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# Good clinical results but moderate osseointegration and defect filling of a cell-free multi-layered nano-composite scaffold for treatment of osteochondral lesions of the knee

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**Abstract**

*Purpose* The aim of this retrospective study was to evaluate the clinical and radiological results of a nano-composite multi-layered three-dimensional biomaterial scaffold for treatment of osteochondral lesions (OCL) of the knee. It was a particular radiological interest to analyse the osseointegration, filling of the defects and the bone tracer uptake (BTU), and it was hypothesised that this scaffold, which was created to mimic the entire osteo-cartilaginous unit, is integrated within the bone 12 months postoperatively and comes along with improved patients symptoms and function.

*Methods* Fourteen patients (male:female = 11:3, mean age ± SD 33.1 ± 10.7 years) treated for OCL (size 1.0–3.5 cm$^2$) were clinically and radiologically evaluated at 1 year postoperatively. The data were prospectively collected including SPECT/CT, Tegner and Lysholm scores. BTU was anatomically localised and volumetrically quantified in SPECT/CT. Defect filling was analysed in CT. Spearman's rho and Wilcoxon test were used for correlation of BTU in SPECT/CT and clinical scores ($p < 0.05$).

*Results* A significant improvement in Lysholm knee score ($p < 0.001$) and slight deterioration in Tegner score were found ($p < 0.01$). A complete filling of the defect was shown in 14%, a partial filling in 14% and only minor filling was seen in 72%. A significant correlation ($p < 0.001$) was found between location of osteochondral lesions and increased BTU. At the lesion sites pre- and postoperative BTU was markedly increased and did not show any decrease at 12-month follow-up. Median Tegner and mean Lysholm scores did not correlate with BTU at any time.

*Conclusions* Treatment of OCL in the knee joint with a nano-composite multi-layered three-dimensional biomaterial scaffold resulted in a significant clinical improvement at 1-year follow-up. However, osseointegration was still ongoing at 12-month follow-up.

*Level of evidence* Case series, Level IV.

**Keywords** SPECT/CT · Knee · Osteochondral scaffold · Articular cartilage resurfacing · Osseointegration · Osteochondritis dissecans · Osteochondral lesion · Cartilage repair · Cartilage surgery

## Introduction

Various surgical treatment options such as Pridie drilling, open or arthroscopic fixation using screws or pins, excision of the osteochondral fragment, microfracturing, osteochondral grafting (with autograft or allograft), and autologous chondrocyte implantation (ACI) as well as tissue-engineered construct (TEC) derived from synovial mesenchymal stem cells (MSCs) and hydroxyapatite artificial bone have been proposed as treatment for osteochondral lesions (OCL). However, to date there is a common gold standard

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yet to be established [1, 2, 4, 10, 11, 17, 35, 36, 52–54, 57, 60].

Pure fragment excision leaves a clinically relevant defect. Pridie drilling or microfracturing also leaves the defect mostly unfilled, and clinical results are not promising for OCL [5, 44, 59]. The problem of ACI is the fact that it needs to be done in a sandwich technique and also requires a two-stage setting. To date, there is insufficient evidence for the superiority of ACI to other treatment strategies for treating OCL in the knee [5, 7]. Allografts have a low availability in many European countries, whereas in the USA fresh allograft tissue is commonly available [22]. Autografts come along with a considerable harvesting morbidity [48].

For these reasons, biomimetic scaffolds were introduced for treatment of OCL. The theoretical advantage is that these scaffolds are commonly available off the shelf and can be implanted in a one-stage surgery. The scaffold used in the present study is a cell-free three-layered collagen–hydroxyapatite biomimetic scaffold. Excellent short-to-midterm results were reported [20, 39, 51, 58].

Few authors have also evaluated the osteochondral repair potential of this biomimetic scaffold using MRI [8, 13, 16, 21, 39, 40]. Some authors found no improvement at any time point [13], others found improved MOCART values over time [8, 21, 39, 40].

In the last decades, single photon emission computerised tomography/computerised tomography (SPECT/CT), which as a three-dimensional hybrid imaging modality consists of a 3D bone scan and a conventional CT, has been increasingly used in patients with painful knees [25–28, 30–34, 49, 55, 56]. In particular, its ability to visualise the in vivo bone loading and to correlate such findings to biomechanical considerations has been highlighted [25, 32, 33, 47, 49, 50]. In contrast to MRI, SPECT/CT is able to provide information on alignment, structural pathologies, osseous physiology and metabolism together [12, 30]. In recent studies of Konala et al. [42] and Hirschmann et al. [27], the diagnostic value of SPECT/CT in patients who underwent treatment for OCL was highlighted. The scaffold used consists of hydroxyl-apatite and collagen, and osseointegration of this scaffold can be monitored by SPECT/CT as the tracer is targeted towards hydroxyl-apatite produced by active osteoblasts.

A combined evaluation of osseointegration and clinical results of cell-free multi-layered nano-composite scaffold for treatment of osteochondral lesions of the knee using SPECT/CT is yet lacking in the current literature.

The aim of this retrospective study was to evaluate the clinical and radiological results of a nano-composite multi-layered three-dimensional biomaterial scaffold for treatment of osteochondral lesions (OCL) of the knee. It was a particular radiological interest to analyse the osseointegration, filling of the defects and the bone tracer uptake (BTU), and it was hypothesised that this scaffold, which was created to mimic the entire osteo-cartilaginous unit, is integrated within the bone at 12 months postoperatively and comes along with improved patients symptoms and function.

## Materials and methods

Fourteen consecutive patients (mean age ± standard deviation 33 ± 10 years, range 18–47 years, right:left = 6:8, 11:3 = male:female) with knee pain due to OCL and with International Cartilage Repair Society (ICRS) grade 3 to 4 chondral and osteochondral lesions of the knee, as evaluated by MRI and confirmed intraoperatively, were included. All patients presented to a specialised knee clinic from 2010 to 2012. Osteoarthritis was graded preoperatively according to Kellgren–Lawrence, and patients with Kellgren–Lawrence >2 were excluded.

The defect size of the treated lesions determined during surgery was 1.0–3.5 $cm^2$. OCLs involved the medial femoral condyle in eight patients and in each two patients the trochlea, the lateral femoral condyle and patellar facet.

SPECT/CT was used to evaluate fourteen patients after and ten patients before scaffold implantation. Restoration of the subchondral bone plate was described as no (<25%), partial (25–75%) and complete (75–100%). At 1-year SPECT/CT evaluation, a complete filling of the defect was shown in 14%, a partial filling in 14% and only minor filling was seen in 72%.

Four patients received an isolated filling of the osteochondral defect using a cell-free three-layered biomimetic scaffold, while ten patients had undergone the following associated treatments: Six patients underwent high tibial valgus osteotomy (one patient additional medial meniscal repair), one patient isolated medial meniscal repair, one patient tuberosity osteotomy, one patient autologous chondrocyte implantation and one patient ACL reconstruction and lateral meniscal repair.

In all patients, a cell-free three-layered biomimetic scaffold (MaioRegen Finceramica, Faenza S.p.A., Italy) was used for reconstruction of the osteochondral defect. The scaffold consists of a porous nano-structured three-layered biomimetic matrix designed to mimic the physiological osteochondral tissue. Being resorbable, it is thought to facilitate the regenerative process by being gradually replaced by native tissue [39].

After an arthroscopic evaluation of the knee, a medial or lateral parapatellar arthrotomy was performed to expose the OCL. The sclerotic subchondral bone was partially removed using an osteotome, and the host bone was prepared to a depth of 8 mm. The scaffold was cut and sized and then implanted press fit into the defect.

After surgery, all patients underwent a standardised treatment protocol following the implant producing company's guidelines: Early mobilisation using continuous passive motion and weight bearing was limited to maximum 15 km for 6 weeks. At this time, active functional training was started allowing full weight bearing.

Clinical outcome measurements were performed preoperatively and at 12 months after the surgery using the Tegner score and Lysholm knee score. In all cases, SPECT/CT was performed 12 months pre- and postoperatively. SPECT/CTs were prospectively collected and retrospectively analysed using a standardised protocol. All patients received a 500–700-MBq Technetium 99 m hydroxymethylene diphosphonate (HDP) injection (Malinckrodt, Wallerau, Switzerland). SPECT/CT was performed using a Symbia T16 (Siemens, Erlangen, Germany), which consists of a pair of low-energy, high-resolution collimators, a dual-head gamma camera and an integrated 16-slice CT scanner (collimation of 16 × 0.75 mm). A standardised imaging protocol was used which was based on the Imperial Knee Protocol [23]. CT slice thickness was 0.75 mm. SPECT was performed in the delayed phase three to four hours after bone tracer injection (matrix size, 128 × 128; angle step, 32; and time per frame, 25 s). BTU on SPECT/CT was analysed using a specialised software allowing 3D volumetric quantitative analysis of SPECT data [34]. A recently validated localisation scheme for anatomical localisation of the SPECT/CT tracer activity was used (Fig. 1) [50]. Maximum intensity values of BTU in each area of interest were volumetrically recorded. In a previous study, the localisation of BTU in an anatomical scheme and grading of BTU showed excellent intra- and inter-observer reliability [50].

Osseointegration of the scaffold into host bone and defect filling was evaluated at 1 year postoperatively in SPECT/CT by a musculoskeletal radiologist.

All patients gave their informed consent, and the study was approved by the local ethical committee (EK 2015-396).

### Statistical analysis

Data were analysed using IBM SPSS Statistics for Windows 22.0 (Armonk, NY: IBM Corp.). Wilcoxon signed-rank test was used as a non-parametric paired difference test for analysis of SPECT/CT bone tracer uptake and clinical outcome measures. To investigate relationships between two variables, Spearman's rank correlation analysis was performed. The threshold of significance was set at a $p$ value less than 0.05.

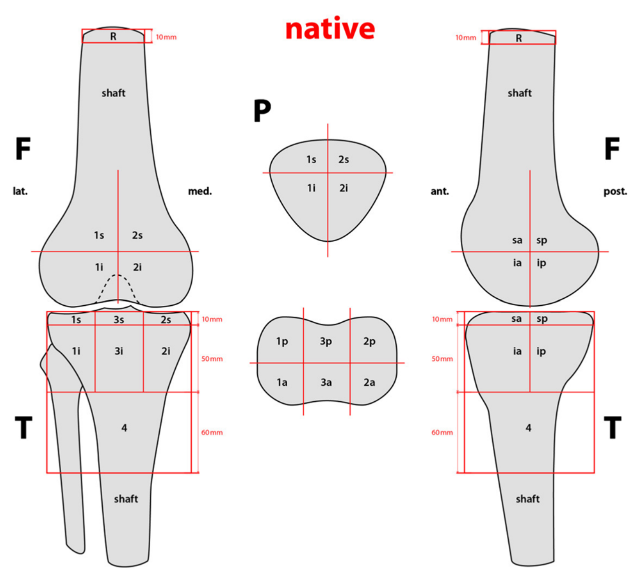


**Fig. 1** Mapping scheme used for localisation of areas of increased SPECT/CT tracer uptake values in native knees. *F* femur, *T* tibia, *P* patella, *R* reference zone, *1* medial, *2* lateral, *3* tibial intercondylar area, *4* distal plate area, *s* superior, *i* inferior, *a* anterior, *p* posterior

A post hoc power analysis showed the number of 14 patients to be sufficient to detect a moderate one-sided significant Spearman's correlation of rho ≥0.45 between BTU and clinical findings.

## Results

A statistically significant improvement in Lysholm knee score was found between preoperative and 1-year follow-up. The mean Lysholm score was 65.6 ± 12.6 before surgery and 90.1 ± 10.0 after 1 year ($p < 0.001$) (Fig. 2). The median Tegner score was 6.0 (range 3–9) before surgery and 4.5 (range 2–9) after 1 year ($p < 0.01$) (Fig. 3).

A high correlation ($p < 0.001$) was found between the location of OCL and increased BTU. Compared to the non-affected anatomical regions of the knee joint, the OCL showed significantly increased BTU pre- and postoperatively (Fig. 4). Comparing BTU values of the OCL pre- and postoperatively, there was no difference (mean 6.3 ± 3.9, respectively, 6.0 ± 4.4) (Figs. 5, 6).

Higher BTU values did not correlate with lower Tegner or Lysholm scores, neither pre- nor postoperatively.

## Discussion

The most important findings of the present study were the following: The use of the biomimetic scaffold for treatment of OCL led to good clinical functional outcomes with

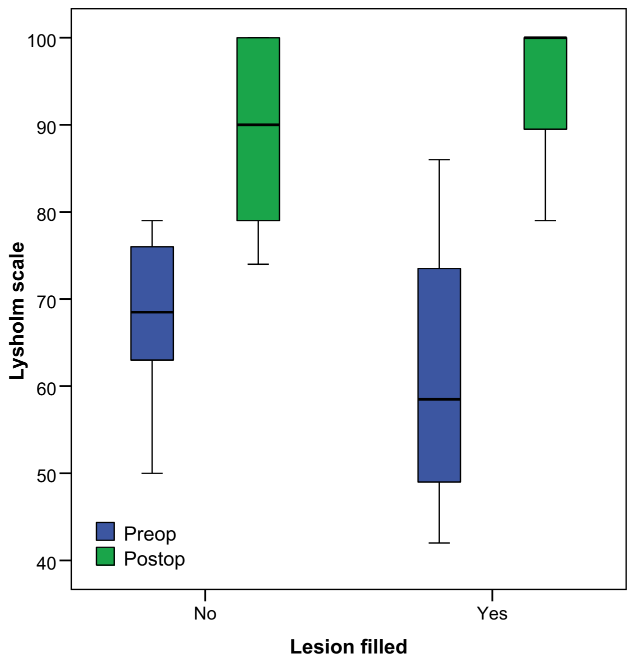


**Fig. 2** Box plot shows the improvement in the Lysholm score from pre- to postoperatively ($p < 0.001$) in relation to the filling of the osteochondral lesion (lesion filled yes/no)

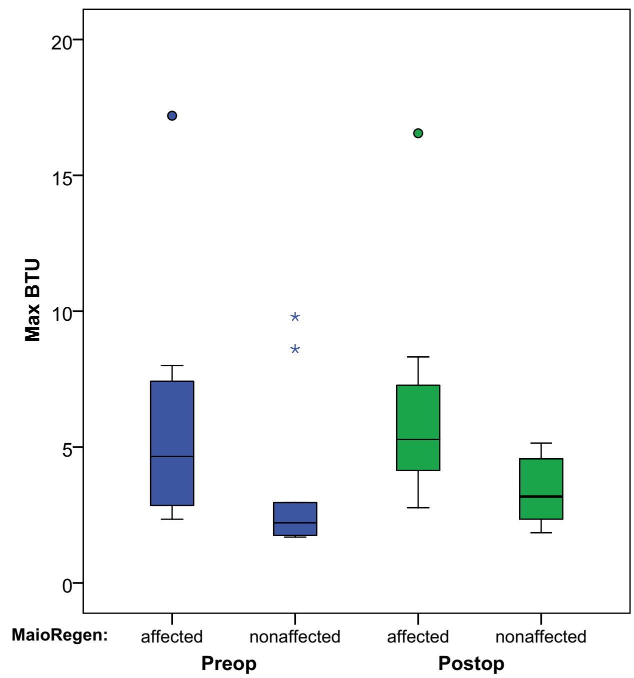


**Fig. 4** Box plot shows increased maximal bone trace uptake in the lesion site pre- and postoperatively ($p = 0.017$ and 0.001)

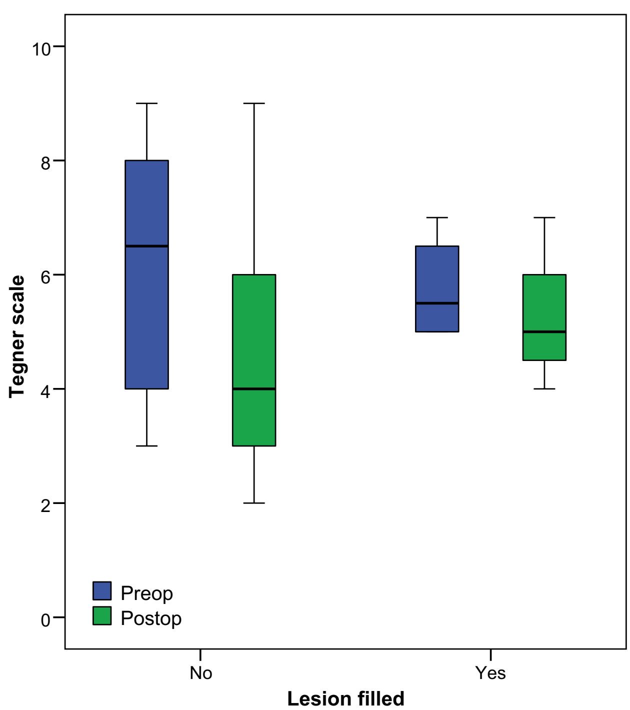


**Fig. 3** Box plot shows the Tegner score deterioration from pre- to postoperatively ($p < 0.01$) in relation to the filling of the osteochondral lesion (lesion filled yes/no)

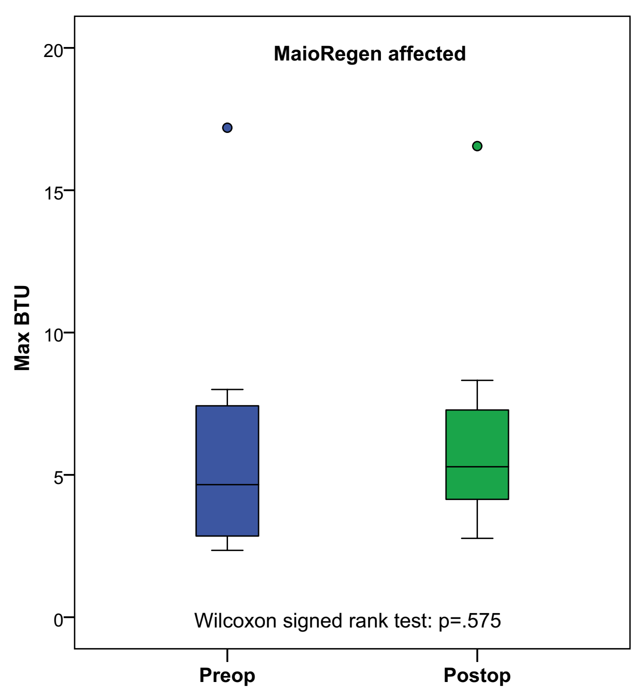


**Fig. 5** Maximal BTU between pre- and postoperatively do not result in statistically significant differences

regard to the Lysholm score, which is in agreement with previous studies [8, 13, 37, 39, 41]. In contrast, the sport and daily activity represented by the Tegner score slightly

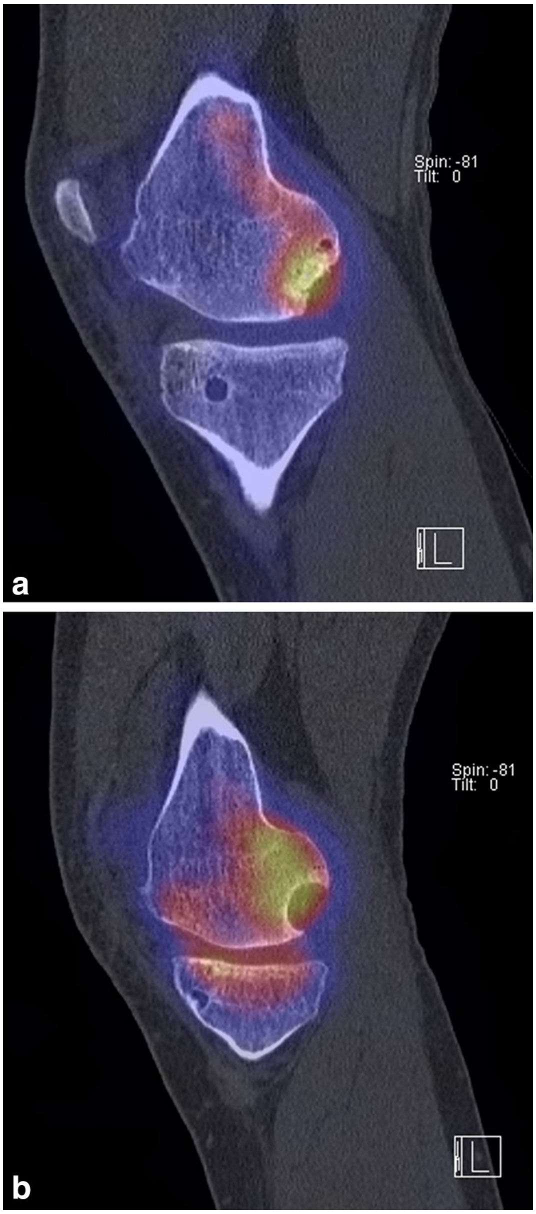


**Fig. 6** SPECT/CT images in sagittal view of the same patient preoperatively (**a**) and at 1-year follow-up (**b**) indicating increasing maximal BTU at the lesion site ($p < 0.001$)

decreased, which might be due to two reasons. One is the fact that the follow-up time was rather short and it could be expected that there is still an increase in activity level over time. The second reason is that subchondral bone restoration is not entirely completed at this time [16, 21, 40]. This hypothesis is confirmed by the BTU findings and incomplete defect filling in SPECT/CT.

Increased BTU in and around the OCL site entails ongoing healing of the OCL through subchondral bone formation and remodelling. The bone tracer used is directed towards hydroxyl-apatite produced by active osteoblasts, representing increased loading and remodelling of the subchondral bone [14, 19, 27]. Histology of the subchondral bone in areas with increased BTU shows increased vascularity and new bone formation [6]. This is in line with an experimental study, which showed how the scaffold used is able to integrate within the bone and surrounding tissues. The authors further reported the regeneration of the entire damaged osteochondral unit including formation of bone and hyaline-like cartilaginous tissue [38, 58].

In most of the previous studies, MRI was used for morphological evaluation based on the MOCART scoring system [45]. To our knowledge, only few authors have compared MRI and SPECT/CT in patients after knee surgery [9, 24, 42, 43, 46]. It is a pertinent question what the pathophysiology behind BTU in SPECT/CT and bone oedema in MRI is and whether these represent similar or different windows into the underlying pathology. In a study comparing BTU in bone scans and bone oedema in MRI, Buck et al. [9] found that there is a correlation of both, but there are also patients with increased BTU and normal bone marrow signal. The study was done in patients complaining about chronic medial knee pain, which is a comparable patient sample as in the present study. BTU might be increased due to increased loading or due to a cartilage lesion. In traumatic cartilage lesions, MRI shows huge areas of bone oedema in the underlying subchondral bone. However, in chronic conditions the findings are not that consistent, which has been shown by Buck et al. SPECT/CT has a more important role in chronic knee joint conditions.

A study of Dordevic et al. [18] showed a significant correlation of BTU in SPECT/CT with the degree and size of chondral lesions on MR images. Based on those findings, the correlation of increased BTU with OCL in this study may in connection with the incomplete reconstruction of the subchondral bone indicate the ongoing osseointegration 1 year postoperatively.

Whereas others found a complete filling of the osteochondral defect and complete osseointegration of the scaffold [8, 21, 39, 40], in the present study only a minority of patients (14%) showed a complete filling of the OCL defects or restoration of the subchondral bone plate at 12-month follow-up. Similar findings have been reported by Christensen et al., who have investigated the defect filling in OCL patients treated with the same scaffold using CT at 1 and 2.5 years postoperatively [13]. It appears that with the use of the scaffold used only minor defect filling can be achieved at 12-month follow-up. Clearly, the osseointegration process is not completed, and more time is needed for full osseointegration.

No direct correlation between BTU in SPECT/CT and outcome scores was found, which might be due to the small sample size. In addition, previous studies were not able to establish a clear correlation between clinical and radiological outcomes [15, 16, 21, 39, 40]. However, controversial results have been published in recent studies analysing the clinical value of SPECT/CT in patients with knee pain [3, 28, 29, 32]. It is currently still unclear whether BTU shows a significant correlation with clinical outcome parameters in patients with OCL. In our opinion, the persistent increased BTU represents an ongoing remodelling process.

The study bears a considerable number of limitations to be acknowledged. Firstly, the sample size was rather small. However, it represents the largest sample ever analysed in vivo osseointegration of the scaffold used. Secondly, the follow-up period is rather short, but this was done to minimise the radiation burden of SPECT/CT in these young patients. Thirdly, there was no control group, patients were variable in terms of OCL locations (femoral condyle, trochlea and patella) and need for additional surgery, which may be a confounding factor.

On the basis of this study, the scaffold used is a valuable single-stage treatment option for patients with OCL, although no entire defect filling and osseointegration were observed. In future, augmentation of cells and growth factors might improve osseointegration.

## Conclusion

This study is the first combined evaluation of osseointegration and clinical results of cell-free multi-layered nanocomposite scaffold for treatment of osteochondral lesions of the knee. Treatment of OCL in the knee joint with the scaffold used resulted in a significant clinical improvement at 1-year follow-up. However, an ongoing defect filling was found at 12-month follow-up.

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**Compliance with ethical standards**

**Conflict of interest** The authors have no conflict of interest.

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**Ethical approval** Ethical approval was obtained from the Ethikkommission Nordwest- und Zentralschweiz (EKNZ, Basel EK 2015-396). All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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

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