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ARTHROSCOPY AND SPORTS MEDICINE

# "One-step" bone marrow-derived cells transplantation and joint debridement for osteochondral lesions of the talus in ankle osteoarthritis: clinical and radiological outcomes at 36 months

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**Abstract**
*Introduction* Ankle osteoarthritis (OA) is a challenging pathology, often requiring surgical treatments. In young patients, joint sparing, biologic procedures would be desirable. Recently, a few reports have described the efficacy of bone marrow stem cells in OA. Considering the good outcomes of one-step bone marrow derived cells transplantation (BMDCT) for osteochondral lesions of the talus (OLT), we applied this procedure for OLT in concomitant ankle OA.
*Materials and methods* 56 patients, with a mean age of 35.6 years (range 16–50), who suffered from OLT and ankle OA, were treated using BMDCT. All patients were clinically checked using AOFAS score, in the pre-operative setting until the final follow-up of 36 months. Weight-bearing radiographs and MRI evaluation using Mocart score were performed, preoperatively and postoperatively.
*Results* The whole clinical outcome had a remarkable improvement at 12 months, a further amelioration at 24 months and a lowering trend at 36 months (77.8 ± 18.3). Early OA had better outcomes. 16 patients required another treatment and they were considered failures. Clinical outcome significantly correlates with OA degree, BMI, associate procedures. Radiographs were in line with clinical results. MRI evaluation showed signs of osteochondral repair.
*Conclusions* BMDCT showed encouraging clinical and radiological outcomes at short-term follow-up. This procedure should be applied in young and selected patients, excluding severe ankle degeneration, where the results are critical. Longer follow-ups and larger case series are needed to confirm these results and if this treatment could be effective in postponing end-stage procedures.
*Level of evidence* IV.

**Keywords** Ankle osteoarthritis · Osteochondral lesions of the talus · Bone marrow-derived cells transplantation · One step

## Introduction

Ankle osteoarthritis (OA) is a debilitating pathology affecting 1 % of the world's adult populations, causing pain and disability [1]. Few valuable treatments are currently available for ankle OA [2]. In early OA, arthroscopic debridement may achieve valuable short-term results; nevertheless, a major procedure is required in 28 % of cases at 5 years follow-up [3]. More advanced degeneration involves end-stage treatments, as arthrodesis or total ankle replacement: these procedures are not desirable in young patients due to premature foot joints OA and high rate of prosthetic revision, respectively [2].

Nevertheless, it is believed that ankle OA may result from a focal chondral defect, giving the way to a more diffuse and severe ankle degeneration [4–7]. In such cases, where osteochondral lesions and OA coexist, cartilage repair procedures may be an appropriate treatment, as recently suggested by Gomoll for similar conditions in knees [8, 9]. The aim of this approach is to delay or even arrest the degenerative process [8, 9].

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Among the many suggested treatments concerning cartilage repair in OA, mesenchymal stem cells were proposed as a possible treatment for articular degeneration of the knee, due to their trophic, anabolic and paracrine effects [10–12]. Few papers reported the clinical results of mesenchymal stem cells' applications in degenerated joints (mostly knees, few ankles), with encouraging results [12–15]. The injective approach was preferred in case of diffuse OA, whereas the scaffold loaded with mesenchymal stem cells was used in case of osteochondral lesions with concomitant OA [11–15]. Hence, due to very good outcomes in the treatment of osteochondral lesions and promising clinical and laboratorial findings about osteoarthritis environment [10, 13, 16–18], a surgical procedure including joint debridement and one-step bone marrow-derived cell transplantation (BMDCT) was suggested to treat osteochondral lesions of the talus (OLT) in concomitant OA. The aim of this study is to retrospectively evaluate the clinical and radiological outcomes of BMDCT application and joint debridement for OLT in ankle OA at 36 months follow-up.

## Materials and methods

56 consecutive patients (56 ankles) with OLT and concomitant joint degeneration treated with BMDCT were retrospectively identified. Inclusion criteria required the presence of all these conditions:

- Persistent pain in the ankle.
- Weight-bearing radiographic evaluation: Van Dijk's classification for ankle OA was used and all the ankles staged 1, 2, 3 were included; in case of radiographic stage 0, cases with the presence of MRI degeneration signs according to AOSS classification, including at least 4 major criteria (full thickness defects with subchondral bone involvement >5 mm, bone marrow edema and subchondral cyst) and 2 minor criteria (one of which was pathological soft tissue structures), were included [19, 20].
- MRI and/or arthroscopic evaluation showing OLT (Giannini's classification: stage II or IIA) [17, 18].
- Patients between ages 15–60 years.
- No rheumatic or hematologic etiology.
- Minimum follow-up of 36 months.

Exclusion criteria were patients younger than 15 years or older than 50 years, focal OLT with no signs of joint degeneration (MRI and X-rays evaluations), bony spurs in the absence of OLT, OLT staged III in Giannini's classification, patients with rheumatoid arthritis or hematologic disorders [17–20]. All patients were investigated for their complete medical history. All the patients underwent ankle physical examination. A preoperative AOFAS score was collected [17, 18]. A weight-bearing radiographic evaluation and a preoperative MRI were performed in all the cases.

A standard protocol including AOFAS score at established follow-ups (6, 12, 18, 24, 36 months) was performed. Weight-bearing ankle X-rays were taken every year to investigate OA progression. MRI scans were performed at 36 months, including a Mocart score evaluation to assess cartilage repair [21].

Preoperative demographical and surgical data of the patients included in the study are listed in Table 1.

All the patients involved gave their informed consent. The study was approved by our local ethical committee. The study was carried out in accordance with the World Medical Association Declaration of Helsinki

### Surgical procedure

The day before surgery, autologous platelet-rich fibrin (PRF) was obtained to provide growth factors and a fibrin clot to fasten the implanted biomaterial. 120 ml of patient's venous blood was processed through Vivostat system (Vivolution A/S, 3460 Birkeroed, Denmark): a final product of 6 ml was provided. The PRF was then cryopreserved until the surgical treatment.

The bone marrow was collected and processed with the technique reported by Giannini et al. the day of surgery, in a sterile regimen, under general or spinal anesthesia

**Table 1** Demographical, pre-operative and intra-operative parameters of the patients: the 10 associate procedure included 1 calcaneal osteotomy, 1 fibular lengthening, 2 hardware removal, 3 Achilles tendon lengthenings, 1 calcaneal osteotomy and concomitant hardware removal, 2 other foot joints debridement

| *Demographical, pre-operative and intra-operative parameters* | |
|---|---|
| Number of patients | 56 |
| Male/female patients | 37/19 |
| Right/left ankle involvement | 30/26 |
| Medial/lateral location | 32/24 |
| Mean age (years) | 35.6 ± 9.4 |
| Smokers | 20 (35.7 %) |
| BMI (kg/m$^2$) | 24.9 ± 3.1 |
| Mean lesion size (cm$^2$) | 2.4 ± 1.3 |
| Mean lesion depth (mm) | 6.6 ± 2.8 |
| Open-field/arthroscopy | 23/33 |
| Scaffold (hyaluronate/collagen) | 56 (25/31) |
| Bone filling (DBM/autologous bone) | 22 (9/13) |
| Associate procedures | 10 (17.9 %) |
| Patients with a traumatic etiology | 43 (76.8 %) |
| Fracture etiology | 21 (37.5 %) |
| Patients with previous surgery | 28 (50 %) |
| Pre-operatory AOFAS (points) | 52.3 ± 14.2 |

[17, 18]. The patient was positioned in prone decubitus: using a bone marrow needle (size 11, G 9, 100 mm), 5 ml of bone marrow aspirate was taken from the posterior iliac crest and collected in a blood bag containing heparin. Repeated movements of clockwise rotations and withdrawings of the needle were performed to harvest the maximum amount of stem cells [22]. 60 ml of bone marrow were eventually collected.

The bone marrow aspirate underwent a process of concentration using the Smart PReP1(Harvest Technologies Corp, Plymouth, MA, USA) and the dedicated kit BMAC1 (Harvest Technologies Corp.) or the newer kit IOR-G1 (Novagenit, Mezzolombardo, Italy). 6 ml rich in nucleated cells like stem cells, monocytes, lymphocytes and bone marrow resident cells were obtained.

After the bone marrow harvesting phase, the ankle joint was approached using an arthroscopic or open-field procedure. Open-field technique was preferred in the case of severe osteoarthritis or previous surgeries.

Arthroscopy was performed through two standard approaches. Fibrous and osseous impingement was debrided; loose bodies were removed when present. The area of OLT was detected and removed; then, it was measured using a calibrated probe. Biomaterial composites to be implanted were prepared, loading the membrane with 2 ml of cellular concentrate. The membrane was sized and shaped to fit for the OLT. Bone filling using demineralized bone matrix (DBM) was used in case of defects deeper than 5 mm. Autologous cancellous bone filling was preferred in case of OLT deeper than 10 mm or concomitant subchondral cysts. The biomaterials were implanted using a specific instrumentation developed for autologous chondrocytes implantation (Citieffe, Calderara di Reno, Bologna), previously described in other papers [18]. A layer of PRF was then sprayed onto the implanted biomaterial to improve biological process and stabilization of the composite. A final check was performed with multiple flexion–extensions.

In case of open-field approach, antero-medial incision was performed, retracting medially the anterior tibial tendon; capsulotomy was performed. Impingement and OLT were removed. Bone filling was performed when necessary, as specified above. Biomaterial was prepared and placed on the lesion: it was regularized using a flat probe. To promote the stability of the implant and provide growth factors, PRF was applied onto the lesion. Before suturing and bandaging, multiple flexion-extensions were performed to check the result.

Rehabilitation timetable included a first step of weight-bearing protection and continuous passive movements: mobilization was started from the first day after surgery and it was progressively increased as tolerated. After 6 weeks, weight-bearing was progressively allowed. Low impact sport activities (cycling, swimming) were started at 4 months after surgery. High impact sport activities were proscribed up to 10–12 months.

### Statistical analysis

All continuous data were expressed in terms of the mean and the standard deviation of the mean. The categorical data were expressed as frequency and percentages. The Kolmogorov–Smirnov test was performed to test the normality of continuous variables. The Repeated Measures General Linear Model (GLM) with Sidak test for multiple comparisons was performed to assess the differences at different follow-up times. The Jonckheere–Terpstra test was used to assess the existence of a correlation between AOFAS score and OA grading. The Spearman rank Correlation was used to assess the correlation between continuous data. The Kendall tau correlation was used to assess correlation between ordinal data. The ANOVA test was performed to assess the between-group differences of continuous, normally distributed and homoscedastic data; the Mann–Whitney test was used otherwise. The Kruskal–Wallis test evaluated by Monte Carlo methods was performed to assess the differences among more than two groups. The Mann–Whitney test with the Bonferroni correction for multiple tests was used as post hoc pairwise analysis. For all tests, $p < 0.05$ was considered significant. All statistical analysis was performed using SPSS v.19.0 (IBM Corp., Armonk, NY, USA).

## Results

### Clinical results

No postoperative complications were noted. No patients were lost to the final follow-up of 36 months.

Starting from the pre-operative AOFAS score of 52.3 ± 14.2, the whole clinical trend progressively improved at 6, 12 and 18 months, and peaked at 24 months (78.5 ± 17.3): the final result of 77.8 ± 18.3 was achieved at 36 months.

The best percentage improvement was achieved at 24 months (54.2 % ± 34.5).

OA stage was found to be significantly correlated with the AOFAS score at all the established follow-ups of 6, 12, 18, 24, 36 months (respectively, $p$: 0.014; $p$: 0.008; $p$: 0.009; $p$: 0.004; $p$: 0.002). According to the preoperative radiological investigations, four groups were identified: Group 1, 2 and 3 according to radiographic Van Dijk classification for ankle OA [20]. A further group including only MRI signs, Group 0 (with the presence of full thickness defects with subchondral bone involvement >5 mm, bone marrow edema, subchondral cyst and fibrous impingement) was acknowledged, following AOSS classification [19, 20].

Clinical trends of the four OA groups were significantly different at 6, 24 and 36 months (respectively, *p*: 0.022; *p*: 0.026; *p*: 0.015) (Fig. 1).

Group 0 achieved a value of 82.3 ± 20.9 AOFAS points at 36 months, reaching a stable result. Similar trend with a similar final result (82.6 ± 15.7) was evident for Group 1, with a higher presence of outliers. Group 2 achieved a final result of 74.0 ± 18.3 points, whereas Group 3 arrived at 60.3 ± 15.9 points (Fig. 1).

Best percentage improvements were achieved for OA groups 0 and 1 at all the established follow-ups, with higher standard deviations in Group 0. Lower percentage improvements were reached in OA groups 2 and 3, the last cluster achieving the worst outcomes.

AOFAS score at 36 months was not influenced by patient's age, sex, traumatic etiology, smoke, previous surgeries, size and depth of the lesions, subchondral cysts, fibrous impingement, arthroscopic or open-field approach, scaffold choice, and bone filling. Parameters influencing the results at 36 months were associate procedures and BMI (significant associations, respectively, *p*: 0.008 and *p*: 0.005), fracture etiology (trend, *p*: 0.07) (Figs. 2, 3). Multivariate analysis showed that associate procedures were the most important predictor of the final outcome ($p < 0.05$).

16 failures (patients requiring a new procedure) were recognized at the final follow-up (28 %). 9 arthrodesis, 1 bipolar allograft transplantation, 5 arthroscopy, and 1 BMDCT were performed in case of failures.

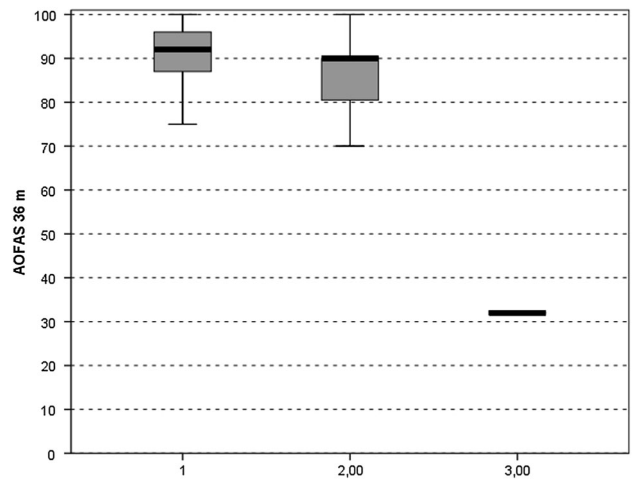


**Fig. 2** BMI significantly influenced the clinical results at 36 months. 1, 2 and 3, respectively, refer to BMI lower than 25 kg/m$^2$, between 25 and 30 kg/m$^2$, higher than 30 kg/m$^2$

Higher rates of failures were achieved in the case of preoperative severe joint degeneration (statistically significant: *p* 0.002; $\tau$ 0.359). Group 0 had no failures, whereas a percentage of 23, 33 and 71 % was achieved by Groups 1, 2 and 3, respectively (Fig. 4).

## Radiographic results

No patients were lost to the final follow-up.

In 15 patients (26.3 %), a radiographic OA progression was acknowledged compared to the preoperative radiographic status.

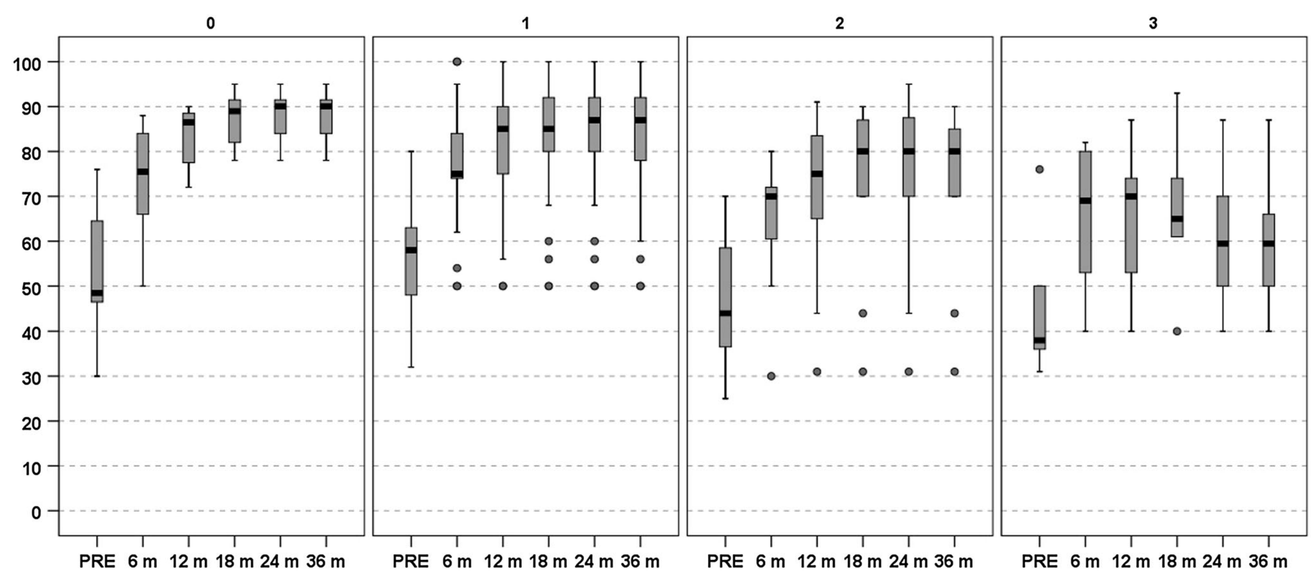


**Fig. 1** AOFAS clinical outcomes of the four groups showed average excellent results in Group 0. Lower outcomes with some outliers were evident in Group 1. Group 3 had the worst results, with decremental trend

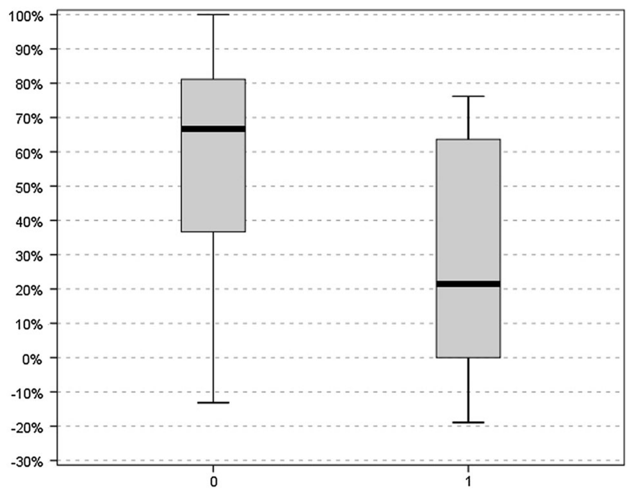


**Fig. 3** Associate procedures significantly influenced the clinical results at 36 months. Patients with no associate procedures (*0*) had much higher outcomes than patients requiring at least an associate procedure (*1*)

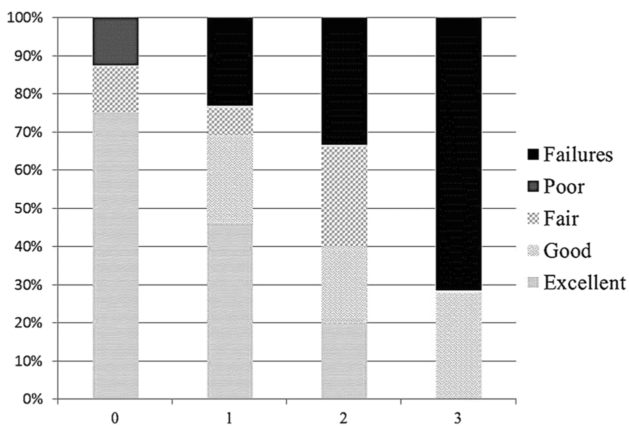


**Fig. 4** AOFAS results of the four groups were divided into excellent (>90 points), good (>80 points and <90 points), fair (>70 points and <80 points) and poor (<70 points) outcomes. Failures included patients requiring another surgical procedure

In Group 0, 7 patients (87.5 %) did not experience any change in their OA stage; 1 case (12.5 %) showed bony spurs formation (Fig. 5).

In Group 1, 17 patients (65.4 %) experienced no osteophytes reappearance; 4 patients (15.4 %) had recurrence of the bony spurs; 5 cases (19.2 %) had narrowing of the joint space (Fig. 6).

In Group 2, 8 patients had no OA progression (53.3 %), whereas 7 patients (46.7 %) had a further reduction of the joint space (Fig. 7).

In Group 3, 3 patients (42.9 %) had no OA progression, and 4 cases (57.1 %) experienced further narrowing of the joint space (Fig. 8).

At 36 months, radiographic evaluation showed a significant association with the AOFAS score at 36 months ($p$: 0.03).

### MRI results using mocart score

MRI with Mocart score evaluation was performed in 22 patients [21].

Group 0 achieved the best MRI outcome, whereas lower performances were in Group 3 (Figs. 9, 10, 11, 12). A complete degree of filling achieved in large majority of the patients, with complete integration of the borders and homogenous surface of the repaired tissue. Most of the patients experienced subchondral bone edema; a high rate of joint effusion was evident in many cases (Table 2).

Mocart score showed no significant correlation with the clinical and radiographic results at 36 months.

## Discussion

Ankle OA is a severe disabling condition, frequently requiring a surgical treatment [2, 6]. In case of young patients' involvement, an efficient joint sparing treatment is currently lacking: arthroscopic debridement is efficient only in case of impingement [3, 20, 23, 24]. In more advanced cases, it leads to decremental results after 2 years; concomitant OLT are poor prognostic factors [3, 20, 23, 24]. Biological treatments could be proposed in early and advanced OA [8, 9]. The aim of this treatment is to arrest (in case of early OA) or to delay (in case of advanced OA) the degeneration, postponing end-stage procedures [8, 9]. Biological treatments encompass procedures like autologous chondrocytes implantation (ACI), osteochondral autograft transfer (OAT), and scaffolds implantation [8, 9, 16, 17]. The major drawbacks of all these procedures are the limits given by subchondral bone status, dimensions of the lesions and the inflammatory and catabolic joint environment [8, 9, 16, 17]. BMDCT may be a favorable approach for at least three reasons: the drawbacks of alternative treatments, capability to focus on the OLT and on the OA at the same time, few encouraging applications in OA [10–15].

Coleman et al. highlighted that mesenchymal stem cells may be held back by the OA environment, but at the same time they could modulate the progression of the disease [10]. Veronesi et al. reviewed mesenchymal stem cells application in different joints with OA: clinical results were generally favorable [12]. Hauser reported favorable clinical outcomes in a patient with diffuse ankle OA, using mesenchymal stem cells' injection [14]. Buda et al. described positive outcomes in degenerated ankles of hemophilic


**Fig. 5** Lateral pre-operative (**a**) and post-operative (**b**) X-rays of a 32-year-old patient of Group 0. The patient had soft tissue impingement with an OLT submined by a subchondral cyst; after 36 months, there were no signs of OA progression


**Fig. 6** Lateral pre-operative (**a**) and post-operative (**b**) X-rays of a 28-year-old male patient of Group 1. Talar and tibial bony spurs were evident; after 36 months, recurrence of talar bony spurs occurred


**Fig. 7** Anterior pre-operative (**a**) and post-operative (**b**) radiographs of a 38-year-old male patient in Group 2. No further narrowing was present at 36 months


**Fig. 8** Lateral pre-operative (**a**) and post-operative (**b**) radiographs of a 33 year old female patient in Group 3. No further narrowing was present at 36 months: however, the patient underwent arthrodesis for severe symptomatology

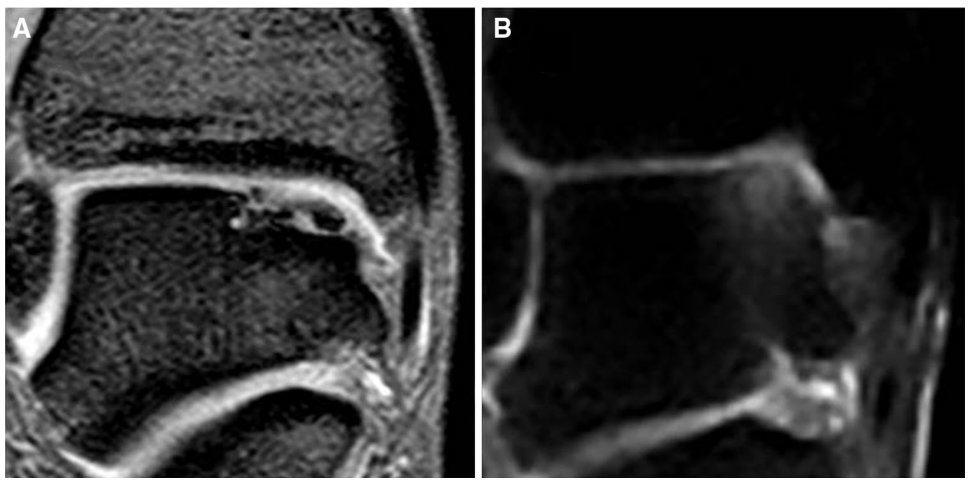


**Fig. 9** Coronal T2-weighted pre-operative (**a**) and post-operative (**b**) MRI scan of a 35 years old male patient of Group 0: good subchondral bone reconstruction and cartilage repair at 36 months

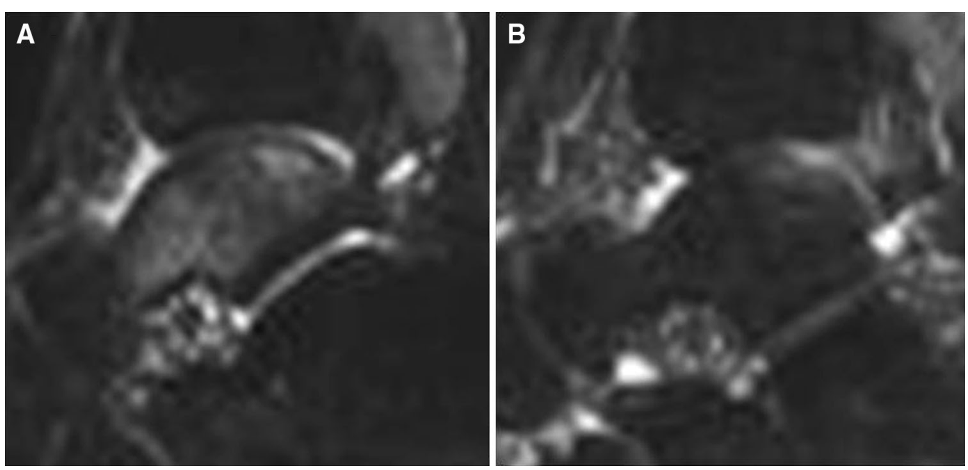


**Fig. 10** Compared to the pre-operative (**a**), the axial T2-weighted post-operative (**b**) MRI scan of a 27-year-old male of Group 1 showed persistence of the subchondral bone edema and the talar bony spur, with good signs of osteochondral repair

patients, treated with "one-step" BMDCT on collagen membrane [13].

To our knowledge, this retrospective study is the first paper describing the application of one-step BMDCT for cartilage repair in ankle OA. In our case series, we included young patients with a wide spectrum of OA, ranging from an early stage to advanced degenerations. Encouraging results were achieved at 36 months follow-up. Clinical

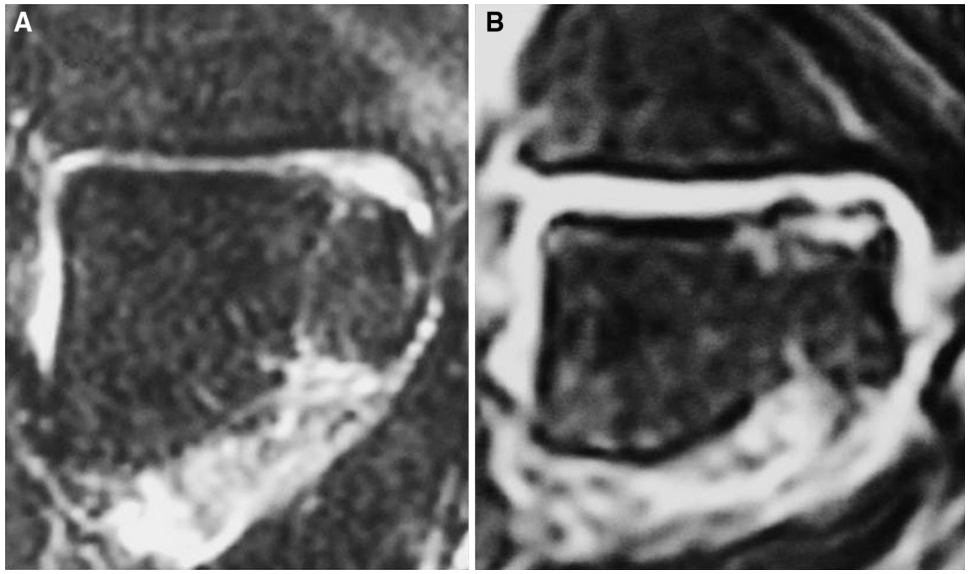


**Fig. 11** 40 years old female patient in Group 2 had post-operative (**b**) axial T2-weighted MRI scan with non-homogenous cartilage repair and subchondral bone sufferance: no apparent narrowing of the joint space was evident in comparison with pre-operative (**a**) scan

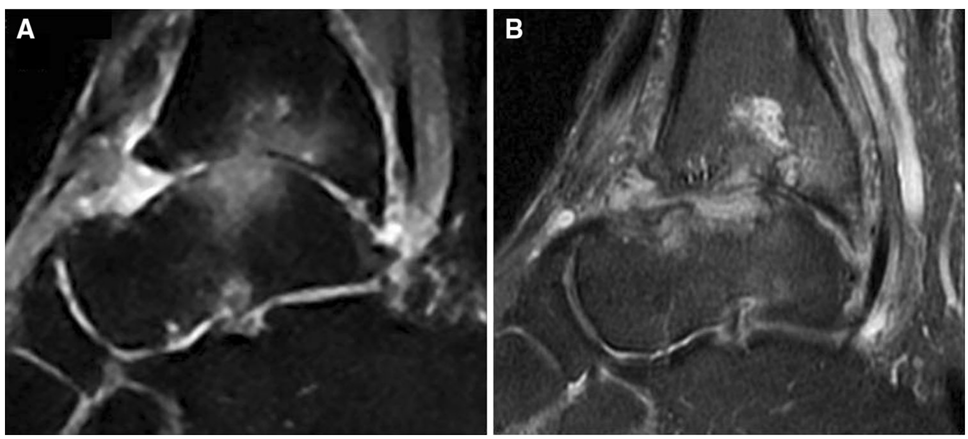


**Fig. 12** Severe OA in the axial T2 weighted MRI scans in the pre-operative (**a**) and post-operative (**b**) settings. However, the 38 years old male of Group 3 had a good clinical outcome

outcomes were significantly dependent on preoperative OA stage, showing better results in early OA. Dimensions of OLT did not influence the results. Radiographic outcomes were in line with the clinical findings, with best improvements in early OA. MRI scan evaluated using Mocart score showed signs of cartilage repair, with better results in patients with modest degeneration (non-significant correlation).

Although the four clusters had statistically independent outcomes, three main groups could be roughly made: an early OA grading 0 and 1 according to Van Dijk, a more advanced degeneration grading 2, and severe OA in Group 3 [19].

In early OA, a high rate of excellent/good results, a radiographic outcome demonstrating a stable/improved condition, MRI signs of osteochondral repair and few failures seem to make the BMDCT a valuable approach, with a possible OA sparing aim. On the contrary, advanced OA requires a more cautious approach. In case of narrowing of the joint space, BMDCT rationale is presumably to delay OA progression, still a considerable target in young patient. However, patients with this OA stage should be warned about the considerable risk of failure (1/3 at 36 months). In case of severe OA, BMDCT seems not to be recommendable due to the very high rate of failures (2/3 at 36 months). In these cases, an alternative biologic approach that could be considered is fresh bipolar allograft transplantation, which could restore both the articular surface at the same time [25].

This study has some limitation: first of all, it is a retrospective case series with a short-term follow-up (36 months). Moreover, a wide spectrum of OA with few patients in Groups 0 and 3 is included: more calibrated studies with more participants would be desirable to draw more appropriate conclusions. At the same time, a precise, widespread definition of early OA would be necessary to better focus the future studies.

**Table 2** MRI scans of 22 patients evaluated using mocart score: non-significant association with OA stage

| Parameters and grade | Patients (%) | | | |
|---|---|---|---|---|
| | Group 0 (5 pt) | Group 1 (7 pt) | Group 2 (6 pt) | Group 3 (4 pt) |
| Degree of filling of the osteochondral defect | | | | |
| Complete | 80 | 71 | 67 | 50 |
| Hypertrophic | 0 | 0 | 17 | 0 |
| Incomplete >50 % | 20 | 29 | 17 | 25 |
| Incomplete <50 % | 0 | 0 | 0 | 25 |
| Exposure of subchondral bone | 0 | 0 | 0 | 0 |
| Integration to the border zone | | | | |
| Complete | 80 | 71 | 67 | 0 |
| Incomplete | 20 | 29 | 33 | 100 |
| Surface of the repaired tissue | | | | |
| Homogenous | 80 | 57 | 50 | 25 |
| Nonhomogenous | 20 | 43 | 50 | 75 |
| Signal intensity of the repaired tissue (DPFSE) | | | | |
| Isointense | 60 | 57 | 50 | 0 |
| Moderately hyperintense | 40 | 43 | 33 | 25 |
| Markedly hyperintense | 0 | 0 | 17 | 75 |
| Status of the subchondral lamina | | | | |
| Intact | 20 | 14 | 0 | 0 |
| Non intact | 80 | 86 | 100 | 100 |
| Integrity of the subchondral bone | | | | |
| Intact | 20 | 29 | 0 | 0 |
| Non intact | 80 | 71 | 100 | 100 |
| Presence of complications | | | | |
| Joint effusion | 40 | 43 | 67 | 75 |
| Subchondral edema | 60 | 85 | 83 | 100 |

BMDCT for OLT in concomitant ankle OA achieved interesting clinical and radiological results at 36 months follow-up. Early OA seems to improve considerably, with low rate of failures: in this case, BMDCT could be performed with an OA sparing aim. More advanced degeneration requires a strict selection of patients to achieve successful outcomes. Nevertheless, in these cases, BMDCT could be appropriate to delay OA progression only. In severe OA, BMDCT should be discouraged. More calibrated studies with larger case series and longer follow-ups are required to better understand whether BMDCT could only delay the OA progression or it is a successful procedure in arresting joint degeneration.

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