

Regenerative treatment in osteochondral lesions of the talus: autologous chondrocyte implantation versus one-step bone marrow derived cells transplantation

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Abstract

Purpose Osteochondral lesions of the talus (OLT) usually require surgical treatment. Regenerative techniques for hyaline cartilage restoration, like autologous chondrocytes implantation (ACI) or bone marrow derived cells transplantation (BMDCT), should be preferred. The aim of this work is comparing two clusters with OLT, treated with ACI or BMDCT. **Methods** Eighty patients were treated with regenerative techniques, 40 with ACI and 40 with BMDCT. The two groups were homogenous regarding age, lesion size and depth, previous surgeries, etiology of the lesion, subchondral bone graft, final follow-up and pre-operative AOFAS score. The two procedures were performed arthroscopically. The scaffold was a hyaluronic acid membrane in all the cases, loaded with previously cultured chondrocytes (ACI) or with bone marrow concentrated cells, harvested in the same surgical session (BMDCT). All the patients were clinically and radiologically evaluated, using MRI Mocart score and T2 mapping sequence.

Results Clinical results were similar in both groups at 48 months. No statistically significant influence was reported after evaluation of all the pre-operative parameters. The rate of return to sport activity showed slightly better results for BMDCT than ACI. MRI Mocart score was similar in both groups. MRI T2 mapping evaluation highlighted a higher presence of hyaline like values in the BMDCT group, and lower incidence of fibrocartilage as well.

Conclusions To date, ACI and BMDCT showed to be effective regenerative techniques for the treatment of OLT. BMDCT could be preferred over ACI for the single step procedure, patients' discomfort and lower costs.

Keywords Ankle · Osteochondral lesions · Regenerative techniques · Bone marrow · Autologous chondrocytes implantation · T2 mapping

Introduction

Osteochondral lesions of the talus (OLT) are defects of the cartilaginous surface and the underlying subchondral bone, mostly traumatic in origin [1]. The poor spontaneous healing potential of chondral tissue may give way to disabling conditions and even degenerative joint diseases [2, 3]. Surgical treatment is the best choice to relieve pain, improve range of motion and prevent the degeneration, relegating conservative approaches to small lesions in non-active patients [2, 3]. The goal of the finest surgical procedure should be the regeneration, restoring worn tissue with high biomechanical quality hyaline cartilage. To date, only osteochondral grafts and regenerative techniques, like autologous chondrocyte implantation (ACI) and bone marrow-derived cell transplantation (BMDCT), have proven effective at this purpose [4–13]. Nevertheless, osteochondral autograft is a technically demanding procedure with many drawbacks, and other techniques may be preferable [4].

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ACI, firstly proposed for knee lesions, is a consolidated and valuable technique for OLT, even at long-term follow-up [4–8]. The chondrocytes are harvested from a non-bearing area of the knee joint, a peri-lesional area or a loose body, then are cultured, expanded and seeded on a scaffold [5]. After three to four weeks, they are implanted at the site of the lesion. The technique was firstly performed open-field; then, thanks to the use of scaffolds, an arthroscopic approach was developed, making the procedure easier and faster and reducing the morbidity and costs [5, 9–12].

The “one step” BMDCT technique is based on the mesenchymal stem cells coming from the aspiration of bone marrow [8, 14]. These cells are capable of differentiation in many lineages, like bone and cartilage, under the stimulation of paracrine factors from the micro-environment [13, 15, 16]. After the aspiration of the stem cells and their “niche” from the iliac crest, the whole bone marrow aspirate is concentrated directly in operating room and then loaded on a scaffold and implanted [5, 8, 13]. The procedure can be easily performed arthroscopically, in a single surgical procedure [5, 8].

ACI is still considered one of the most reliable procedures for OLT, while BMDCT was applied with satisfactory results at four-year follow-up [4, 5, 10, 11, 17]. However, no studies comparing the outcomes of the two techniques in similar lesions are currently available. The purpose of this retrospective investigation was comparing the clinical and radiological results of two clusters of patients who underwent arthroscopic ACI or arthroscopic BMDCT for OLT, at the same follow-up of 48 months.

Methods

Eighty patients with focal, isolated osteochondral lesions of the talar dome were addressed to arthroscopic regenerative procedures: 40 patients underwent ACI and 40 underwent BMDCT. The OLT were all classified as type II or IIA ($>1.5 \text{ cm}^2$ in area and $<$ or $>5 \text{ mm}$ deep, respectively) [5, 8]. We excluded patients younger than 15 years or older than 50 years, patients with fibrous or bony impingement, osteoarthritis or kissing lesions of the ankle, and patients with rheumatoid arthritis or hematological disorders.

The complete clinical history of the patients was recorded and analysed. All the patients underwent ankle physical examination. The preoperative AOFAS score of every patient was calculated [5, 8]. A standard radiographic weight-bearing examination and MRI scan of the affected ankle were performed pre-operatively.

The AOFAS score of every patient was investigated at 12, 36 and 48 months after surgery. Radiological evaluation with weight-bearing X-rays was planned every year. MRI was taken at the final follow-up of 48 months. The MRI scans were evaluated using Mocart score and T2 mapping.

Mocart score is an objective evaluation based on nine parameters describing the morphology and signal intensity of the repair tissue, compared with the native cartilage. The repair evaluation includes the thickness of the tissue, integration of the margins, smoothness of joint surfaces and the subchondral bone status. The signal intensity of the repair tissue was assessed in fast spin-echo (dual T2-FSE) and fat-suppressed gradient-echo (3D-GE-FS) sequences [18].

T2 mapping is a MRI sequence for the evaluation of water content of the newly formed tissue [19–21]. T2-mapping is a multiecho (8 echoes train) and multislice (18 slices) sequence, collecting a total of 144 images. It requires a specific post-processing T2 map software, using grading-color maps for normal and pathologic hyaline cartilage, and two presets (Preset1: ten–50 ms; Preset2 : 51–80 ms), adopted before imaging elaboration [20]. It allows to discriminate from hyaline cartilage, fibrocartilage, and remodeling tissue evaluating the increased or decreased water content; the percentage of altered tissue is related to the whole regenerated defect volume. The range suggestive of hyaline cartilage is between 35 and 45 msec. Higher values are considered compatible with remodeling tissue, whereas lower ones with fibrocartilage [19–21].

The scaffold used for both techniques is a hyaluronic acid membrane (HYAFF1-11, Anika Therapeutics, Bedford, MA). The chondrocytes were seeded on scaffold during the laboratory phase in the ACI technique, whereas the mesenchymal stem cells were loaded on the membrane during the surgical procedure of BMDCT (Figs. 1 and 2).

ACI

Forty patients were included in the ACI group, 25 males and 15 females, with a mean age of 31.4 ± 7.6 years. A summary of the pre-operative demographic and surgical data is reported in Table 1. Twenty-six patients practised a pre-lesion sport activity (recreational level in 20 cases, professional level in four patients). In 21 cases, the sport activity was classified as contact sports (soccer, basketball) and in five patients as noncontact sports (volleyball, tennis, swimming, cycling, ballet, aerobics) (Table 2).

Surgical procedure

The ACI technique was performed as previously described [9, 12]. It consisted of two steps, with an average time lag of 22.8 ± 2.7 days.

In the first step, through two standard arthroscopic approaches to the ankle, the lesion was detected and shaved off to healthy subchondral bone. Then a source of viable chondrocytes to culture was found, e.g. a detached osteochondral fragment, or a small area of cartilage tissue from the margins of the defect or from the anterior margin of

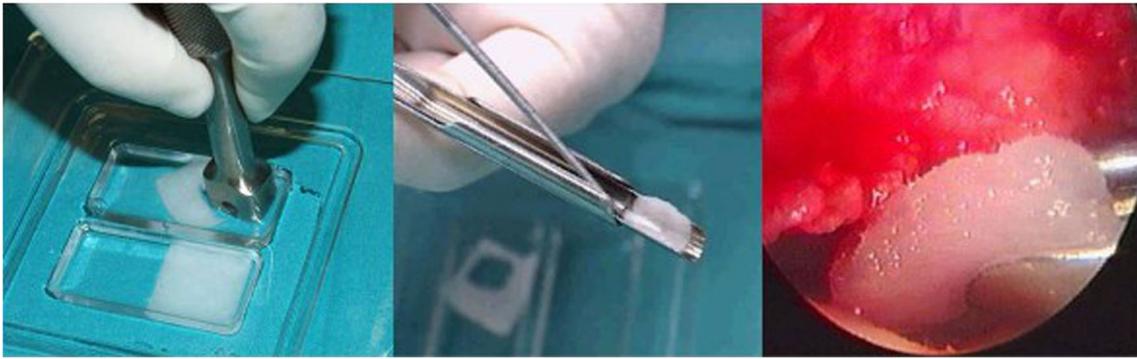


Fig. 1 The hyaluronic acid membrane (HYAFF1-11, Anika Therapeutics, Bedford, MA) with the chondrocytes seeded during the laboratory phase was sized; using a stainless steel cannula and a sliding positioner, the biomaterial was arthroscopically delivered to the lesion

the tibia. Early passive motion with progressive weight bearing as tolerated was advised postoperatively.

The chondrocytes were expanded in GMP laboratory and then seeded on the scaffold.

In the second-step arthroscopy, using the same arthroscopic approaches of the first procedure, the lesion was detected and accurately measured to correctly size the hyaluronic acid scaffold (Fig. 1). The biomaterial, accurately shaped, was delivered to the lesions with a specific instrumentation (Citieffe, Calderara di Reno, Bologna, Italy), then multiple flexions and extensions of the ankle were performed in order to check the press-fit stability of the biomaterial (Fig. 1).

The patients performed active and passive ankle motions since the day after surgery. The range of motion was gradually increased and, after three weeks, walking with crutches with no weightbearing was admitted. After six to eight weeks, partial weightbearing increasing to complete weightbearing was permitted. Low-impact sports activity could be resumed four months after surgery and high impact not before 12 months.

BMDCT

The BMDCT group consisted of 40 patients, 27 males and 13 females, with a mean age of 30.2 ± 9.7 years. The features of

BMDCT group are reported in Table 1. Twenty-six patients practised a pre-lesion sport activity (recreational level in 20 cases, professional level in six patients). In 17 cases, the sport activity was classified as contact sports (soccer, basketball) and in nine patients as noncontact sports (volleyball, tennis, swimming, cycling, ballet, triathlon) (Table 2).

Surgical procedure

The BMDCT procedure was performed as previously described in other papers [5, 8, 17]. The BMDCT procedure started the day before surgery, with platelet-rich fibrin (PRF) gel collection. A total of 120 ml of the patient's venous blood were harvested and processed through the Vivostat System (Vivolution A/S, 3460 Birkerød, Denmark) until 6 ml PRF gel were obtained. The product underwent cryopreservation in order to be used for the surgical procedure the day after.

With the patient in a prone decubitus position and under general or spinal anaesthesia, the bone marrow harvesting was performed from the posterior iliac crest in a sterile regimen, using a marrow needle (size, 11 G 9 100 mm). Through few perforations of the iliac crest, 60 ml of bone marrow were collected thanks to multiple aspirations of 5 ml bone marrow. In order to remove most of the red cells and plasma, the bone marrow was concentrated with a cell separator-concentrator



Fig. 2 The hyaluronic acid membrane (HYAFF1-11, Anika Therapeutics, Bedford, MA) was loaded with bone marrow concentrate during the surgical procedure; using the same instrumentation as

autologous chondrocytes implantation (ACI), the biomaterial was positioned and a layer of PRF was sprayed with a dedicated pen

Table 1 Preoperative features of ACI and BMDCT groups

Characteristic	ACI	BMDCT
Number of patients	40	40
Male/female patients	25/15	27/13
Right/left ankle involvement	22/18	23/17
Mean age (years)	31.4±7.6	30.2±9.7
Patients with a traumatic etiology	30	31
Patients with previous surgery	15	17
Mean lesion size (square cm)	1.7±0.6	1.8±0.6
Mean lesion depth (mm)	4.0±0.9	4.2±0.9
Lateral location	7	10
Medial location	33	30
Pre-operative AOFAS (points)	58.7±13.3	57.3±16.0
Bone grafting	5	4
Associate procedures	1	4

ACI autologous chondrocyte implantation, BMDCT bone marrow-derived cell transplantation

The two groups were homogenous for all the parameters, apart associate procedures

(Smart PRP1; Harvest Technologies Corp, Plymouth, MA) by a sterile and disposable dedicated kit (BMAC1; Harvest Technologies Corp, Plymouth, MA). At the end of the process, 6 ml of concentrate, full of nucleated cells, was obtained. After the bone marrow harvesting phase, ankle arthroscopy was performed through two standard approaches, with the patient in a supine position. The lesion site was debrided to the healthy bone. The lesion size was measured. Then, the biomaterial to be implanted was prepared. Hyaluronic acid membrane was sized following the area of the lesion and loaded with 2 ml of bone marrow concentrate and 1 ml of

Table 2 Pre-operative and postoperative comparison between sport activities in ACI and BMDCT

Measure	ACI	BMDCT
Pre-operative values		
Practised sport activity	26	26
Practised contact sport	21	17
Practised non-contact sport	5	9
Professionists	4	6
Post-operative values at 48 months		
Resumed at the same level	18 (69%)	18 (69%)
Resumed at a lower level	3 (11.5%)	7 (26.9%)
Shifted to non-contact sport	5 (19.2%)	1 (3.8%)
Gave up sports	4 (15%)	0 (0%)
Professionists come back to sport	4 (100%)	6 (100%)

ACI autologous chondrocyte implantation, BMDCT bone marrow-derived cell transplantation

Both the groups had the same rate of pre-lesion sportsmen and the same rate of sport resumption at the same level at 48 months after surgery

PRF gel. The same instrumentation was used as for arthroscopic autologous chondrocyte implantation (Citieffe, Calderara di Reno, Italy) as well as the same technique even for the implantation of the biomaterial in BMDCT (Fig. 2).

The advised postoperative treatment was the same as ACI.

Ethical considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent was obtained from all individual participants included in the study.

Statistical analysis

All continuous and interval variables were expressed in terms of mean and standard deviation of the mean. The paired *t*-test was used to determine any significant differences between the pre and postoperative scores. One-way ANOVA was performed to test hypotheses about means of different groups. When the Levene test for homogeneity of variances was significant ($p < 0.05$), the Mann–Whitney test (two independent groups) or the Kruskal Wallis test (three or more independent groups) were used. The Scedé test was performed as post hoc pairwise analysis of ANOVA, and the Mann–Whitney test with Bonferroni correction was performed as post hoc pairwise analysis of the Kruskal Wallis test. Spearman rank correlation analysis was performed to investigate relationships between two quantitative measurements. Life table survival analysis with Wlcoxon Gehan test was performed to assess the influence of grouping variables on the surgery survival; Cox regression survival analysis was performed to assess the influence of continuous and interval variables on the surgery survival. For all tests $p < 0.05$ was considered significant. Statistical analysis was carried out by means of the Statistical Package for the Social Sciences (SPSS) software version 14.0 (SPSS Inc., Chicago, USA). The percent recovery was calculated as follows: $(\text{post-op} - \text{pre-op}) / (100 - \text{pre-op}) \times 100$.

Results

Clinical results

Both ACI and BMDCT showed better AOFAS outcomes at the final follow-up compared with the pre-operative scores ($p < 0.0005$).

In the ACI group, the pre-operative AOFAS score was 58.7 ± 13.3 points. At 12 months, the AOFAS score improved to 86.4 ± 14.2 points. The peak was at 36 months, 89.7 ± 13.5 points. At the final follow-up (48 months), the AOFAS recorded 89.7 ± 13.3 .

In the BMDCT group, the pre-operative AOFAS score was 57.3 ± 16.0 points. The AOFAS score at 12 months was 89.9 ± 7.6 points. The AOFAS score peaked at 36 months (91.6 ± 10.2), reaching a final value of 91.3 ± 10.6 points (48 months). In both groups, the curve trends were similar with no statistically significant difference, dramatically improving at 12 months, peaking at 36 months and maintaining the trend at 48 months (Fig. 3).

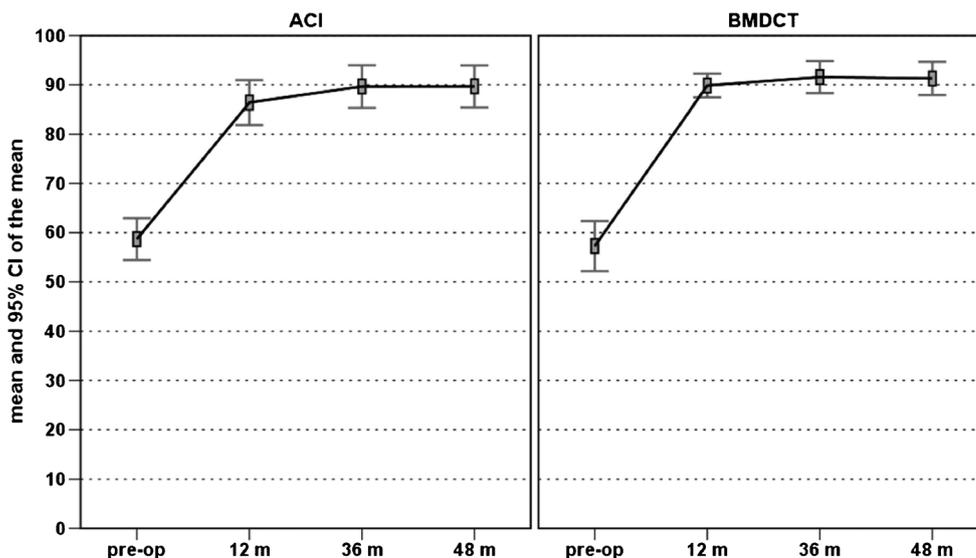
Both the techniques achieved excellent results, with a mean final AOFAS at 48 months of 90.5 ± 12.0 points (ACI range 41–100; BMDCT range 66–100).

The percent improvements were higher for BMDCT than ACI at 12 months (BMDCT: 73.4 ± 22.9 ; ACI: 66.5 ± 33.2), at 36 months (BMDCT: 78.8 ± 29.9 ; ACI: 74.3 ± 31.3) and at 48 months (BMDCT: 78.7 ± 29.9 ; ACI: 73.3 ± 32.4), with lower standard deviations.

In the BMDCT and ACI groups, the influence of age, size, depth and site of the lesions, previous surgeries, traumatic etiology, bone graft, and associated surgeries on the clinical outcomes at every follow-up were not statistically significant ($p > 0.0005$).

With regard to sport activity, ACI and BMDCT clusters achieved the same rate of return to sport (69 %) at the final follow-up of 48 months. All the professional athletes resumed sport activity. In ACI, only 11.5 % of patients practising sports resumed at a lower level, whereas the percentage in the BMDCT cluster was higher (26.9 %). On the other hand, no BMDCT patients at the final follow-up gave up sports, whereas four patients in the ACI group dropped sport activities (Table 2).

Fig. 3 Clinical outcomes of autologous chondrocytes implantation (ACI) and bone marrow derived cells transplantation (BMDCT). The trends were similar, with excellent results; nevertheless, BMDCT tended to slightly overcome ACI



At the final follow-up, ACI groups experienced three failures due to persistence of symptoms and incomplete filling of the defect (arthroscopic and MRI findings). BMDCT had one failure, related to persistence of symptoms and subchondral bone cyst (arthroscopic and MRI finding). All the failed cases were addressed to another BMDCT procedure.

Radiographic results

The X-ray projections taken at every follow-up showed no signs of joint degeneration in every patient of both groups.

MRI results

Twenty patients which underwent ACI and 20 patients which underwent BMDCT were evaluated using MRI MOCART score. The results are reported in Table 3.

Twenty patients in the group of ACI and 20 in the group of BMDCT were evaluate using the T2 mapping scale. The T2 values of the repair tissue were in the range compatible with hyaline cartilage in 85 % of the BMDCT and in 75 % of the ACI. In less than 10 % in both groups, the T2 mapping value was greater than 45 msec, probably suggesting a remodeling tissue with a high percentage of water. The ACI group demonstrated a higher percentage of T2 mapping value < 35 msec, which is suggestive of fibrocartilage (Fig. 4).

Discussion

According to literature, BMDCT and ACI [4, 8, 22–25] seem to meet the criteria of promising regenerative techniques. Remarkable clinical and radiological results were reported for both the techniques. Moreover, the histological samples, along with the results of the new MRI qualitative evaluation,

Table 3 MRI evaluation using Mocart score in ACI and BMDCT

Mocart parameters	ACI	BMDCT
Complete integration of the repair tissue 13 (65%)	12	(60%)
Complete filling of the defect 14 (70%)	13	(65%)
Intact quality of the repair tissue 14 (70%)	14	(70%)
Homogenous structure of the repair tissue 14 (70%)	13	(65%)
Hypertrophy of the repair tissue	5 (25%)	8 (40%)
Subchondral edema 17 (85%)	16	(80%)
Presence of complications (adhesions, joint effusion)	3 (15%)	4 (20%)

ACI autologous chondrocyte implantation, BMDCT bone marrow-derived cell transplantation

Both the groups had similar outcomes at 48 months after surgery

showed a tissue with biomechanical and structural properties close to normal hyaline articular cartilage [4, 5, 8, 22–25]. Despite the reported positive outcomes, no comparative study analysing the indications, advantages and drawbacks of ACI and BMDCT is currently available at follow up of 48 months. The aim of this study was reporting the clinical and radiological results of two homogeneous groups of patients affected by OLT, treated with ACI or BMDCT, at mid-term of follow up.

Both the groups were homogenous for pre-operative and intra-operative parameters, like AOFAS score, age, previous

surgeries, lesion dimensions and final follow-up. The only different parameter was related to the associate procedures, which were more in BMDCT than ACI, with no influence on the outcomes.

The clinical results, evaluated through serial AOFAS scores, were similar for both the groups, dramatically improving in the first 12 months and achieving stable values at 36 and 48 months, with better improvements for BMDCT. The mean results were excellent in both groups, with BMDCT slightly overcoming ACI (BMDCT: 94.7; ACI: 93.9). The final result of both the groups was not influenced by any pre-operative parameters (lesion location, size and depth, patient age and sex, previous surgeries, traumatic etiology, associated procedures, bone graft).

The return to sport was good for both techniques, showing ACI and BMDCT to be good solutions for sportsmen, despite the long time needed for rehabilitation (12 months). The resumption at the same level was similar for both the procedures. Nevertheless, ACI showed a higher rate of drops in sports activity. In three cases, the patients complained about pain and discomfort, and one case was afraid of re-injury. Both the techniques shared the same rehabilitation program, eliminating a possible confounding factor. Though, larger and more calibrated case series are needed to evaluate this topic.

The Mocart MRI results were substantially similar, showed good integration of the borders, satisfying filling of the defects and had a remarkable persistence of subchondral edema in the two groups. In the T2 mapping series, a higher rate of tissue compatible with hyaline like values were found in BMDCT, with a consistent reduction of fibrocartilage tissue like

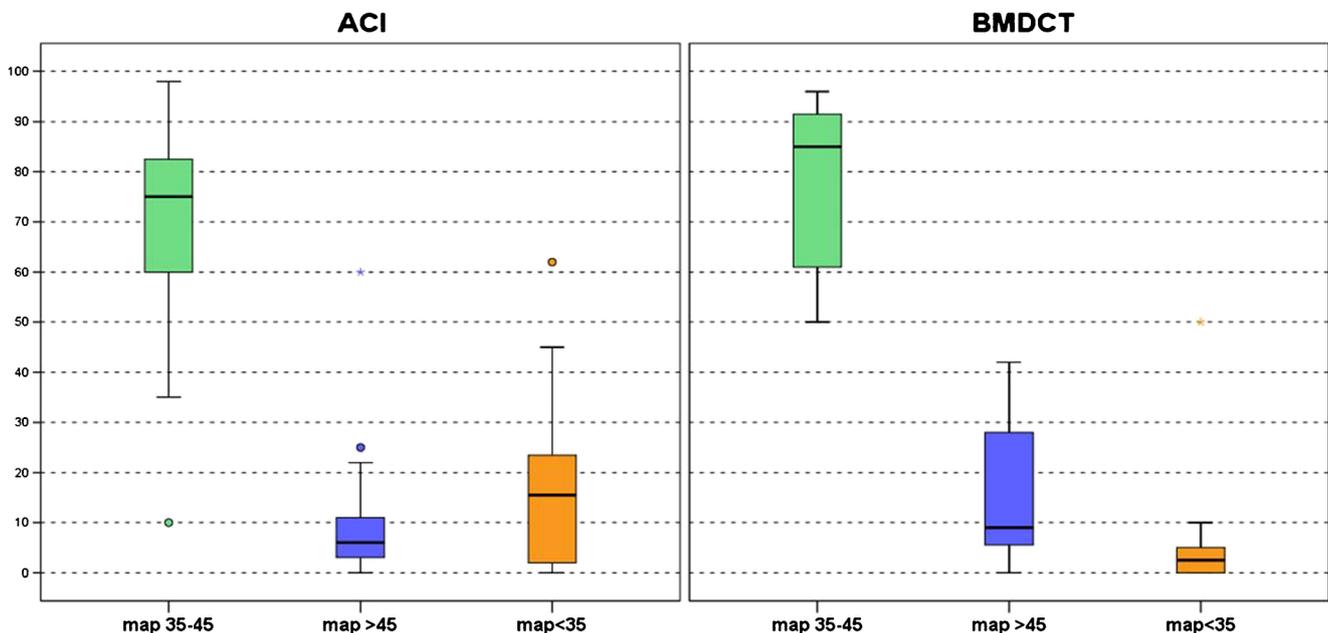


Fig. 4 T2 mapping evaluation in autologous chondrocytes implantation (ACI) and bone marrow derived cells transplantation (BMDCT) showing values suggestive of hyaline cartilage (35–45 msec, green), remodeling

tissue (>45 msec, blue) and fibrocartilage (<35 msec, orange). BMDCT seemed to have better qualitative outcomes at repair site evaluation

percentage. However, this finding should be confirmed by histological evaluation, which is not included in this work.

Beyond the clinical and radiological results, it is important to highlight that ACI and BMDCT have two different profiles regarding practicality. ACI is a double-step procedure, with high costs due to two hospitalizations and the costs of a GMP laboratory facility for the cell culture. BMDCT, which was developed to overcome these limitations, is a one-step technique, with a single hospitalization and no need of cell culture.

This study had some limitations. First, the patients were retrospectively evaluated. Second, the two groups analysed were substantially homogenous, but they had different rates of associate procedures which did not influence the outcome. Moreover, the qualitative evaluation of the regenerated tissue was performed using T2 mapping MRI, which is currently lacking standardization of the range values [19–21]. Histological evaluation was not performed in this comparative study. Nevertheless, the osteochondral regeneration of both techniques was confirmed by histological samples in previous papers [6, 8, 9, 12, 17].

To date, ACI and BMDCT seem effective regenerative techniques supplying hyaline cartilage in OLT. Comparing two clusters, clinical outcomes were quite similar at mid-term follow-up, with BMDCT slightly overcoming ACI scores. The rate of return to sport seemed to be in favour of BMDCT, but more calibrated series are needed to confirm this finding. T2 mapping MRI evaluation showed a higher percentage of tissue with signal compatible with hyaline tissue in BMDCT than in ACI, suggesting a better qualitative outcome. Moreover, BMDCT offered some practical advantages: it was a fast, easy and cheap technique, with no need of complex laboratory process, and, above all, it was a one-step technique. Considering the clinical and radiological outcomes of this study, BMDCT could be preferred over ACI for better results and practicality. Nevertheless, prospective randomized controlled trials including histological evaluation are needed to confirm the superiority of one technique over the other.

Conflict of interest The authors declare that there is no conflict of interest.

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