was sent back to the hospital for the second (arthrotomic) surgical stage. The defect was carefully cleansed until healthy cartilage was reached, avoiding perforation of subchondral bone. Haemostasis, if necessary, was obtained with adrenalin. The final defect was measured and MACI was cut to size and fixed over the defect (Fig. 1b) with fibrin glue (Tissucol; Baxter). The stability of MACI was tested with some flexo-extension movements.

In knees with a joint-related pathology, our surgical approach was first to correct the existing pathology during arthroscopy and then, after a period of rehabilitation, to correct the cartilage lesions. Such a surgical strategy has now been modified, and we correct all related pathological conditions during the arthrotomic step, in order that patients are subjected to just one rehabilitation period.

All of the patients followed the same rehabilitation program, but were differentiated if the lesions had femoral-tibial rather than a femoral-patellae localization. For femoral-patellae lesions, full loading was permitted with the use of an extension-tutor for

4 weeks, with a movement range of 0°–20° for 10 days during walking only, with further increments of 20°/week. On the other hand, for the femoral-tibial lesions only a partial weight-bearing, using crutches, was indicated for 4–6 weeks, and progressive increments of loading until full-bearing in 8–12 weeks. Mobility was immediately permitted over a range of 0°–40°, with further increments of 30°/week. Mobilisation was encouraged and was combined with physiotherapy and quadriceps contraction exercises. At this point, we encouraged other activities such as swimming, and gentle cycling; impact loading and twisting strains of the knee were avoided. Soft sport activities were permitted after 8–10 months, delaying high impact sport activities to 1 year after MACI.

Clinical outcomes

Clinical data were evaluated according to the ICRS guidelines, following standard protocols for parameters and time. We took into consideration the subjective, objective and, whenever possible, histological parameters:

1. *Subjective parameters* included pain intensity score, well-being, functional state, and symptoms during specific activities. These were evaluated before surgery (basal) and at different postoperative periods. Pain was scored on a visual analog scale (VAS) [10] ranging from 0 (no pain) to 10 (maximum pain). Well-being was scored on a scale from 1 (good) to 3 (bad). Pain and well-being were evaluated at baseline and then after 1, 3, 6, 12 and 24 months. Functional state was scored from 1 to 4 (1, no limitation; 2, a few limitations; 3, some limitations; 4, total limitation). Symptoms associated with activity (pain at beginning, swelling, blocks and pain during activity) were evaluated with a scale from 1 to 4 (1, never; 2, almost never; 3, sometimes 4, always) at baseline and then after 3, 6, 12 and 24 months.
2. The *objective parameters* were evaluated according to the ICRS/IKDC surgeon form [11] (1, normal; 2, nearly normal; 3, abnormal; 4, severely abnormal) and the Lysholm scores [12] at basal level and after 6 months, while the Tegner score [13] was determine at baseline and after 12 and 24 months.
3. Whenever possible, the newly formed tissue was evaluated after an arthroscopic second look and at biopsy. At least 12 months after implantation, biopsies were obtained from 3 patients after informed consent. The regenerated tissue was taken according to the ICRS standardised procedure. The specimens were stained with safranin-O and alcian-blue, polyclonal anti-S-100 protein antibody and monoclonal anti-chondroitin sulphate and anti-collagen types I and II antibodies. Furthermore, the number of cells per area was quantitatively assessed by a histomorphometric method (Quantimet 500+). The specimens were evaluated using the ICRS visual histological assessment scale [14].

Statistical analysis

All the parameters, except VAS, were analysed as median, interquartile range, and patients' number for each class. Differences were statistically evaluated with Wilcoxon's test applied to uncorrected data. For the VAS, we calculated the mean and standard deviation for each time-point and the differences were analysed with Student's *t* test. The basal levels of all parameters were statistically analysed versus time to closest possible level recorded (subjective parameters: baseline vs. 3 months; VAS: baseline vs. 1 month and 3 months; objective parameters: baseline vs. 6 months).

Results

The clinical outcome of matrix-induced autologous chondrocyte implantation (MACI) was evaluated in 35 patients (36 knees) at a mean follow-up period of 22 months (range, 6–39 months). We had treated 30 single and 6 multiple chondral defects (19 in the left knee and 17 in the right knee; among the latter was a femoropatellar kissing lesion), with a mean size of 4 cm^2 (but sometimes greater than 12 cm^2). The aetiology, anatomical distribution and concomitant pathologies are shown in Table 1. More than 50% of the 36 knees had post-traumatic defects, about 17% had osteochondritis dissecans while almost 30% had lesions of an undefined aetiology which were often associated with concomitant joint-related conditions. Twenty six of the lesions were localized on the femoral condyles

Table 1 Characteristics of 36 knees with chondral defects treated with matrix-induced autologous chondrocyte implantation (MACI)

	n (%)
Aetiology of defect	
Trauma	20 (55.6)
Osteochondritis dissecans	6 (16.6)
Other	10 (27.8)
Anatomical sites[a]	
Medial femoral condyle	19 (44.2)
Lateral femoral condyle	7 (16.3)
Trochlea	6 (13.9)
Patella	9 (20.9)
Medial tibial plateau	2 (4.7)
Related pathologies	
Patellar instability	4
Patellar dislocation	1
ACL lesion	7
ACL lesion and tibia vara	1
LM lesion	3
LM and MM and tibiavara	1
Total	17 (47.2)

[a]More than 1 anatomical site was involved in some patient's knees
ACL, anterior cruciate ligament; *LM*, lateral meniscus; *MM*, medial meniscus

Table 2 Subjective evaluation of clinical outcome in 35 patients (36 knees) treated by MACI

	Follow up period, months					
	Baseline	1	3	6	12	24
Patients assessed, n	35	35	35	34	29	13
Knees assessed, n	36	36	36	35	30	14
Pain score (VAS)[a]	5.52 (1.53)	2.80 (1.49)*	0.68 (0.72)	1.00 (1.52)	0.44 (0.79)	0.20 (0.40)
Well-being score[b]	2.21 (0.43)	1.92 (0.26)	1.30 (0.43)‡	1.32 (0.40)	1.09 (0.30)	1.00 (0.22)
Functional state score[b]	2.56 (0.50)	NP	1.25 (0.40)§	1.12 (0.30)	1.06 (0.26)	1.00 (0.19)
Symptoms in activity						
Pain at beginning	3.04 (0.66)	NP	1.66 (0.42)	1.64 (0.63)	1.47 (0.46)	1.15 (0.31)
Swelling	2.97 (0.75)	NP	1.35 (0.40)	1.13 (0.30)	1.04 (0.23)	1.00 (0.22)
Blocks	2.50 (0.84)	NP	1.03 (0.23)	1.05 (0.49)	1.00 (0.23)	1.00 (0.23)
Pain during activity	3.21 (0.55)	NP	1.62 (0.53)	1.17 (0.30)	1.48 (0.51)	1.16 (0.33)

* Student's test for correlated data, t=11.37; p=1.4x10^{-12}; ‡ Wilcoxon's test for not correlated parameters, z=4.007; p=2.9x10^{-5}; § Wilcoxon's test for not correlated parameters z score z=4.573; p=4.1x10^{-6}; [b] Values are median (interquartile range); *NP*, not performed; [a] Values are mean (SD)

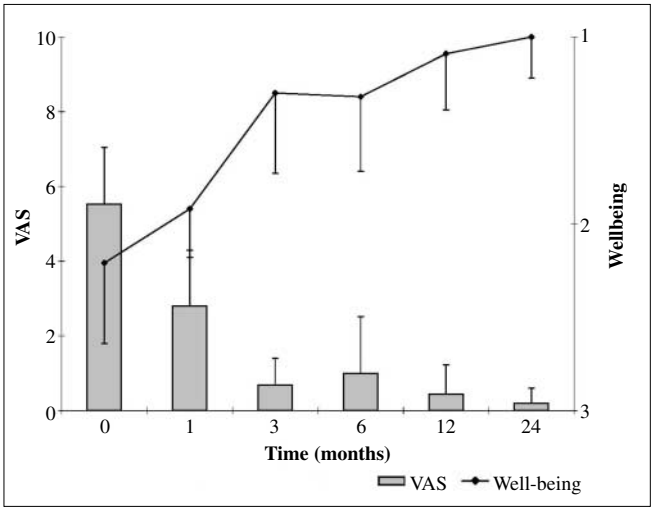

Fig. 2 Subjective evaluations of pain and well-being, at baseline and during follow-up. Pain was scored on a visual analog scale (VAS) in which 0 = no pain and 10 = maximum pain; values are mean and standard deviation. Well-being scores (1 = good; 3 = bad) are reported as median and interquartile range

(19 on the medial condyle, 7 on the lateral condyle), 6 on the trochlea, 9 on the patellae, and 2 on the tibial plateau. All the patients had an uncomplicated post-surgical course without any adverse events due to MACI and were evaluated starting 15 days after implantation up to over 3 years.

Subjective parameters were evaluated at regular intervals up to 24 months (Table 2).

The VAS pain score showed significant improvement 1 month after surgery vs. baseline (t=11.34; p<0.0001), and this was confirmed at the other time-points (Fig. 2). The well-being score showed significant improvement vs. baseline at 3 months (z=4.009; p<0.0001, Fig. 2). The functional state, initially very compromised in almost all the knees, showed significant improvement 3 months after surgery in more than 65% of the treated joints (3 months vs. baseline: z=4.573; p<0.0001, Fig. 3). All the symptoms during specific activities confirmed the findings described for the other parameters. After 3 months, improvements were almost complete and stable over time.

On the IKDC scale (surgeon's part), 97% of baseline scores were at least abnormal. Six months after MACI, 60% of scores were at least nearly normal (Fig. 4) and in this way significantly improved (6 months vs. baseline: z=4.167; p<0.0001). The IKDC forms were also evaluated in the sub-classes: *effusion-compartments findings*, *passive motion deficit*, *ligament examinations* and *functional test*. Thirty-nine percent of joints had "abnormal" baseline scores for *effusions-compartment findings*, while after 6, 12 and 24 months all the joints were normal or nearly normal. Six months after MACI, all the joints showed no *passive motion deficit* (score 1 for 94.28% of joints). The *functional test*, strongly abnormal at baseline *(scores* 3 and 4 for more than 85% of joints), was normal or near normal in more than 85% at 6 months after MACI, as well as after 12 and 24 months.

The evaluation according to the Lysholm assessing scale (Fig. 5, Table 3) showed a near-complete recovery at 6 months after MACI, with a significantly improved mean score from baseline (6 months vs. baseline score: z=3.621; p<0.0001). Evaluation according to the Tegner assessing

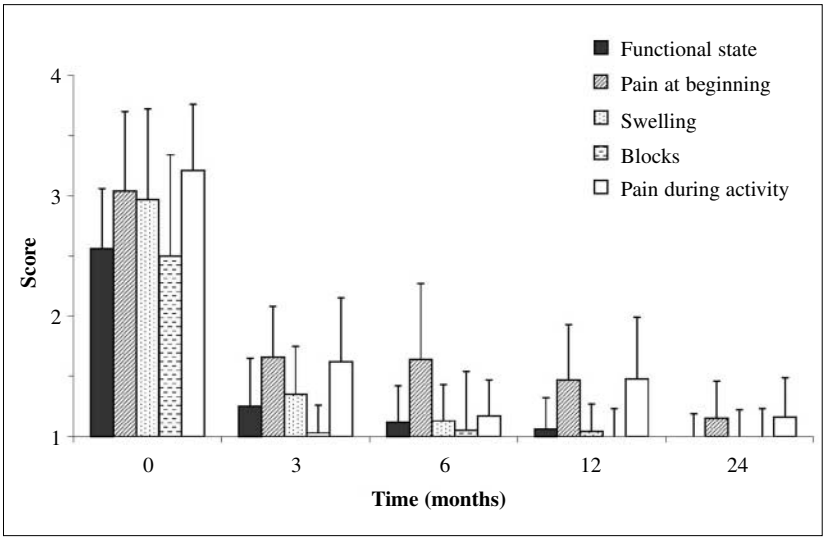

Fig. 3 Subjective evaluations of functional state and symptoms associated with activity (pain at beginning, swelling, blocks and pain during activity), at baseline and during follow-up. Data are reported as median and interquartile range

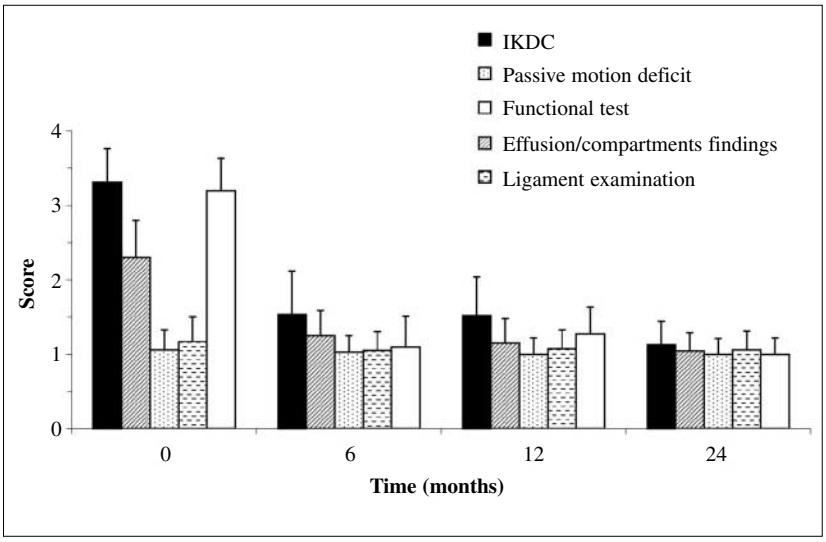

Fig. 4 Objective evaluation of outcome according to IKDC scores (total IKDC, passive motion deficit, functional test, ligament examination, effusion and compartments findings), at baseline and during follow-up. Data are reported as median and interquartile range

scale (Fig. 5, Table 3) showed recovery after 12 months and stability at 24 months, but our data are still preliminary.

Our series included one patient who presented with a right knee femoropatellar "kissing lesion", consisting of a 2.5x2.5 cm Outerbridge's degree IV trochlear defect opposing a 2.0x2.0 cm degree III patellar lesion. The patient, an athletic 31-year-old man, suffered a traumatic patellar dislocation 8 years before MACI implantation. Since then, he complained of progressive pain and increasingly frequent articular blocks, which ultimately prevented him from playing not only his usual sporting activities (football and volley ball), but also from walking without pain, even for short distances. Symptoms and functional tests were poor at inclusion, with severe pain at rest (VAS score, 9), significant functional limitation (<40% performance of the affected knee compared to the

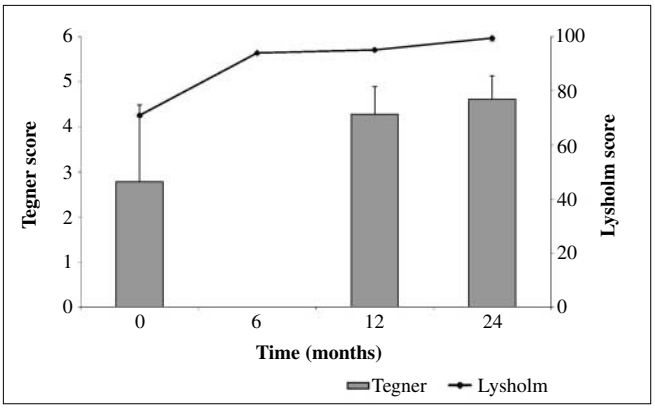

Fig. 5 Objective evaluation of clinical outcome on the Lysholm and Tegner scales, at baseline and during follow-up. Data are reported as median and interquartile range

Table 3 Objective evaluation of clinical outcome for 36 knees (35 patients) treated by MACI. Values are median (interquartile range)

	Follow-up period, months			
	Baseline	6	12	24
Knees assessed, n	36	34	29	13
IKDC score	3.31 (0.45)	1.53 (0.59)*	1.52 (0.52)	1.13 (0.31)
Effusion/compartments findings	2.30 (0.50)	1.25 (0.34)	1.15 (0.33)	1.04 (0.25)
Passive motion deficit	1.06 (0.27)	1.03 (0.22)	1.00 (0.22)	1.00 (0.21)
Ligament examinations	1.17 (0.33)	1.05 (0.25)	1.07 (0.26)	1.06 (0.25)
Functional test	3.20 (0.43)	1.10 (0.41)	1.27 (0.36)	1.00 (0.22)
Lysholm score	70.94 (0.66)	94.03 (0.55)‡	95.17 (0.51)	99.54 (0.97)
Tegner score	2.78 (1.71)	NP	4.28 (0.61)	4.61 (0.52)

NP, not performance

*Wilcoxon's test for not correlated parameters z score z=4.167; p=1.5x10^{-5}; ‡Wilcoxon's test for not correlated parameters z score z=3.621; p=0.0001

opposite joint), frequent articular blocks, and painful squatting. We treated the patient by combining the second (arthrotomic) MACI surgical step with patellar stabilization through a tibial tuberosity transfer according to Elmslie-Trillat. Objective and subjective findings improved promptly after surgery. Pain, crepiti and blocks showed improvement as early as 1 month, and were normal 3 months after MACI. After 1 year, an MRI assessment of the affected knee showed normal or nearly normal cartilage surface both at the trochlea and the patella. Two years after surgery, the patient still had a painless and fully functional knee; he resumed all his previous sporting activities, including frequent downhill skiing.

None of the patients who were evaluated by arthroscopic second look underwent histological examination due to clinical or functional irregularities. The morphological criteria observed for the three biopsies performed are reported in Table 4. The biopsies taken two years after implantation showed a smooth and continuous surface (I: 3), hyaline matrix (II: 3), columnar cell distribution (III: 3), predominantly viable cells (IV: 3), normal subchondral bone (V: 3) and normal cartilage mineralization (VI: 3). In the biopsy taken just 1 year after implantation, the regenerated cartilage appeared to be in proper evolution towards the formation of hyaline-like cartilage, as shown by a still irregular surface (I: 0) and a mixed clusters/columnar cell distribution (III: 2). All the sections were clearly stained with safranin O and alcian-blue, and so were positive for the presence of proteoglycans (Fig. 6a), strongly reactive against S-100 protein and positive for chondroitin-S and type-II collagen, and hence positive for hyaline typical cellular and extracellular markers (Fig. 6b).

Table 4 Histological evaluation: morphological criteria according to ICRS guidelines [14] are reported for three biopsies obtained one year (patient 1) and two years (patients 2 and 3) after surgery

		Patient 1		Patient 2		Patient 3	
Surface	I	Discontinuities, irregularities	0	Smooth, continuous	3	Smooth, continuous	3
Matrix	II	Hyaline	3	Hyaline	3	Hyaline	3
Cell distribution	III	Mixed columnar/clusters	2	Columnar	3	Columnar	3
Cell population viability	IV	Predominately viable	3	Predominately viable	3	Predominately viable	3
Subchondral bone	V	Normal	3	Normal	3	Normal	3
Mineralization	VI	Normal	3	Normal	3	Normal	3
Follow-up biopsy		1 year		2 years		2 years	

Fig. 6a, b *Histological analysis*. **a** Extracellular matrix stained with alcian blue (200x, *left panel*) or safranin O (50x, *right panel*). **b** Immunochemical evaluation of chondrocytes by anti-S100 protein (200x, *left panel*) and anti-type II collagen (100x, *right panel*) staining

Discussion

Autologous chondrocyte implantation today is a consolidated surgical procedure even if the original procedure set up by Peterson et al. [16] presented some difficulties and contraindications in connection with both the sutured periosteum flap and the localizations. Among the ACI-based techniques which have been developed and used over the last four years, MACI represents a valid surgical procedure even if there are not many scientific publications available. We reported our clinical data obtained from 36 treated joints that had been followed by us for several years. Our data confirmed the excellence of this treatment procedure: all patients showed a significant improvement in the subjective and objective parameters and, in our opinion, MACI represents an exciting procedure. The remarkable aspect of this therapy is that not only does it relieve pain and disability by regenerating cartilage, but of greater importance it can regenerate the proper articular hyaline cartilage, thus preventing the progression of cartilage damage to early onset osteoarthritis. The tough and ideal articular cartilage is a type II collagen sponge, where cells and water are locked-in by the proteoglycan-based matrix where cell movement and replication are restricted as soon as cartilage differentiation is accomplished. Microfracture and drilling can be used when surface damage is present and when the subchondral bone is exposed, but the repairing process produces fibrocartilage containing type I collagen, with resistance and characteristics that have been described as neither appropriate nor long-lasting [17]. Patients treated with such therapies frequently return to their surgeons complaining of pain and joint inadequacy.

An alternative treatment for cartilage defects is mosaicplasty. This therapy is an autograft transplantation that overcomes problems connected with the different types of cartilage regeneration in relation to the therapies described previously. On the contrary, however, it is obviously difficult to treat defects which are larger than 1 cm^2. This could result in incomplete filling of defects and, independently of this, difficulties can arise from the fact that the autografts are transplanted to areas where the stresses and cartilage thickness are different from those in their native site [3]. The best result that can be achieved is a mixture of hyaline and fibrocartilage which is difficult to think of as long-lasting.

For these reasons, in addition to the excellent results reported in the literature, it can be affirmed that the treatment of cartilage defects with biotechnological techniques such as MACI, rather than with the conventional therapies, is almost routine today; the success of these new techniques is attributed to both the remission of pain and adequate filling of defects with a hyaline cartilage. Patients treated with MACI have shown significant therapeutic success in the remission of pain as early as 1 month after surgery, further confirmed by a recovery of the general well-being and functional state. All the improved subjective parameters remained stable during the entire follow-up period.

Likewise, the results of the analysis of the objective parameters were maintained over time. As early as 6 months, the IKDC and Lysholm scores confirmed functional recovery in the vast majority of the treated joints.

Although the more conservative therapies like mosaicplasty and microfractures can lessen pain and functional disability, their shortcomings are the limitation of the lesion area that can be treated and their short duration of curability. The real hope of treating cartilage defects with ACI-based therapies such as MACI lies in the fact that these treatments are able to generate new cartilage which is similar to the original one, as well as in a high expectation that chondral defects can be finally repaired and resolved. Our histological data reported here, although obtained from 3 patients only, have confirmed that the regenerated cartilage is a typical hyaline cartilage, with a valid tide-mark with subchondral bone, well-organized cell-clusters and strong reactivity for hyaline markers. Even if our data are from only a few biopsies, it seems that one year after surgery the regenerated cartilage is still in a remodelling phase, reaching complete hyaline differentiation by two years after autologous implantation. Based on such evidence, and in accordance with the ICRS recommendations, we are now considering a second-look assessment of MACI-treated patients not earlier than 18–24 months after surgery, so as to be able evaluate and confirm the results attained so far. Among the other advantages, MACI also seems to overcome a great limitation still present with first-generation ACI techniques. Our experience, although limited, suggests that MACI can be effectively adopted for the treatment of "kissing lesions", at least in the femoropatellar location. Such conditions, although rare but severely limiting the patient's knee performance if present, could not be treated with Peterson's chondrocytes liquid suspension systems since the concomitant presence of a high reactive tissue such as periosteum, and the suture-suture friction, contraindicated its use, and besides the overall outcome of this procedure has been poor.

In our experience, ACI-based treatments could indeed be the real future possibility to solve the problem linked with different tissue regeneration: experiences collected for at least 9 years [15] and our preliminary data seem to indicate that a correct therapeutic approach has been embarked upon, but we would need more time and data to confirm the promising results. Likewise, the biotechnological applications to orthopaedics are now producing tools that are ever more user-friendly, and with shorter surgical intervention time, all leading to greater patient safety. Our early data discussed in this paper confirm that MACI could be a first choice treatment for knee-chondral defects in patients with a sufficiently high life expectancy, and with no compromised subchondral bone.

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