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Multilayered biomimetic scaffolds for cartilage repair of the talus. A systematic review of the literature

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ABSTRACT

Objective: The aim of the present review was to analyze the available evidence in the literature on the clinical and radiological outcomes of multilayered biomimetic scaffolds in the treatment of osteochondral lesions of the talus (OLTs).
Design: A systematic search was performed in three databases to identify clinical trials, where the multilayered biomimetic scaffolds were used for the treatment of OLTs. The PRISMA guidelines were followed. Qualitative analysis of the relevant data of the included studies was executed. The methodological quality of the analyzed studies was assessed with a modified Coleman Methodology Score (CMS).
Results: A total of 10 studies with 87 patients were included in the analysis. Only three multilayered biomimetic scaffolds have been investigated in clinical trials for the treatment of OLTs. The worst clinical and radiological outcomes, as well as safety profile were observed for the TruFit scaffold (Smith & Nephew, Andover, MA, USA), which had already been withdrawn from the market. The other two scaffolds (MaioRegen, Finceramica, Italy; Agili-C, Cartiheal, Israel) performed significantly better in the majority of the reviewed studies, especially in the clinical aspect. The radiological findings, the improvements of MOCART scores, the completeness of lesions' fill, and the structure of regenerated tissue were much more inconsistent.
Conclusions: Two of the multilayered biomimetic scaffolds demonstrated an adequate potential in the treatment of complex OLTs. However, limited studies availability and their low level of medical evidence request further high-level investigations before the clinical decision making for such scaffolds in the treatment of OLTs can be defined.

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1. Introduction

Approximate daily incidence of ankle injuries is 1 in 10,000 people [1]. Osteochondral lesions of the talus (OLTs) occur in up to

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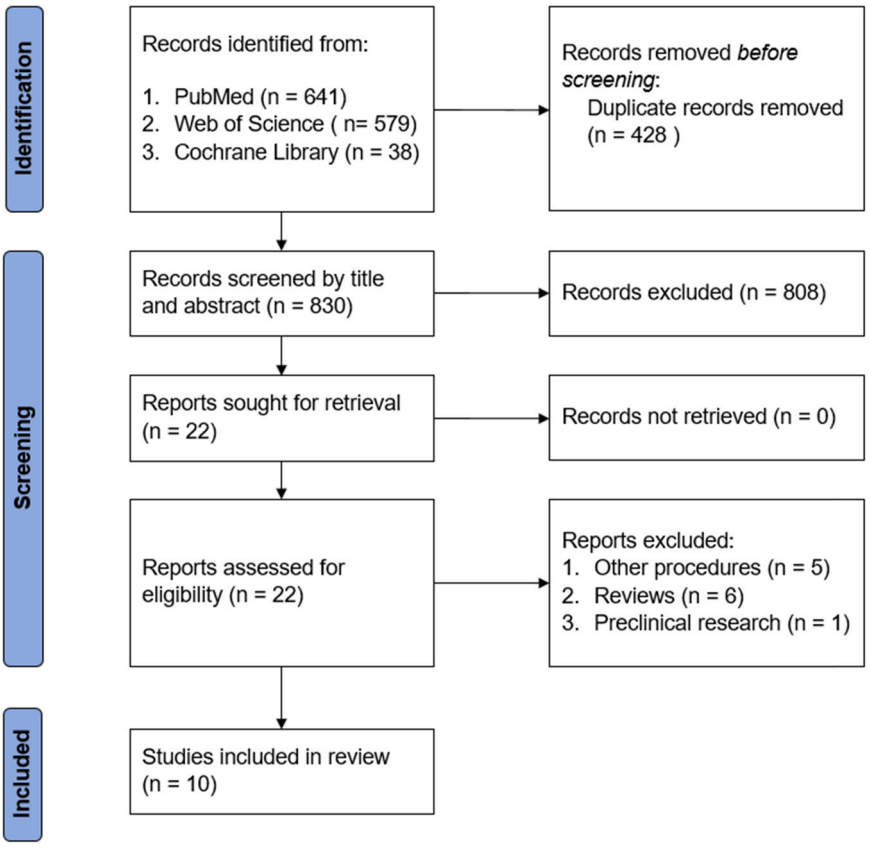

Fig. 1. PRISMA flowchart of the searching and selection process.

70% of acute sprains, and are defined as joint surface lesions affecting both parts of the osteochondral unit, the cartilage and its underlying subchondral bone [2,3]. They may cause debilitating symptoms and present a risk factor for the development of a secondary osteoarthritis, if left untreated [4]. Treatment of articular surface lesions still represent one of the most challenging problems in orthopedic surgery, mostly due to the limited intrinsic capacity of avascular hyaline cartilage to heal and repair [5].

Conservative treatment of cartilage lesions with physiotherapy, immobilization, nonsteroidal anti-inflammatory drugs, and intra-articular injections is offered first, but fails in up to 50% [6]. Operative techniques can be broadly divided into 3 groups: cartilage repair, replacement, and regeneration strategies [7]. Arthroscopic lesion debridement and bone marrow stimulation represents the golden standard for uncomplicated smaller lesions with an area under 1.5 cm^2 [8]. Complex cases, defined as larger, deep or cystic lesions, and revision surgeries typically involve more advanced surgical techniques [9]. Some of the most frequently utilized are: osteochondral autografts, allografts, and partial metal implants. Certain disadvantages in their utilization, such as donor site morbidity of autografts, availability, safety and low biologic potential of allografts, and peri-implant loosening of metals, promoted further developments in the treatment of OLTs [10,11].

The ultimate goal of treating an OLT is to achieve a hyaline-like cartilage restoration fully integrated with surrounding cartilage, and the underlying bone of good quality. Increasing awareness for subchondral bone restoration, as it exhibits crucial role in the cartilage degeneration, has promoted the development of multilayered biomimetic scaffolds [12]. These are advanced constructs of cartilage and bone phases, which provide a temporary 3-dimensional structure, mimicking osteochondral architecture, that favour cartilage and bone restoration in the appropriate parts of the osteochondral unit [13,14]. An implantation of a multilayered scaffold in the ankle mostly requires an open surgical approach with concomitant medial malleolar osteotomy, which is per-se associated to certain disadvantages: (1) direct operative injury to adjacent structures; (2) mid-term malleolar non-union; (3) long-term progression of local cartilage degeneration and osteoarthritis [15].

Only a few multilayered biomimetic osteochondral scaffolds have been approved for a clinical usage: TruFit (Smith & Nephew, Andover, MA, USA), MaioRegen (Finceramica, Faenza, Italy), Agili-C (CartiHeal, Kfar Saba, Israel), BioMatrix CRD (Kensey Nash, Exton, PA, USA), and ChondroMimetic (TiGenix, Leuven, Belgium) [16]. Due to the inconsistent clinical results and lesser performance compared to the other traditional treatments, the TruFit had already been withdrawn from the market. MaioRegen and Agili-C demonstrated promising short- to mid-term results, especially in the knee, and are still investigated in the clinical trials [17]. There has not been reported any clinical data for BioMatrix CRD, while extensive literature search identified one small long-term study with promising clinical and radiological results of ChondroMimetic scaffold in the treatment of mosaicplasty donor sites and femoral condyles cartilage defects [18].

In contrast to the knee, where systematic reviews, meta-analysis and even patient-focused consensus recommendations have already been reported, there has not been published a single review of multilayered biomimetic scaffolds in the OLTs treatment.

The present systematic review therefore aims to elucidate the available literature evidence on the clinical results and safety of multilayered biomimetic scaffolds for the treatment of OLTs.

2. Methods

A systematic review of the literature on the multilayered biomimetic scaffolds for the treatment of OLTs was performed. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed [19]. The search was conducted

on PubMed, Web of Science, and Cochrane databases on February 15, 2022. The following string was applied: (cartilage OR chondral OR osteochondral) AND (scaffold OR matrix OR implant) AND (ankle OR talus). The inclusion criteria were: clinical studies, written in the English language, on multilayered biomimetic scaffolds for the treatment of OLTs. Studies of monophasic/layered scaffolds, reviews and preclinical research were excluded. Initially, all abstracts and titles were screened. For those meeting the inclusion criteria, the full texts were obtained and reviewed to reconfirm their eligibility. A flowchart of the literature screening is presented in Fig. 1.

Relevant data of the included studies (publication year, study design, number of patients, demographic data, location, size and grade of the lesions, type of scaffold, length of follow-up, results, complications) were extracted and presented in the qualitative analysis. The methodological quality of analyzed studies was assessed with a modified Coleman Methodology Score (CMS), which is specially suited for cartilage repair research [20].

The whole process of searching, collecting, reviewing and analyzing the data was performed by the first author (MK) under the supervision of the senior author (MD).

3. Results

The initial search identified 1258 articles. After removal of the duplicates, 830 records were screened by the title and abstract. Based on the inclusion and exclusion criteria, 808 records were excluded, while the remaining 22 articles were sought for retrieval and assessment of full-text versions for eligibility. Further, 12 of them were excluded. Therefore, 10 studies were included in the present review (Fig. 1). The characteristics of included studies are presented in Table 1 [21–30].

The first two studies were published in 2010, one relevant study was published in years 2012, 2013, 2015, 2016, and the last four were released in 2017 and 2021 (two each year). Among the included studies, there were no randomized clinical trials (RCTs) or comparative studies, but only 4 prospective and 5 retrospective case-series, while in one study the type of case-series was not defined as either retro-or prospective. MaioRegen was analyzed in 5 studies, TruFit in 4, while the analysis of Agili-C implant was part of 2 studies. However, in both the same 4 patients were studied, therefore only the results of Drobnič et al. [21], that analyzed Agili-C scaffold selectively, are included in the present review.

In general, the quality of the reviewed studies, evaluated with modified CMS [20], was low, with mean score of 45.8 ± 12.2 (range: 19–61). Only 1 study had higher than 60 CMS score, 4 scored between 50 and 59, 3 between 40 and 49, while 2 obtained CMS score substantially lower than 40.

A total of 87 patients were treated with multilayered biomimetic scaffolds for OLTs and 1 for osteochondral lesion on the distal tibia, and was therefore excluded from the present review. Among the included patients, 4 were treated with Agili-C, 49 with MaioRegen and 34 with TruFit scaffolds. 3 studies reported outcomes at short-term (≤ 24 months), 6 at mid-term (24–60 months) and 1 at long-term follow-up (≥ 60 months).

Many different clinical scores (PROMs; Patient Reported Outcome Measures) were used for the evaluation of patients. The most frequently was used American Orthopedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Score [31], which was applied in 6 studies, Pain on Visual Analogue Scale (VAS-Pain) [32] and Tegner Activity Scale (TAS) [33] in 3, Foot and Ankle Outcome Score (FAOS) [34], EQ-5D [35] and 36-Item Short Form Health Survey (SF-36) [36] in 2, while Foot and Ankle Disability Index (FADI) [37], Mazur score [38], Ankle Osteoarthritis Score (AOS; pain/disability) [39] and Foot Function Index (FFI; pain/disability) [40] only in 1 study. One of the studies had not used scores to report clinical outcomes. Radiological control was performed with MRI in 8 studies and Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) [41] score was calculated in 4 of them. Computer tomography (CT) was used only in 1 study, primarily for the evaluation of osseous phase.

Favorable clinical results with significant postoperative improvements in the applied outcome measures were documented in the only study on Agili-C, in 4 out of 5 studies on MaioRegen, and in 2 out of 4 studies on TruFit scaffolds.

Radiological control with MRI and/or CT showed promising results in 3 out of 8 studies, in which the evaluation was performed. Only in 2 studies the comparison of pre- and postoperative MOCART values was made, while in 2 others only postoperative MOCART scores were calculated. In the Agili-C group almost complete fill (75–100%) was determined in 4 out of the 5 treated lesions. For MaioRegen, there was MRI and/or CT evaluation available only in 3 studies. In 2 of them predominantly propitious radiological results were obtained. Albano et al. [22] reported significant postoperative improvements of MOCART values, and Kaipel et al. [23] reported complete defect fill in 3 out of 4 evaluated lesions and mean postoperative MOCART score of 75, however biochemical MRI analysis was inconclusive about the quality of repair tissue, as increased relaxation times were observed at 18 months follow-up. Christensen et al. [24] reported poor radiological results with no significant improvements of MOCART scores at 1 and 2.5 years follow-up, while only significant reduction of subchondral edema was observed. They also described limited bone formation in the osseous parts of OLTs in all patients available for postoperative CT evaluation; in 2 only 0–10% and in 1 patient 50–75%. After TruFit implantation, in only 1 study moderate radiological findings were observed, while in 3 others MRI showed no formation of repair tissue or its poor quality with high signals, edema, sclerotic rim and lack of integration with surrounding bone and cartilage. Lin et al. [27] reported radiographic failure with ghost hole or lucency consistent with persisting lesion in 12 out of 13 patients.

Serious adverse events (SAE) and failures were described separately for individual treatment approaches with multilayered biomimetic osteochondral scaffolds in 9 of the reviewed studies, while Brulc et al. [26] reported them for the whole cohort, regardless of 4 different types of procedures analyzed in their study. In the Kaipel et al. [23] study, the only included patient, who started complaining for persistent pain and swelling at 24 month follow-up, relocated and refused to undergo further MRI and clinical examination. Therefore, 64 patients in 9 studies were available for the analysis of SAE and failure rates. SAE were defined as any hospitalization or revision surgery (arthrofibrosis, synovitis, impingement, infection, thrombosis, neural injury, hardware problems, etc.), and failures were defined as revision surgery to the lesion or confirmed indication for it. SAE occurred in 8, and failures were documented in 11 patients, giving a total incidence of 29.7%. In the Agili-C group, only 1 patient underwent hardware removal, while failures and SAE related to the graft did not occur. Between 26 patients that were suitable for the analysis of SAE and failures in the MaioRegen treatment group, SAE occurred in 2 patients and failures in 5 patients, giving an overall incidence of 26.9%. The most complications developed in 34 patients treated with TruFit scaffold, where 5 SAE and 6 failures were observed, resulting in a 32.4% combined incidence.

4. Discussion

The present review demonstrates the scarcity of data in the field of OLTs treatment with biomimetic multilayered scaffolds. Both implants, that are still used in the clinical practice, MaioRegen and Agili-C, showed promising clinical outcomes in the majority of the reviewed studies. However, the limited literature, the low overall quality of available studies, and inconsistent radiological findings demand further high level research in this field.

Table 1
Relevant data of the included studies.

Author; Journal; Year of publication	Study design	Number of patients	Age (years); Sex (M/F); BMI (kg/m^2);	Mean follow-up (months)	Lesions' size; Location; Grade	Scaffold	Results (clinical, radiological) and complications (SAE, failures)	CMS
Drobnič et al.[21]; JFAS; 2021	Prospective case series	4 (5 lesions)	42.3 ± 12.7; 2/2; 33.6 ± 4.4	26.0 ± 7.1	2.0 ± 0.2 cm^2; Talus: 4 med./1 lat.; Hepple[48]: grade 4–5	Agili-C (CartiHeal)	Improvements of all PROMs (FAOS, TAS, EQ-5D-3 L). MRI: 75–100% defect fill in 4 lesions, 25–50% fill in 1 lesion. 1 SAE not related to the graft. No failures.	61
Albano et al.[22]; BMC Musculoskelet Disord; 2017	Retrospective case series	16	42.6 ± 18.4; 8/8; 26.3 ± 5.2	30.0 ± 16.9	> 1.5 cm^2; Talus: not specified; Giannini[49]: type II or IIA	MaioRegen (Finceramica)	Significant reduction of VAS-Pain and increase of AOFAS Ankle-Hindfoot Score. Good postoperative FFI-D and FFI-P scores. MRI: MOCART significantly increased. No SAE. 5 failures.	45
Kaipel et al.[23]; Foot Ankle Surg; 2016	Prospective case series	4	27; 2/2; Not reported	At 6, 12, 18, 24 months	2.6 cm^2; Talus: all med.; Not reported	MaioRegen (Finceramica)	FADI and AOFAS Ankle-Hindfoot Score significantly increased. MRI: Mean postoperative MOCART was 75. Complete defect fill in 3/4 lesions. Biochemical imaging indicated questionable quality of repair tissue. No SAE and failures. 1 patient started complaining about pain and swelling, but refused further clinical and radiological follow-up.	51
Christensen et al.[24]; KSSTA; 2015	Prospective case series	4 talus (6 knees)	Reported for all 10 patients: 27 ± 7; 5/3; Not reported	At 12 and 30 months	Reported for all 10 patients: 3.0 ± 1.9 cm^2; Talus: not specified; Not reported	MaioRegen (Finceramica)	AOFAS Ankle-Hindfoot Score increased, but not significantly. TAS (for all 10 patients) without significant improvement. MRI: MOCART (for all 10 patients) without significant increase, only significant reduction of subchondral edema. CT: very limited bone formation and ingrowth; in 2 patients only 0–10% and in 1 patient 50–75%, 1 did not show up. No SAE and failures.	52
Ribeiro[25]; Procedia Eng; 2013	Retrospective case series	3 MaioRegen (4 ACI with fibrin chondrograft)	Reported for all 7 patients: 43 (32–65); 4/3; Not reported	Reported for all 7 patients: 35 (12–58)	Reported for all 7 patients: 1.9 cm^2; Talus: all med.; Not reported	3 MaioRegen (4 ACI with solid fibrin chondrograft Tisseel)	Reported for all 7 patients: In 85% good or excellent results. Mazur score increased from 51 (37–66) to 84 (51–98). No radiological control. No failures. 2 patient treated with MaioRegen had SAE - revision arthroscopy due to synovitis (macroscopically implant area looked filled with indistinguishable cartilage from surrounding and complete marginal integration).	19
Brulc et al.[26]; Foot Ankle Surg; 2021	Prospective case series	22 MaioRegen, 4 Agili-C selectively analyzed by Drobnič et al.[21], and 73 (debridement, BMS, absorbable gels); total: 99	Reported for all 99 patients: 33 ± 14; 41/58; 26.4 ± 4.8	Reported for all 99 patients: 42 ± 22	Reported for all 99: < 1 cm^2: 11%, 1–2 cm^2: 38%, > 2 cm^2: 51%; Talus: 75% med./ 25% lat.; Not reported	22 MaioRegen, 4 Agili-C, 73 (debridement, BMS, absorbable gels: CartiFill, ChondroFiller, Beriplast, Vivostat)	Reported for the whole cohort: All FAOS subscales and general quality of life measures (EQ-5D-3 L, EQ-VAS) significantly improved, while increase in TAS was insignificant. The operative techniques were not correlated with PROMs improvements. No MRI/CT control was performed. 13 graft-related and 6 unrelated SAE, and 21 failures occurred.	54

(*continued on next page*)

Table 1 (*continued*)

Author; Journal; Year of publication	Study design	Number of patients	Age (years); Sex (M/F); BMI (kg/m^2);	Mean follow-up (months)	Lesions' size; Location; Grade	Scaffold	Results (clinical, radiological) and complications (SAE, failures)	CMS
Lin et al.[27]; JFAS; 2010	Retrospective case series	13	36.4 (16–57); 6/7; Not reported	17.5 (2–40)	0.83 (0.2–3.14) cm^2; Talus: not specified; Berndt and Harty [50]: IV	TruFit (Smith & Nephew)	VAS-Pain significantly decreased. Mean postoperative AOFAS Ankle-Hindfoot Score was 67.3. Mean SF-36 scores were postoperatively significantly lower than established US norms in all domains. On 12 out of 13 postoperative ankle radiographs, there was a ghost hole or lucency consistent with persisting lesion. Only 2 postoperative MRI scans obtained showed persisting or enlarged lesions. 5 SAE and 2 failures were documented.	32
Di Cave et al.[28]; The Foot; 2017	Retrospective case series	12	38.6 (22–57); 9/3; Not reported;	90 (78–104)	Diameter: < 15 mm; Talus: 8 med./4 lat.; Hepple[48]: grade 3–5	TruFit (Smith & Nephew)	AOFAS Ankle-Hindfoot Score and VAS-Pain scores improved significantly. MRI: Mean postoperative MOCART was 61.1. Complete filling was found in 50%, normal signal intensity of the repair tissue and complete integration of the graft were identified in 41.7%, subchondral lamina was restored in 75%, and intact subchondral bone was observed in 58.3%. No SAE and failures.	54
Pearce et al.[29]; Foot Ankle Surg; 2012	Case series (not defined as retro- or prospective)	5 talus (1 tibia)	Not reported; 4/1; Not reported	At 12 months	Reported for all 6 patients: Not reported; Talus: all med.; Not reported	TruFit (Smith & Nephew)	Reported for all 6 patients: AOFAS Ankle-Hindfoot Score and AOS disability score significantly improved, while observed improvements in SF-36 and AOS pain score were statistically insignificant. MRI: In all cases high signal within the scaffold and disorganized fibrous cartilage composition. No SAE and failures.	47
Garcia et al.[30]; JBJS; 2010	Retrospective case series	4	27.8 (22–32); 4/0; Not reported	30.5 (25–36)	Not reported; Talus: not specified; Berndt and Harty [50]: V	TruFit (Smith & Nephew)	No clinical evaluation with PROMs was performed. All patients returned to preoperative pain and disability levels on average 9 months after the surgery. MRI: Subchondral edema and lack of homogeneity between scaffold and talus with surrounding sclerotic rim on all scans. Failures in all 4 cases.	43

Abbreviations: BMI - Body Mass Index, CMS - modified Coleman Methodology Score, F - Female, M - Male, SAE - Serious Adverse Events, BMS - Bone Marrow Stimulation, ACI - Autologous Chondrocyte Implantation, med. - medial, lat. - lateral, MOCART - Magnetic Resonance Observation of Cartilage Repair Tissue score, MRI - Magnetic Resonance Imaging, CT - Computer Tomography, PROMs - Patient Reported Outcome Measures, AOFAS - American Orthopedic Foot and Ankle Society, VAS-Pain – Pain on Visual Analogue Scale, TAS - Tegner Activity Scale, FAOS - Foot and Ankle Outcome Score, EQ-5D-3 L - EuroQol 5-Dimensions 3-Level, EQ-VAS - EuroQol-Visual Analogue Scale, SF-36–36-Item Short Form Health Survey, FADI - Foot and Ankle Disability Index, AOS - Ankle Osteoarthritis Score, FFI-D/P - Foot Function Index - Disability/Pain

Among the studied osteochondral scaffolds in the present review, TruFit was the first one introduced to the clinical practice. It is a bilayered scaffold composed of the hydrophilic polymer of poly-lactic-co-glycolic acid (PLGA) and poly-glycolic acid (PGA) in the cartilage phase, and calcium-sulfate in the bone layer. Primarily, it was meant to backfill autologous grafts donor sites, however its usage progressed to mainly off-label osteochondral treatment [42]. The most widely studied osteochondral scaffold is MaioRegen, which is a nanostructured implant consisting of different ratios of equine collagen type I and hydroxyapatite with magnesium ions (Mg-HA) organized in a threelayered system. The multilayered composition mimics the natural architecture of both osseous and cartilaginous layers of the osteochondral unit: the upper cartilage layer is smooth on the surface and consists entirely of type I collagen; the intermediate tide-mark layer consists of type I collagen in 60% and Mg-HA in 40%; and the lower subchondral layer is made of type I collagen in 30% and Mg-HA in 70% [43]. The latest was to the clinical practice introduced Agili-C implant, which is also a cell-free of-the-shelf biomimetic scaffold, derived from the coralline exoskeleton of *Porites* species. It is a bilayered implant with the osseous layer consisting of calcium carbonate in the aragonite crystalline form and the cartilaginous phase composed of modified aragonite [44].

Onwards, there is still much effort needed to completely translate increasingly defined and successful practice of osteochondral treatment from the knee to the ankle joint. In the similar review by Boffa et al. [17] regarding multilayered cell-free scaffolds for the treatment of osteochondral defects in the knee, 34 studies with 1022 patients were included (196 Agili-C, 522 MaioRegen, 304 TruFit); a number that exemplifies the difference to 10 studies with 87 patients in the present review. In the knee joint, the results of individual scaffolds (MaioRegen, TruFit) for osteochondral treatment have already been systematically reviewed [45,46]. Furthermore, the patient-focused consensus recommendations on the indications to use scaffolds for chondral and osteochondral repair on femoral condyles have also been defined [47].

The following limitations of the review are acknowledged. The meta-analysis was not performed due to a very small number of the included patients, variety and inconsistency of outcome measures, and flawed protocols of the reviewed studies. This is clearly reflected in the low quality of analyzed studies with the absence of RCTs and comparative higher level research. Furthermore, some authors evaluated different treatment procedures or the same scaffolds in different joints (knee, ankle) as a part of one cohort without giving any comparison between them. In the majority of reviewed studies, the osteochondral treatment was performed in association with other procedures that could have influenced the outcomes. It also needs to be stressed out that MaioRegen has been the only multilayered scaffold present on the market for a lengthier time period, but limited to the wider European region only. Therefore, the majority of the systematic review data is based on this scaffold.

In spite all the aforementioned limitations, this is the first systematic review of OLTs treatment with multilayered biomimetic scaffolds, which demonstrated some promising results. Based on the available data, we may support the usage of multilayered biomimetic scaffolds for the treatment of complex OLTs. However, we would strongly suggest that all current clinically available data for such scaffolds is gathered and analyzed to get more information from the limited patient series from subspecialized centers. Simultaneously, the protocols and platform for prospective multicenter clinical trials need to be worked on.

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Declarations of interest

None

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