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## Surgical treatment of early knee osteoarthritis with a cell-freeosteochondral scaffold: results at 24 months of follow-up

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*Purpose:* “Early Osteoarthritis (EOA)” has been defined combining clinical, imaging and surgical parameters, with the aim to identify patients in early degenerative phases, who might benefit from the use of available regenerative procedures. Aim of this first clinical trial is to prospectively evaluate the results obtained in a group of patients meeting the inclusion criteria of “EOA” as proposed by the ESSKA Cartilage Committee, and surgically treated with the implantation of a multi-phasic osteochondral scaffold.

*Methods:* 23 patients were prospectively evaluated at 12 and 24 months of follow-up. Etiology of the chondral or osteochondral defect was rated as microtraumatic or degenerative in 18 cases, and traumatic in 5 cases. Patients included were complaining of clinical symptoms like knee pain and affected by chondral and osteochondral lesions located at the femoral condyles or trochlea and MRI findings demonstrating articular cartilage degeneration and/or meniscal degeneration and/or subchondral bone marrow lesions.

*Results:* All patients increased significantly in any clinical score adopted. The IKDC subjective score increased from  $42.8 \pm 13.8$  at basal evaluation to  $74.3 \pm 17.4$  at 12 months’ ( $p < 0.0005$ ), being stable ( $74.9 \pm 20.4$ ) up to the final follow-up of 24 months. Tegner score showed a statistically significant improvement in sports activity from  $3.3 \pm 2.7$  pre-operative to  $4.6 \pm 2.2$  at 12 months ( $p < 0.005$ ), with a slight improvement to the final evaluation ( $4.7 \pm 2.1$ ; n.s.). However, the activity level was significantly lower than the pre-injury one ( $6.1 \pm 2.6$ ;  $p = 0.004$ ). A significant difference was shown between patients younger versus older than 40 years, with younger patients had better clinical improvement ( $76.0 \pm 18.6$  vs  $45.1 \pm 38.8$  respectively,  $p = 0.037$ ).

*Conclusions:* The implantation of a multi-phasic osteochondral scaffold represents a good option after failure of conservative management for Early OA patients, where younger age represent an important factor for a better outcome.

Longer follow-up is needed to evaluate the benefit over time.

## Introduction

Osteoarthritis (OA) is one of the most widespread orthopaedic diseases, characterized by joint pain and decreased function [1]. It is most common in patients over 50 years old, but with the increase of physical activity in the aging population it is not rare to find degenerated knees even in younger patients.

In recent years, there has been an increasing interest in identifying early phases of OA, so that the degenerative processes might be arrested or delayed. In this context, the definition of early OA has been recently proposed by combining both clinical, imaging, and surgical parameters, to identify patients in these early degenerative phases at risk for progression, who might still benefit from the use of regenerative procedures. In fact, young patients with OA symptoms frequently present with an altered joint biomechanical environment responsible for an imbalance between the mechanical demand and the ability of the joint to maintain and repair itself, thus resulting in premature degenerative changes [2,3]. Thus, once identified, predisposing factors can be addressed to prevent further degeneration, favour

a better chance of success with biological treatments and delay the need for more invasive procedures.

In fact, whereas metal resurfacing can provide a high success rate and satisfaction for older patients, high functional demand and longer life expectancy of young patients are an issue for joint arthroplasty. However, recommendations have traditionally excluded regenerative procedures for the treatment of cartilage lesions in OA patients, because of the poor expected results. However, leaving degenerative defects untreated accelerates the rate of cartilage loss [4,5], and early OA patients, too young for joint replacement, might benefit from a biological reconstruction to restore the articular surface.

One of the main challenges in the treatment of degenerative lesions is that cartilage is not the only tissue involved. For example recently there has been increasing interest and awareness in the importance of the subchondral bone, that may be affected by the degenerative pathological processes as well [6]. Thus, to obtain a repair tissue that closely resembles the native articular surface and might last over time, restoring the physiological properties of the entire osteochondral unit may be key in these degenerative patients. An osteochondral treatment is challenging, due to the different healing capabilities of the two tissues, but new regenerative procedures are emerging as promising approaches to manage these lesions [7,8]. Among these, a biomimetic nanostructured osteochondral scaffold [9,10] was proposed to restore the articular surface, by addressing both the chondral layer and the underlying subchondral bone.

The aim of this clinical trial is to evaluate prospectively the results obtained in a group of patients meeting the criteria of "Early OA" and surgically treated with the implantation of a multi-phasic cell-free osteochondral scaffold.

## Materials and methods

The study was approved by the Hospital Ethics Committee and Internal Review Board, and informed consent was obtained from each patient.

The patients met the previously proposed criteria for early OA [11] "clinical symptoms, such as knee pain (at least two episodes of pain for more than 10 days in the last year) and MRI findings demonstrating articular cartilage degeneration and/or meniscal degeneration and/or subchondral BMLs", and affected by chondral and osteochondral lesions located at the femoral condyles or trochlea. Exclusion criteria were: lesions at the patella or tibial plateau, osteochondritis dissecans (OCD), and patients with non-corrected misalignment or instability of the knee. Patients presenting infectious, neoplastic, metabolic and inflammatory pathologies, as well as those not able to comply with the required post-operative rehabilitation regimen, were also excluded from this study. Conversely, patients with an axial deviation or an anterior cruciate ligament (ACL) lesion who underwent realignment or ligament reconstruction in the same surgical session as the scaffold implantation were included.

Twenty-four patients were consecutively enrolled and treated and 23 of them (19 men and 4 women) were prospectively evaluated pre-operatively, at 12 and 24 months of follow-up, whereas one patient was lost to follow-up. Mean age was  $38.0 \pm 8.2$  years and average BMI was  $25 \pm 2.9$ . Five patients had multiple lesions, making a total of 29 defects treated, located as follows: 12 medial femoral condyle (MFC), 9 lateral femoral condyle (LFC), 6 trochlea, plus 1 tibial plateau and 1 patella lesion that were included and treated as secondary lesions. Average defect size was  $3.2 \pm 1.9$  cm<sup>2</sup>. Etiology was rated as microtraumatic or degenerative in 18 cases, and traumatic (not acute) in 5 cases. Seven patients were surgically treated for the first time, whereas 17 patients had undergone previous surgeries (6 of them had previous cartilage surgery): 11 meniscectomy, 6 ACL reconstruction, 4 microfracturing, 4 debridement, 1 loose body removal, 1 tibial plateau fracture treatment, and 1 autologous chondrocyte transplantation. In 17 patients other procedures were performed at the same time as surgery: 4 ACL reconstruction, 3 meniscal scaffold implantation, 2 meniscectomy, 1 loose body removal, 2 high tibial osteotomy, 2 distal femoral osteotomy, 1 meniscal allograft implantation, 1 microfracturing, and 1 postero-lateral corner repair.

### *Surgical procedure*

The surgical procedure was performed with the patient under general or spinal anesthesia and in the

supine position with a pneumatic tourniquet around the proximal thigh. The defects were exposed through medial or lateral mini-arthrotomic para-patellar approach and prepared with an osteotome by removing the sclerotic subchondral bone. An 8-mm-deep lodging with perpendicular sides was created to allow press-fit fixation of the implant [12]. Stability was then visually tested by cyclic bending of the knee, both before and after tourniquet removal.

### *Patients evaluation*

The patients were prospectively evaluated preoperatively and postoperatively at 12 and 24 months of follow-up. The clinical outcome was assessed for each patient using the Cartilage Standard Evaluation Form as proposed by the ICRS (International Cartilage Repair Society) [13]. The sport activity level was analysed with the Tegner score and compared with pre-operative and pre-injury values.

Also, magnetic resonance imaging (MRI) evaluation of the implant was performed for 26 defects in 21 patients at 12 months and 21 lesions in 16 patients at 24 months of follow-up. Examinations were performed using a 1.5-T superconducting magnet (General Electric Co, Fairfield, Connecticut) with a dedicated quadrature detection knee coil (Quadknee; diameter, 18 cm), using the same sequences previously described for this imaging analysis [14]. The MOCART scoring system was applied for the evaluation of the implant at follow-up times [15]. The evaluation was performed in consensus by an orthopaedic surgeon and a musculoskeletal radiologist both experienced in cartilage procedures, who blindly assessed and reviewed the images.

### **Statistical methods**

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 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 Friedman non parametric test, followed by the Wilcoxon post hoc pairwise comparison corrected by Bonferroni method for multiple comparisons, was used to the differences at different follow-up times of not normally distributed scores. The ANOVA test was performed to assess the between groups differences of continuous, normally distributed and homoscedastic data, the Mann Whitney test was used otherwise. The ANOVA test followed by the Scheffè post hoc pairwise comparison was used also to assess the among groups differences of continuous, normally distributed and homoscedastic data, the Kruskal Wallis test followed by the Mann Whitney test with the Bonferroni correction for multiple comparison was used otherwise. The Spearman rank Correlation was used to assess correlation between continuous data. The Kendall tau correlation was used to assess correlation between ordinal data. The Pearson Chi square test evaluated by Exact Methods for small samples was performed to investigate the relationships between grouping variables. The analysis on the MRI findings were evaluated by the Monte Carlo method for small samples. 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**

No major adverse events were reported in the present series, besides two patients who required knee mobilization under narcosis, respectively 2 and 4 months after surgery, due to articular stiffness. Two patients (8.3%) failed, according to a more comprehensive definition [16] including both surgical and clinical criteria, being re-treated due to persistent symptoms within the follow-up period.

The patients significantly improved in all the clinical scores adopted. In detail, the IKDC subjective score increased from  $42.8 \pm 13.8$  at basal evaluation to  $74.3 \pm 17.4$  at 12 months ( $p < 0.0005$ ), being stable ( $74.9 \pm 20.4$ , n.s.) up to the final follow-up of 24 months (Fig. 1). The Tegner score showed a statistically significant

improvement in sports activity from

$3.3 \pm 2.7$  pre-operatively to  $4.6 \pm 2.2$  at 12 months ( $p < 0.005$ ), with stable results at the final evaluation ( $4.7 \pm 2.1$ ; n.s.). However, the activity level at follow-up was significantly lower than that before injury ( $6.1 \pm 2.6$ ;  $p = 0.004$ ) (Fig. 2).

A positive trend was also recorded by analysing the IKDC objective score. At the basal evaluation 12 knees (64.5%) were considered “normal” or “nearly normal” (6 grade A, 6 grade B). At the 12 months’ evaluation a significant improvement was documented: 21 knees (14 grade A; 7 grade B) were considered “normal” or “nearly normal” (93.3%;  $p < 0.0005$ ). This result was later confirmed at the final follow-up evaluation (19 “normal” or “nearly normal” knees of which 13 were grade A and 6 grade B).

A further analysis was performed to identify patient characteristics that might influence the clinical outcome. The following parameters did not correlate with the clinical results in this series: sex, BMI, lesion size, lesion site, and aetiology, concurrent or previous surgeries, while a significant difference in terms of IKDC subjective score improvement was shown for patients under 40 years old, who had better results ( $86.7 \pm 9$  vs  $67.3 \pm 22$ , respectively  $p = 0.037$ ) (Fig. 3).

Twenty-six lesions in 21 patients and 21 lesions in 16 patients were evaluated by MRI at 12 and 24 months, respectively. At 12 months the MOCART parameters showed a complete filling of the cartilage layer in 65.3% of the lesions, complete integration of the graft in 76.9% of cases, intact surface of the repair tissue in 38.5% of the cases, homogeneous structure of the repair tissue in half of the cases, and iso-intense graft signal intensity with the adjacent native cartilage in 69.2% of the cases, independently from the sequence used. Subchondral bone alterations were present in 42.3%, and the lamina was intact in only 2 sites (7.7%). One patient had adhesions (3.9%), whereas effusion was observed in 65.4% of the cases. At 24 months a complete filling of the cartilage was shown in 61.9% of the lesions, complete integration of the graft was detected in 66.7% of cases, the repair tissue surface was intact in 57.1%, while its structure was nonhomogeneous in 61.9% of the cases. The graft signal intensity was iso-intense with the adjacent native cartilage in 57.1% and 66.6% of the cases in dual T2-FSE and 3D-GE-FS sequences, respectively. Subchondral bone alterations were observed in 57.1% of the cases, and the subchondral lamina appeared intact in 2 cases (9.5%). No adhesions were shown and 57.1% had some effusion. Finally, the total MOCART score was stable between 12 and 24 months of follow-up ( $72.9 \pm 13.6$  and  $70.8 \pm 13.2$ , respectively), and no correlation was found for either the MOCART variables and total score with the clinical parameters.

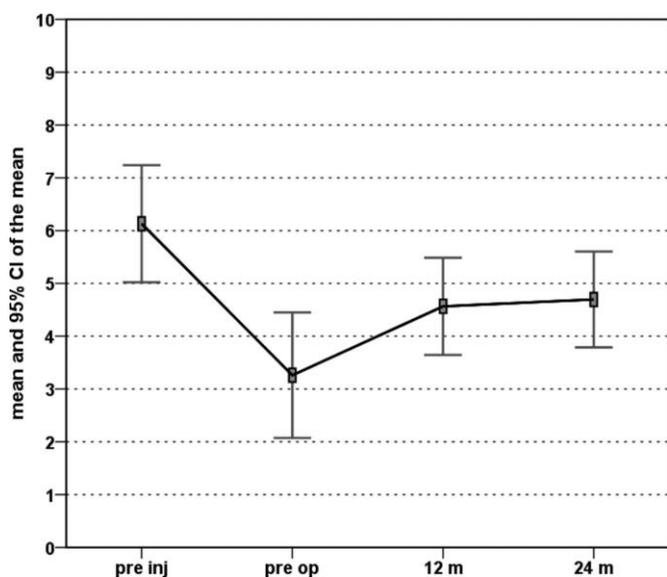
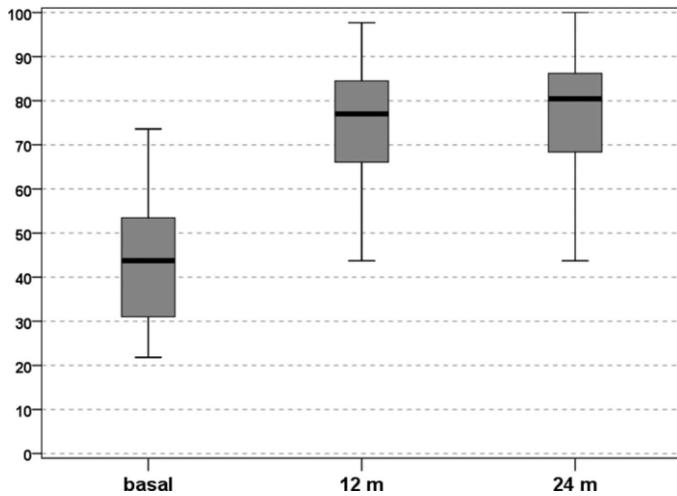


Fig. 1. IKDC subjective score evaluation up to 24 months of follow-up.



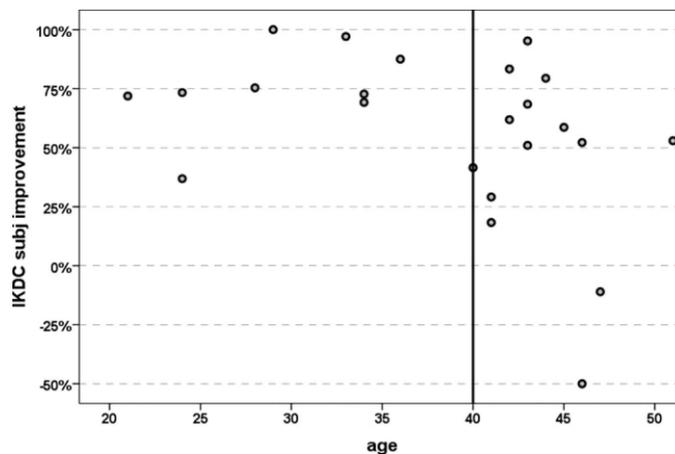
**Fig. 2.** The Tegner score significantly improved from pre-operative level, even if remained significantly lower than the pre-symptoms value.

## Discussion

The main finding of the present study is that the implantation of this osteochondral scaffold offered satisfactory results at short-term follow-up and may therefore be a possible treatment solution for patients affected by Early OA of the knee.

Since their introduction into the clinical practice two decades ago, regenerative approaches have shown they can promote the restoration of a hyaline-like articular surface [17] with satisfactory clinical outcomes [18,19]. In particular, the literature reports that these techniques may be successfully applied in young active patients with large chondral lesions, whereas limits emerged when applied to degenerative or complex joint disease [20-22].

Tissue engineering applied to the treatment of articular degenerative lesions presents some additional problems: healthy tissues are key to provide stable sides for the implant, whereas in a degenerative process the surrounding areas may be involved, thus limiting the stability of the graft, and the altered



**Fig. 3.** Age differences: patients under 40 years old had better IKDC subjective score improvement.

joint environment may hinder the offered outcomes [23,24]. Preclinical trials have shown that a disturbed joint environment produces unfavorable conditions for tissue regeneration, with a negative

influence on cartilage formation [25-27]. Rodrigo et al.

[26] found that synovial fluid contains factors able to stimulate chondral healing in the acute period following traumatic injury, whereas it has inhibitory effects when the lesions turn chronic.

However, some authors have shown that regenerative procedures may still produce satisfactory results also in joints affected by degenerative changes. Hollander et al. [28] observed tissue regeneration even for implants inside OA joints, and laboratory studies confirmed the potential usefulness of regenerative procedures in joints with degenerative lesions, even when the osteoarthritic process has already started [29,30], thus suggesting that OA does not inhibit the regeneration process and justifying a possible clinical use [29].

Interesting findings have been reported using regenerative procedures in humans. Minas et al. [20] treated 153 patients with autologous chondrocyte transplantation (ACT) for early-stage OA. Good function was observed at 5 years in 92% of them, thus delaying the need for joint replacement. Ossendorf et al. [31] reported pain, symptoms, and quality of life improvement after the implantation of a polymer-based autologous cartilage graft for mild degenerative cartilage lesions or focal knee OA defects. Subsequently, Kreuz et al. [32] confirmed stable results for 4 years, with a significant improvement in the patients' condition and a good defect filling on MRI. However, Filardo et al. [22] analysed the clinical outcome of patients treated with 2<sup>nd</sup> generation ACT for small or medium isolated degenerative knee cartilage lesions, with no signs of OA, and showed poorer results and higher failure rates than those reported in not degenerative patient populations [32-34], and even worse results have been reported by the same group treating focal lesions in OA joints [21]. Finally, Nehrer et al. used MACT as a salvage procedure for patients with kissing lesions or early OA changes, previously treated for the same cartilage defect, and found 87.5% of failures in this category [35].

A possible reason for the poor reported outcome with cartilage regenerative procedures in degenerative lesions is the long time lapse between cartilage damage and onset of the clinical symptoms, which is likely in case of OA changes and may result in treatment delay, that has been shown to be a factor limiting the success of regenerative procedures [34]. In fact, in degenerative lesions an imbalance of joint homeostasis has already occurred with subchondral bone involvement in the pathologic changes [27,36].

Recently, the development of biomaterial technology has led to new constructs, thus offering the possibility to treat subchondral bone disease by implanting multi-layered scaffolds designed to provide the regeneration of cartilage and bone tissues, both altered in a degenerative joint environment [9]. A previous comparative study showed that the same osteochondral scaffold used in this series produced better results than a chondral one for the treatment of complex knee lesions [37], and promising findings had been reported even in unicompartamental OA patients [38].

The results of this study confirm the potential of this cell-free multi-layer scaffold in providing a successful outcome in early OA joints. Nonetheless, patients presented mainly a partial improvement and the overall results are poorer than those previously reported using the same procedure in different groups of patients [12,39,40]. Thus, although an osteochondral scaffold may be successful in restoring the damaged articular surface, this approach may not take into account other important aspects key for a complete success in this patient population. Results are probably limited by the degenerative and inflammatory changes that affect the entire environment of a joint that has already undertaken the path of OA [2], thus making a treatment of the damaged articular surface, even with the correction of concurrent biomechanical alterations, inadequate to address the multiple targets related to the disease.

Moreover, early OA typically affects patients in an age range where the biological healing potential may be already reduced. The importance of age has been confirmed in this series, where older patients presented a reduced clinical improvement. This is not surprising, since the potential of cartilage procedures, in particular in case of a cell-free approach, relies on the body's self-renewing potential, which is an age-related feature [41]. Age leads to degenerative changes in all cartilage elements [42], thus impairing its properties and healing potential [43]. Accordingly, older patients have traditionally been excluded from regenerative treatment recommendations, and only a few studies report results in this patient population thus confirming the limited outcome regardless of the surgical technique used.

Microfracturing (MF) produces age-dependent results and a greater improvement in patients younger than 35 years, as observed by Steadman et al. [44]. Moreover, Kreuz et al. [41] reported poorer clinical results in patients over 40 years old. Marcacci et al. found a better clinical and functional outcome in younger patients treated with mosaicplasty procedure [45], so did Gudas et al. [46].

Similarly, even though cell-based regenerative approaches have been successfully tested in older patients, they offered poorer outcomes than those expected for younger ones. Kon et al. used MACT in non-OA patients over 40 years old [47], with a significant improvement in all scores at medium-term follow-up, but inferior results and higher failure rates with respect to younger study populations. Knutsen et al. reported better clinical outcomes in active and younger (<30 years) patients [48], who had either undergone MF or ACT. Krishnan et al. used collagen-covered ACT for the treatment of 199 patients, with a negative correlation between clinical result and older age [49]. More recently, this age dependency was confirmed by de Windt et al. [50] when analysing microfracture or 1st or 2nd generation ACT at the knee, and reported a better clinical improvement in patients under 30 years old.

Although most authors agree that the outcomes of different cartilage procedures are age-dependent, there is no agreement on a precise age cutoff, and thresholds vary in different studies. This may be due to the fact that the biological stage of the joint may be as important as the patient age itself. With regards to this, a new classification was proposed for “Early” OA, to focus better on the status of the affected joint, by identifying patients before the “point of no return”. This might be a key aspect for a positive clinical result, rather than age, as suggested also by the interesting results obtained by other authors in older patients affected by cartilage lesions [51]. This paves the way to successfully defining a patient category with older age but who can still benefit from biological procedures to improve symptoms and delay further joint degeneration.

This study shows that this patient category may benefit from a biological reconstruction, even though the partial improvement documented underlines the complexity of the early OA environment, with degenerative processes that may have already affected the whole joint. Inflammatory, cellular or molecular factors, are involved in OA development [27], and cytokine secretion [52] from degenerative tissues around the implant might cause dedifferentiation or apoptosis and impair the quality of the regenerative tissue [53]. Thus, an increased knowledge of the whole joint degenerative biochemical environment is crucial to develop integrated treatments, able to improve the obtainable clinical outcome by addressing both the osteochondral unit and the intra-articular homeostasis. In the meanwhile, until new integrated approaches have been developed, the indication of this cell-free osteochondral scaffold implantation for early OA joints should be limited and considered as a salvage procedure for compromised knees of young patients, otherwise doomed to more invasive and sacrificing procedures.

This study presents some weaknesses: first, it lacks histological evaluations. However, this is a preliminary study testing the effects of a scaffold-based regenerative treatment in a group of patients affected by Early OA, with most of the patients having a significant clinical benefit in the short-term after the implantation of this osteochondral substitute. Moreover, MRI findings showed the presence of several abnormal findings. However, the MOCART evaluation of the MRI scans showed stable results between 12 and 24 months of follow-up. Accordingly with most of the available Literature [54,55], we have found a lack of correlation between the clinical outcome and MOCART parameters: MRI is a useful and easy tool to evaluate the repair tissue, but its role in predicting or reflecting the clinical outcome is questionable. The available MRI scoring systems have been specifically focused on the chondral layer, thus they don't take sufficient account of the complexity of osteochondral regenerative procedures. Maybe new scoring tools or the use of CT scans might give a better evaluation of tissue quality and clinical significance.

A further weakness is the relatively high number of combined surgical procedures, that may confuse the evaluation of the scaffold implantation, thus making it difficult to determine whether the clinical benefit is related to osteochondral defect treatment or to the concurrent procedures. However, OA is a multifactorial disease and chondral lesions are frequently a combined feature in this pathology, thus this kind of patient is unlikely to be found with isolated lesions and the patients documented in this

study reflect those found in the clinical practice. The lack of a control group is another weak point. Finally, longer follow-up studies are needed to evaluate whether the positive outcomes obtained remain stable over time. However, despite the above-mentioned limitations, this study is the first one to focus on this specific patient population treated with this osteochondral scaffold, and demonstrate that this approach may provide a clinical improvement for the treatment of cartilage defects in an early OA degenerative context. This is particularly relevant considering that even small and isolated defects of the articular surface can lead to more extensive joint damage [56, 57] and accelerate the degenerative process of the entire joint. Thus, the surgical treatment of chondral lesions in early OA patients may be useful not only for pain relief, but also to avoid or delay further joint degeneration and the need for joint replacement. Nonetheless, we recommend giving patients realistic expectations when considering this surgical approach for early OA joints.

## Conclusion

The implantation of this cell-free osteochondral scaffold offered satisfactory results at short-term follow-up and may therefore be a possible treatment solution for patients affected by early OA of the knee. However, patients presented mainly a partial improvement and the overall results are lower than those previously reported using the same procedure in different group of patients. Until new integrated approaches are developed to address all the factors responsible for the altered environment of degenerated joints, the indication of this treatment for early OA joints should be limited and considered as a salvage procedure for compromised knees of young patients.

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