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Is there clinical evidence to support autologous matrix-induced chondrogenesis (AMIC) for chondral defects in the talus? A systematic review and meta-analysis

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ABSTRACT

Background: The aim of this study is to systematically review the literature on clinical outcomes of patients who have undergone autologous matrix-induced chondrogenesis (AMIC) for treatment of osteochondral lesions of the talus (OCL) and compare the studies' outcomes.
Methods: Pubmed and Embase were searched in January 2020 for articles concerning OCL surgery. Studies were included if they had a minimum 1-year follow-up and the primary measures were functional outcomes. The meta-analysis compared the Visual Analogic Score (VAS), the American Orthopedic Foot and Ankle Score (AOFAS), and the Foot Function Index (FFI) between baseline and follow-up of 1–2 years, and 3–5 years. A random effects model was used to evaluate outcome changes.
Results: The search returned 15 studies, with a total of 492 patients. The VAS improved 4.45 and 4.6 points from baseline to the 1–2 year and 3–5 year follow-up, respectively ($p < 0.001$). AOFAS improved 31.59 and 32.47 points from baseline to the 1–2 year and 3–5 year follow-up, respectively ($p < 0.001$). The FFI showed a significant improvement of 30.93 points from baseline to year 3–5 ($p < 0.001$). A total of 6 patients with revision surgeries have been reported within the follow up period. It was not possible to correlate clinical features like lesion size, surgical approach, and bone marrow stimulation technique to the reported outcome.
Conclusion: Surgical treatment of OCL via the AMIC procedure provided significant improvement in the functional outcome and pain scores when compared to the pre-operative values. Improvements were observed up to 5 years post-operatively.

1. Introduction

Ankle sprains are one of the most common musculoskeletal injuries. In a meta-analysis that included 144 papers, with most of those being high-quality studies, Doherty et al. [1] reported an incidence of up to 11.55 sprains per 1000 exposures in sports,. Additionally, 50% of acute ankle sprains result in some form of chondral damage [2]. In chronic ankle instability, talar cartilage lesions have been found in 51% of the patients [3]. Therefore, it is

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distinctly probable that osteochondral lesions of the talus (OCL) are a significant, clinically relevant problem. Unfortunately, articular cartilage has a very low potential for intrinsic repair and regeneration. Thus these lesions likely predispose the patients to degenerative joint disease [4]. With chondral defects leading to changes in the distribution of forces in weight-bearing joints [5], there are several surgical approaches that focus on attempting to restore the congruence of articular surfaces.

In treating OCL, the initial work by Steadman had shown that bone marrow stimulation (BMS) could provide positive clinical outcomes [6]. The underlying theory has been that BMS fosters the recruitment of bone marrow-derived mesenchymal stem cells (MSCs) to the site of injury. These MSCs are then retained within a marrow clot where they proliferate and differentiate into chondroprogenitor cells and produce a fibrocartilage repair [7]. Subsequent work has sought to improves this, investigating various repair techniques to enhance bone marrow stimulation (also called microfracture). Among these procedures are autologous chondrocytes implantation, osteochondral autografts, and allografts, with the treatment option depending on the size, nature, and position of the lesion [8]. As BMS and its subsequent iterations have developed, one of the techniques that have seen substantial growth is the covering of the BMS site with a collagen type I/III membrane and scaffolds based on hyaluronic acid. In the earliest publication, the authors proposed that the use of the collagen membrane could extend the durability of the outcomes as well as allow a larger lesion to be successfully treated [9].

This innovation, known as the autologous matrix-induced chondrogenesis (AMIC) technique, involves debridement of the OCL, BMS, and then coverage of the lesion site by a collagen I/III membrane (Chondro-Gide, Geistlich Pharma AG, Wolhusen, Switzerland). Clinical outcomes following AMIC have been published that demonstrated a considerable improvement for patients who were treated for osteochondral lesions of the knee [10] as well as the hip [11]. Specific to OCL, a meta-analysis of 83 studies in which patients had been treated using either allograft, ACI, BMS, or autologous osteochondral transplantation, a comparison between surgical treatments indicated no significant differences in outcomes, with a notable flaw to the analysis being the low level of evidence of the cited studies [12]. Another study, with a similarly low level of evidence of the studies, suggested that the lesion diameter significantly correlated with clinical outcomes, so the authors proposed that BMS should be reserved for osteochondral lesions less than 1 cm^2 [13], which is smaller than the previously proposed threshold value of 1.5 cm^2 [14,15]. Comparable to the reported results in the knee, talar OCL repair outcomes may vary with follow-up time, as Polat et al. (2016) that at 5 years follow-up, 42% of patients had no symptoms, but 32% had a one-stage increase in their level of degenerative arthritis [16].

Due to the varying levels of evidence in the published literature, as well as the differences in treatment methods, there is a need to evaluate treatment outcomes objectively. Indeed, a recent paper had stated that a methodologically proper meta-analysis could not be performed due to the low level of evidence and the limited number of patients [17]. This was comparable to a report which noted that although the overall clinical success rate was 89.9%, the evidence concerning treatment for osteochondral defects of the talus is still elusive due to the low level of evidence in many papers [18]. However, both of these reviews are dated, with even the article by Lambers, et al. (2018) only including publications up to 2016 [17].

While more recent articles specific to OCL have been published, these have tended to be retrospective, single cohort studies, with few prospective or comparative studies involving AMIC [19–21]. With more recent data being available, it would be helpful to clinicians as well as their patients to assess the data systematically and evaluate its applicability to treatment paradigms for osteochondral lesions. Therefore, we undertook this present systematic review and meta-analysis to assess the outcomes following OCL treatment via AMIC.

2. Methods

2.1. Literature search

A literature search was conducted on the Pubmed database on January 16, 2020, using the following search: "Chondro-Gide" OR "Chondrogide" OR "Autologous matrix induced chondrogenesis" OR (AMIC AND cartilage) AND (talus OR ankle). Publications were excluded if they were review papers, surgical technique articles, or state of the art descriptions. Furthermore, only studies that were reported in English language were considered. Regarding PICO criteria (Population, Intervention, Comparison, Outcome) [22,23], the focus was intervention and outcome, attributable to the limited literature available.

2.2. Selection criteria

Two reviewers independently screened the articles. Case reports were excluded unless they contained safety issues or reported adverse events. Evidence of duplicate or identical patient populations in different publications was assessed in order to avoid the repetition of the same cohort. Studies were included if they were 1) clinical studies with primary measures of functional outcomes and, optionally, a secondary outcome being the quality of the repaired tissue; 2) studies involving cartilage defects of the ankle with a follow-up of at least 1 year; 3) studies that included more than 5 patients.

2.3. Data extraction and critical appraisal

The following study and patient characteristics were retrieved: age, gender, number of patients, clinical scoring system used, and follow-up duration. Pre-operative and post-operative clinical outcome scores were extracted, and if a study reported follow up results after one and two years we used the results after one year. Any safety related information, such as complications or adverse events, were recorded.

2.4. Statistical analysis

All analyses were performed assuming independence between time points and between groups as within patient correlation was not available. Taking within-patient correlation into account and assuming it to be positive, one would expect the true standard deviation to be less than estimated below and, therefore, an even higher significance of the mean differences given below. In order to calculate a fixed-effects model overall treatment effect, we used a weighted average of the studies' reported treatment effects, where the inverse of the squared standard errors of the treatment effect of each study was used as weights. For this standard error, we used the sum of the standard errors in each treatment group.

Due to a relatively small number of studies, only the results of the random-effects models were considered for which the Dersimonian-Laird method was used [2]. For the test on heterogeneity, we compared the weighted sum of squares of the treatment effects about the overall fixed effect estimate to a chi-squared distribution of n-1 degrees of freedom, where n is the number of studies. For this, we used the same weights as above. Significance on a 5% level was interpreted as the presence of heterogeneity between the studies, all confidence intervals (CI) are 95% confidence intervals. All CI and p-values are based on

assuming a normal distribution. If a study reported results for year 1 and year 2 the only the results from year 1 were used. All analyses were performed under R version 3.5.3 and the meta-package version 4.9-7.

3. Results

3.1. Literature search results

Literature selection was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [24–27]. The literature searches on Pubmed and Embase yielded a total of 77 citations. After removal of duplicates, the remaining articles were screened in accordance with the defined criteria, as shown in Fig. 1. We identified 5 studies in which the patients were a subset of those in other studies or were the same patients whose data was reported at different time points. Therefore, we did not include these publications. Of the 15 studies that met the inclusion criteria, 3 used an assessment tool (Visual Analogue Scale Foot and Ankle) that was unique to that study site [28,20,21]. Therefore, these were not included in the quantitative analysis.

3.2. Demographics

The studies that were included in this analysis included a total of 492 patients that had undergone an AMIC procedure. Among these patients, 75% were male, although 2 studies did not report the gender distribution of the patients. The mean age was 36 years, with a range from 12 – 68. The follow-up times ranged from 12 to 60 months, with a mean of 33 months.

3.3. Methodological quality

The majority of the studies were case series, thus classified as Level 4 studies, as based on the criteria for levels of evidence (LOE) published by the Center for Evidence Based Medicine [29]. All articles were assessed for their methodological quality according to the modified Coleman Methodology Score (mCMS) [30,13]. Of the studies included in the quantitative analysis, 9 were case series with enrollment ranging from 17 to 60 patients. There were no randomized controlled trials, but there were 5 prospective cohort studies and one retro-prospective study. The information on the studies is presented in Table 1.

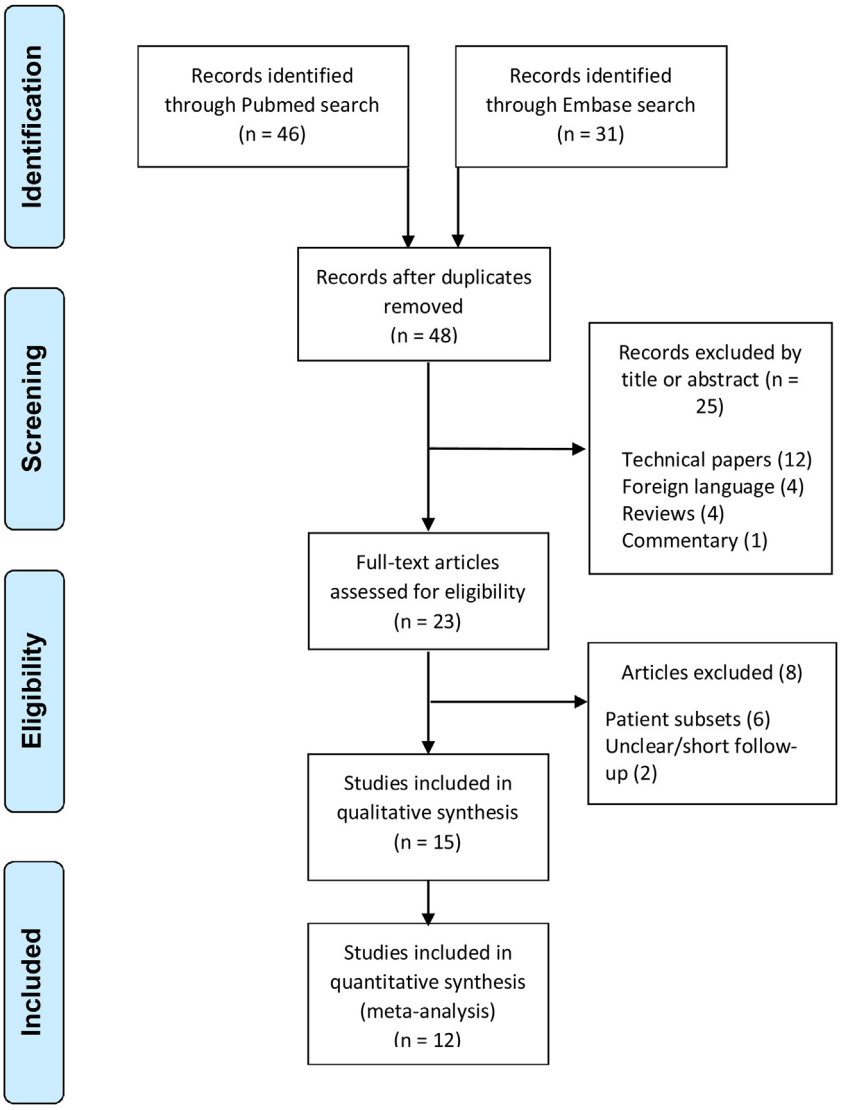

Fig. 1. Literature selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Table 1
An overview of the studies included in this systematic review.

Study	n	LOE	Type of Study	mCMS	Primary Outcomes
Valderrabano et al. 2013 [31]	26	4	Case series	59	AOFAS, MOCART
Wiewiorski et al. 2013 [32]	23	4	Case series	69	AOFAS, VAS, MOCART
Wiewiorski et al. 2016 [33]	60	4	Case series	65	Tegner, AOFAS, VAS
Thermann et al. 2014 [34]	32	3	Prospective cohort	55	HSS, VAS, MRI
Walther et al. 2013 [35]	20	4	Case series	58	AOFAS, FFI, MRI
Gottschalk et al. 2017 [19]	21	3	Prospective cohort	66	FFI
Kubosch et al. 2015 [36]	17	4	Case series	65	AOFAS, FFI, MOCART, VAS
D'Ambrosi et al. 2018 [37]	37	3	Retro-prospective	61	AOFAS, MRI, VAS
Baumfeld et al. 2018 [38]	17	4	Case series	42	AOFAS
Richter, et al. 2013 [28]	25	3	Prospective, consecutive	67	VAS-FA
Richter, et al. 2017&19 [20,21]	144	2b	Prospective, consecutive	73	VAS-FA
D'Ambrosi et al. 2019 [39]	26	4	Case series	64	AOFAS, SF-12, MRI
Sadlik et al. 2019 [40]	24	3	Prospective cohort	76	AOFAS, MOCART, VAS
Usuelli et al. 2018 [41]	20	4	Case series	72	AOFAS, MOCART, VAS

LOE: Level of evidence [29], mCMS modified Coleman Methodology Score (mCMS) [30,13].

Most studies (n = 9) used the American Orthopaedic Foot & Ankle Society Score (AOFAS) to assess clinical outcomes, while the Visual Analogue Scale for pain (VAS) was also common (7 studies). The Foot Function Index (FFI), Hanover Scoring System (HSS), Tegner Score and Activity Rating Scale (ARS) were much less common. Imaging assessments consisted of Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) in 5 studies while 3 studies performed a qualitative MRI assessment.

3.4. Detection of bias

In order to assess the risk of publication bias, we performed a graphical assessment with a funnel plot, which showed no graphical evidence of reporting bias (Fig. 2). In this, each point represents the result of one study. The position of the points outside the funnel indicate a variation between the studies beyond what one would expect if all studies were based on the same population (Baumfeld et al. 2018) [38]. In addition, this indicated that the result from the random effect model was preferred.

3.5. Clinical aspects of the different studies includeed

Although all patients have been treated with AMIC, there was a variability between the surgical strategies. Details on the cohorts including age, bone marrow stimulation technique (BME), lesion size (LE), surgical technique (ST) and follow up are given in Table 2.

3.6. Meta-Analysis of Outcomes: 1–2 years

The results from the random effects model indicated a significant change ($p < 0.0001$) in mean AOFAS between baseline and year 1 or 2 of 31.59 (95% confidence interval (CI) of [27.12; 36.06]). As illustrated by the Forest plot in Fig. 3, this result is notably affected by 1 study (Baumfeld et al. 2018). [38] When compared to the other studies, this one reported a much higher mean difference and a much smaller standard deviation. With study R excluded, the difference between baseline and follow-up score of 29.79 remained significant, with a confidence interval of [26.68; 32.89], however, heterogeneity lost significance ($p = 0.69$).

For the pain VAS the random effect model shows reduction from baseline to year 1 and 2 of -4.45 (CI [-5.20, -3.69]), which is highly significant ($p < 0.001$, Fig. 4)

3.7. Meta-Analysis of Outcomes: 3–5 years

The mean difference in the AOFAS score between baseline and follow-up at year 3−5 of 32.47 (CI [27.65; 37.30]) was highly significant ($p < 0.001$). Fig. 5 shows the forest plot for this result.

Regarding pain VAS, both studies reported the same mean difference between baseline and follow up of -4.60, which was highly significant ($p < 0.001$) with a 95% confidence interval of [-5.18; -4.02] (Fig. 6)

There was a significant difference ($p < 0.001$) in mean FFI score from baseline to year 3−5, with a mean change of 30.93 with a 95% CI of [22.85; 39.01] which is presented in Fig. 7.

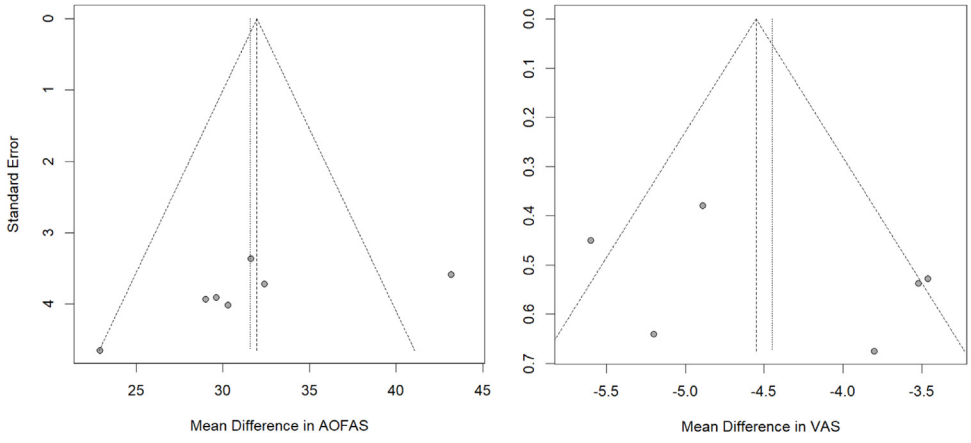

Fig. 2. The funnel plot to depict bias for the AOFAS and VAS scores at year 1 or 2.

Table 2
Epidemiology, technical and clinical details on the studies included.

Study	n	Age	BME	Lesion size	Surgical Technique	CR / RR	FU (months)	Reported Outcome	Remarks
Valderrabano et al. 2013 [31]	26	33 (17–55)	MFX	1589 mm^3 (378–7054)	MO: 21 AT: 5	0/0	31 (24–54)	AOFAS: 89 (61–100) MOCART: 62 (20–95)	Previous OCL surgery: 14 CO: 15 LLR: 3. MLLR: 13, LLR: 1
Wiewiorski et al. 2013 [32]	23	34 (17–55)	MFX	1490 mm^3 (378–7054)	NR	NR/ NR	23 (11–49)	AOFAS: 91 (61–100) VAS: 1.3 (0–7) MOCART: 63 (30–95)	Lesion lateral 4, Lesion medial 19
Wiewiorski et al. 2016 [33]	60	35 (15–58)	MD	>1 cm^2	MO: 58 AT: 2	NR/ NR	47 (24–87)	Tegner: 3.4 SD 2.2 AOFAS: 76 (28-100) VAS: 2.3 (0–6)	Previous OCL surgery: 26 Lesion medial: 46, Lesion lateral: 14 Smoker: 21, CO: 41 LLR: 8, MLLR: 28, MLR: 5
Thermann et al. 2014 [34]	32	37 (15–69)	MFX	>1 cm^2	AS	0/1	12	HSS: 89 SD 7 VAS: 0.6 SD 1.0	No additional procedures; MRI: no score
Walther et al. 2013 [35]	20	39 (19–60)	MD	>2 cm^2	AT: 15 MO: 5	0/1	> 36	AOFAS: 82 SD 13 FFI: 28 SD 21	MRI: no score
Gottschalk et al. 2017 [19]	21	37 (15–62)	MD	1.4 cm^2 (0.2–4.0)	AT	0/0	60	FFI: 24 SD 21	Only arthrotomy without osteotomy
Kubosch et al. 2015 [36]	17	39 (SD 15.7)	MFX	2.4 cm^2 (SD 1.6)	AT: 1 MO: 16	0/0	40 (12–78)	AOFAS: 83 SD 3.4 FFI: 34 SD 24 MOCART: 53 SD 16 VAS: 3.2 SD 2.4	Previous OCL surgery: 6 Defect size > 3 cm^2 had significantly lower values in AOFAS score
D'Ambrosi et al. 2018 [37]	37	34 (14–61)	MFX	1.4 cm^2 (SD 0.7)	AS	0/0	24	AOFAS: 88 SD 10 VAS: 1.8 SD 1.4	MRI: no score
Baumfeld et al. 2018 [38]	17	38 (15–67)	MFX	1.16 cm^2	AS	0/0	12 (8–20)	AOFAS: 90 (82–100)	CO: 3, Lesion medial: 12
Richter, et al. 2013 [28]	25	33 (16–48)	MFX	1.1 cm^2 (0.5–6.0)	AT: 24 MO: 1	0/0	24	VAS-FA: 95 (73–100)	MAST: Matrix associated stem cell transplantation
Richter, et al. 2017&19 [20,21]	144	35 (12–68)	MFX	1.6 cm^2 (0.6–6.0)	AT	0/3	24	VAS-FA: 88 (62–100)	MAST: Matrix associated stem cell transplantation
D'Ambrosi et al. 2019 [39]	26	33 (SD 11.0)	MFX	1.4 cm^2 (SD 0.7)	AS	0/0	43 (SD 11)	AOFAS: 87 SD 12 SF-12: 47 SD 8.1	Lesion medial: 20, Lesion lateral: 6, MRI: no score
Sadlik et al. 2019 [40]	24	34 MO: 35 SD 13.3 AT: 33 SD 14.0	MD	MO: 1.3 cm^2 SD 0.56 988 mm^3 SD 995 AT: 1.2 cm^2 SD 0.35 768 mm^3 SD 516	MO: 11 AT: 13	0/0	22	AT: AOFAS: 84 SD 15, MOCART: 71 SD 17 VAS: 2.0 SD 1.4 MO: AOFAS 81 SD 12 MOCART: 67 SD 18 VAS: 1.9 SD 1.0	No significant difference between patient's treated with and without malleolar osteotomy.
Usuelli et al. 2018 [41]	20	36 (17–58)	MFX	ASK: 1.11 cm^2 SD 0.43 MRI/CT: 1.54 cm^2 SD 0.93	AS	0/0	24	AOFAS: 87 SD 11 MOCART: 51 SD 25 VAS: 2.5 SD 2.2	Lesion size was measured arthroscopically and with CT/MRI; Lesion medial: 18, Lesion lateral: 1, Lesion central: 1

BME: technique of bone marrow stimulation used. MFX: Microfracture. NFX: Nanofracture. MD: Microdrill. NR: Not reported, MO: Malleolar Osteotomy, AT: Arthrotomy without osteotomy, AS: Arthroscopy. CR/RR: Complications/Revisions, FU: Follow up. Remarks: Additional information provided in the paper (CO: Number of patients with additional calcaneal osteotomy. LLR: Number of patients with lateral ligament reconstruction, MLR: Number of patients with medial ligament reconstruction, MLLR: Number of patients with mediolateral ligament reconstruction).

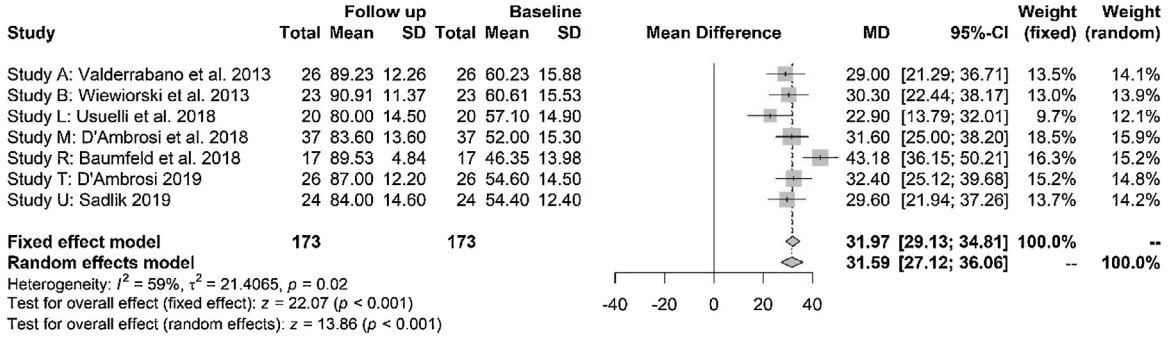

Fig. 3. The Forest plots for the change in AOFAS scores compared to baseline.

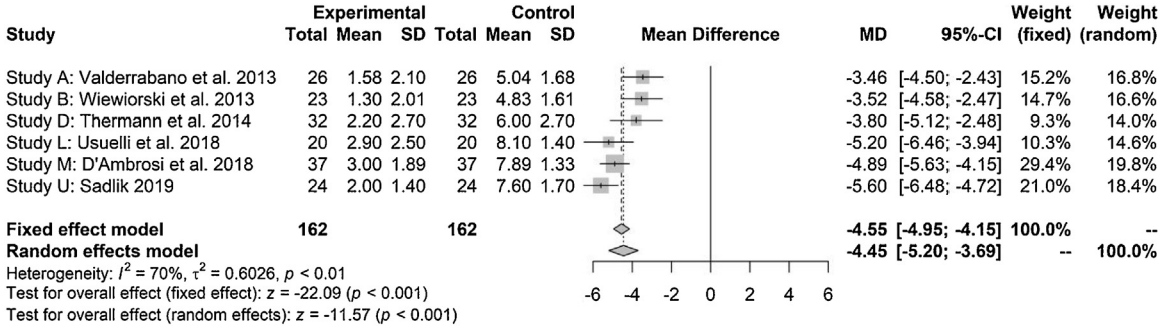

Fig. 4. Forest plots for the change in VAS for pain compared to baseline.

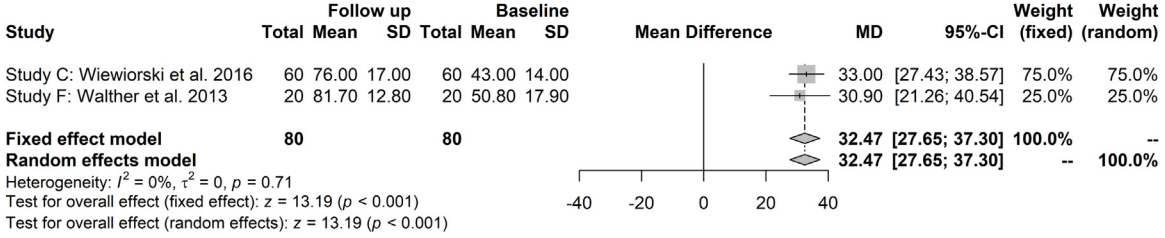

Fig. 5. Forest plot for AOFAS scores at 3 to 5 years.

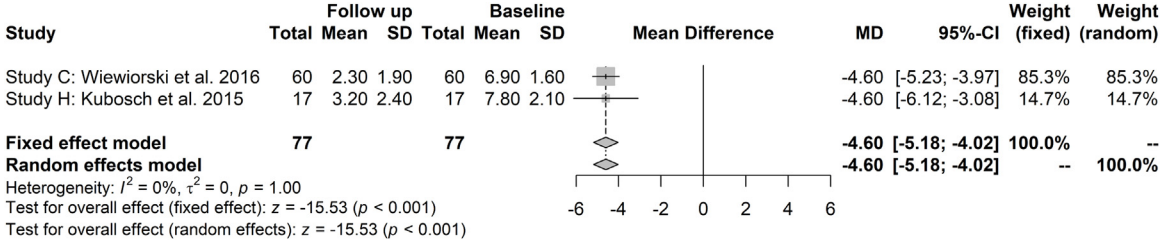

Fig. 6. Forest plot for VAS scores at 3 to 5 years.

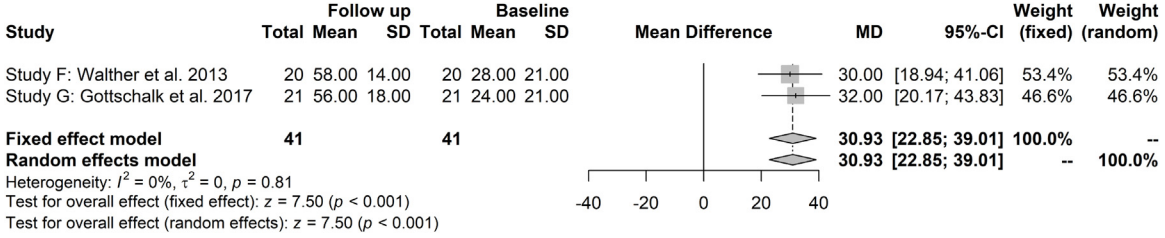

Fig. 7. Forest plot for FFI scores at 3 to 5 years.

3.8. Complications

Intraoperative complications have been not reported. Among the 15 studies (involving 492 patients) 4 studies, revision surgeries have been reported for a total of 6 patients (Table 3). The reported revision surgeries have been indicated due to persistent pain caused by mechanical problems in the joint (arthrofibrosis, hypertrophic scare tissue) or because a of progression degenerative arthritis.

4. Discussion

The results in our literature search returned 15 studies that involved 492 patients, while the studies that were used in the meta-analysis were 12 studies with a total of 323 patients. The random-effects models have shown that there is a significant improvement in patient outcomes, whether at the 1–2 year the 3–5 year follow-up. Regarding safety, there were only 6 patients who required a subsequent surgery within 5 years after the initial procedure. Therefore, this body of clinical evidence supports the use of the AMIC procedure in the treatment of OCL. There were no reported adverse events or complications directly related to the AMIC procedure, while the 6 revision surgeries correspond to 1% of the treated patients. Importantly, no patients required conversion to ankle fusion or arthroplasty.

A statistically significant improvement of the clinical outcome measures was observed among all individual studies through the meta-analysis and reflected the immediate improvement of pain

Table 3
The list of adverse events and complications among the studies.

	n	Complications	Time after index procedure
Thermann, et al. 2014 [34]	1	arthroscopic arthrolysis	9 months
Richter, et al. 2019 [21]	3	A 2nd joint preserving ankle surgery including another MAST procedure.	36 months 39 months 48 months
Walther et al. 2013 [35]	1	Arthroscopic debridement of hypertrophic tissue	NR
D'Ambrosi, et al. 2018 [37]	1	Anterior osteophyte due to hypertrophic proliferation that caused impingement necessitated repeat arthroscopy for osteophyte removal and debridement.	8 months

and functional outcomes among the studies. Furthermore, this improvement was stable over the length of follow-up since no study reported evidence of deterioration, and longer-term studies confirmed the stability of pain and function scoring at 5 years [19,21] as well as the patients' returning to sports activities [33,39]. The longer follow-up that was conducted in 3 of the studies in our meta-analysis is reflective of what has been published for the hip after 8 years follow-up [11] and for 7 years follow-up following AMIC in the knee [42].

In addition to the results that had been used in the random-effects model, there were studies that had not been included owing to their use of a unique patient-reported outcome measure. Specifically, Richter, et al. (2013, 2017, 2019) had used the Visual Analogue Scale Foot and Ankle (VAS-FA) as a means of assessing the patients' outcomes. This instrument had been developed as a simpler means of assessing patent reported outcomes, and had been validated using the SF-36 and Hannover Questionnaire as bases of comparison. [43] The authors who had developed the VAS-FA first reported outcomes in a cohort of 25 patients in a prospective, consecutive, non-controlled clinical follow-up study, with 2 years of follow-up, in which it was reported that a pre-operative score of 49.2 had improved to 94.5 [28]. A significantly larger prospective cohort demonstrated that the VAS-FA improved from 48.5–87.5 [20]. Importantly, these positive outcomes were maintained at 5 years of follow-up, with a mean VAS-FA of 84.4 [21]. With such limited use of this specific outcomes instrument, it can be difficult to draw direct comparisons to other studies, and there is no definition of what constitutes a minimal, clinically important difference. However, it seems that the magnitude of the changes from pre-operative VAS-FA indicate that the patients had experienced positive outcomes and that these improvements were maintained over the duration of the follow-up.

We also analyzed the different clinical and technical aspects of the studies which might influence the outcome. Arthroscopic technique might have a positive effect on the outcome. The AOFAS Score reported for arthroscopically treated patients ranges from 87 to 90 points, which does not differ from the outcome obtained from patients treated with open surgery (Fig. 3). The lowest AOFAS Score reported was found in a paper by Wiewiorski [33]. The rate of medial malleolar osteotomies was 97%. This was the highest percentage of malleolar osteotomies within the studies included. However, Sadlik et al. [40] could not find a significant difference in patients treated with or without medial malleolar osteotomy, although the average scores have been less favorable after osteotomies. The average age was not different between the two studies, but there is no lesion size reported by Wiewiorski [33]. So far there is no evidence, that an arthroscopic approach is related to better results, the effect of the medial malleolar osteotomy seems still unclear.

It should be noted here that the basis for the procedure in our meta-analysis is the development of BMS, which dates to the 1980s [44]. The basis of the therapeutic effect of BMS is that it induces an influx of marrow substrates, for example, mesenchymal stromal cells and growth factors, to repopulate the cartilage defect by removing subchondral bone and thus exposing cancellous bone [45].

Currently three techniques for BMS are used in the talus. Those include microfracture (MFX) as published by Steadman et al. [44], In order to provide deeper subchondral access with smaller diameters, nanofracture (NF) method has been proposed [46]. By this technique, main mechanical limitations of the microfracture method could be eliminated, like the destruction of the subchondral bone plate. Another modification of BMS is micro-drilling (MD) to have less damage to the subchondral bone plate and in combination with deeper holes to release more stem cells. Chen et al. [47] compared microfracture and microdrilling and found distinct differences between microfracture and drilling for acute subchondral bone structure and osteocyte necrosis.

The technique of BMS is also a possible factor which might affect the outcome. Analyzing the papers included, most authors report "microfracture" in the method section, although their intraoperative pictures look more like MD rather than MFX. However, this is in accordance to literature, where MD is classified as a subtype of MFX. So far no consensus regarding a standardized application (e.g. diameter and depth of perforations, pattern, and spacing) of microfracture has been reported. There is also no unity on the devices used to perform microfracture (drill, chondropick, manual or mechanical application) [46]. One example for the unclear definition is the paper of Richter et al. [28]. They reported "microfracture with a 1.6 mm K-wire" which can be classified as microdrilling. The intraoperative pictures confirm multiple drill holes. The inconsistent definition makes it impossible to correlate any results to the BMS technique reported.

While BMS is not an exact replacement for the hyaline cartilage of a healthy synovial joint, it is likely superior to the exposed bone and abnormal joint congruency that resulted from the initial osteochondral lesion. Various membranes and scaffolds have been developed to provide mechanical protection and contain biological factors, resulting from the BMS, within the treated site. Additionally, if a graft is used to fill subchondral bone, a membrane helps to stabilize the graft. [48] The therapeutic concept is that subsequent to BMS a scaffold can maintain, within the treated site, the cells involved in the healing process. This may be considered speculative, but the concept is supported by preclinical data [49]. Additionally, scaffolds may also reduce shearing forces at the treatment site, thus allowing a more suitable environment for healing [50,51].

While the results of our meta-analysis are focused on osteochondral lesions in the talus, there is a substantial body of evidence related to the use of a collagen membrane in the knee and the hip. A recent meta-analysis, which included 12 studies (375 patients), had also noted significant improvement in clinical outcome scores when compared to baseline [51]. Similar to our results, the majority of those studies were case series, with only 1 prospective, randomized, controlled trial (PRCT). In contrast, the average mCMS score was 84 (as opposed to our average of 64),

mainly due to a number of those case series being prospective. Nevertheless, there is consistency between our outcomes and those reported by Steinwachs et al. (2019) [51].

One of the drawbacks of our meta-analysis is that the modified mCMS for the studies that we included indicated a suboptimal design in the majority of the recently published papers, especially regarding study size, type of study, and description of the subject selection process [52]. This is not unique for AMIC studies but applies to many publications on the treatment of OCL [53]. One factor that lowered the mCMS was the high number of associated procedures, but this is inherent to the treatment plan, where patients will often present with a subchondral bone lesion, malalignment or ligamentous lesions. Although these additional procedures may impact the methodology of the study, they are part of the standard treatment algorithms, which aim to simultaneously correct any underlying pathology, particularly ligamentous deficiencies or malalignment. Also, an additional bone grafting procedure must treat the presence of the bone lesion below the OCL. Despite being the standard of care, this is considered an additional procedure and it impacted the mCMS by 10 points in 7 of these studies. These procedures represent the first line of real-life treatment for all joints and can be avoided only in specific clinical studies that may exclude patients for whom an additional procedure is needed. That exclusion criterion could in itself introduce a patient selection bias when compared to the real-world standard of care.

A notable advantage of a meta-analysis is that several different investigators initiated the studies, therefore modulating the risk of a center-induced bias. Similarly, these results could be compared to a systematic review of the outcomes of OCL, where a review of treatment options reported a low level of evidence of most studies, with the authors unable to detect a significant difference between outcomes and the specific surgical treatment [12].

Lambers et al. analyzed 21 studies with a total of 299 patients, covering 11 different treatment strategies [17]. They found, that besides an expected difference in outcome between the autograft transfer procedure and the more extensive procedures of mosaicplasty and the use of an allograft, neither a clear nor a significant difference between treatment options could be demonstrated. Two studies for AMIC have been included with a total of 20 patients [31,36]. In this meta-analysis clinical success was defined AOFAS score 80 and above [54]. Clinical aspects like approach and lesion size have not been discussed, studies with a follow up of more than 6 months have been included.

Another recent systematic review, based on 25 studies (1868 ankles), suggested that the lesion size significantly correlated with clinical outcomes [13]. Therefore, those authors proposed that BMS as a sole treatment should be limited to osteochondral lesions less than 1 cm^2, which is lower than the previous threshold of 1.5 cm^2 [14]. Other data has noted that OCL > 1.5cm^2 were associated with poorer outcomes scores after BMS [15]. In contrast, several studies concerning AMIC have focused on lesions >1 cm^2 [36,20,55,38]. Kubosch et al. [36] reported an average lesion size of 2.4 cm^2. The results reported by her group did not differ from the once, reported on cohorts with smaller lesion [33].

Relative to the lesion size and the use of a scaffold, such as the collagen I/III membrane used in the research we have analyzed, the AMIC technique is consistent with the recommendations that had been formulated by the International Consensus Group on Cartilage Repair of the Ankle [56], as well as with the recommendations of the Working Group for Clinical Tissue Regeneration of German Society of Orthopedics and Traumatology (DGOU) [8]. The experts in this groups established a high level of consensus for the addition of a scaffold to BMS in the following cases: 1) primary and revision cases with lesions >1 cm^2, 2) cases in which a one-step procedure is performed, and 3) in cases where bone grafting may be needed. Our results further strengthen this consensus of expert opinion, as it allows larger lesions to be treated in a one-stage procedure.

Our meta-analysis addressed a treatment population without selection criteria, such as are seen in a prospective clinical study, and the results suggest that AMIC can maintain the initial improvement for 5 years. The treatment with AMIC has the potential to postpone the need for subsequent surgical treatment, for example arthroplasty, for several years. However, there are limitations to the data. As was stated, most of the studies are Level 4, with only 3 publications (2 studies) presenting data from a prospective study, and these were only single-arm studies. This is consistent with the general status of the published level of evidence, where it has already been noted that there is a paucity of Level-1 studies in the peer-reviewed literature. Therefore, a well-designed PRCT can further inform clinicians about interventions that may optimize their patients' outcomes.

5. Conclusion

The systematic analysis of 15 studies, representing 492 patients in a non-selected population supports the use of AMIC. There is evidence that the AMIC procedure for osteochondral lesions of the talus provides significant improvement in patient outcome scores, compared to the preoperative values, up to 5 years post-operatively. Clinical experience suggests that there are factors like lesion size, surgical and BMS technique, as well as the consequent management of associated lesions which might affect outcome. Based on the evidence available today, it is still impossible to weight those factors.

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Conflict of interest

Markus Walther; Victor Valderrabano, Martin Wiewiorski, Federico Giuseppe Usuelli, Martinus Richter, Oliver Gottschalk have been paid speakers at workshops related to the topic.

References

[1] Doherty C, Delahunt E, Caulfield B, Hertel J, Ryan J, Bleakley C. The incidence and prevalence of ankle sprain injury: a systematic review and meta-analysis of prospective epidemiological studies. Sports Med 2014;44(January (1)):123–40, doi:http://dx.doi.org/10.1007/s40279-013-0102-5.

[2] Murawski CD, Kennedy JG. Operative treatment of osteochondral lesions of the talus. J Bone Joint Surg Am 2013;95(June 5 (11)):1045–54, doi:http://dx.doi.org/10.2106/JBJS.L.00773.

[3] Cha SD, Kim HS, Chung ST, Yoo JH, Park JH, Kim JH, et al. Intra-articular lesions in chronic lateral ankle instability: comparison of arthroscopy with magnetic resonance imaging findings. Clin Orthop Surg 2012;4(December (4)):293–9, doi:http://dx.doi.org/10.4055/cios.2012.4.4.293.

[4] Mankin HJ. The response of articular cartilage to mechanical injury. J Bone Joint Surg Am 1982;64(March (3))460–6. . Available from https://www.ncbi.nlm.nih.gov/pubmed/6174527.

[5] Guettler JH, Demetropoulos CK, Yang KH, Jurist KA. Osteochondral defects in the human knee: influence of defect size on cartilage rim stress and load redistribution to surrounding cartilage. Am J Sports Med 2004;32(September (6)):1451–8, doi:http://dx.doi.org/10.1177/0363546504263234.

[6] Steadman JR, Rodkey WG, Briggs KK, Rodrigo JJ. [The microfracture technic in the management of complete cartilage defects in the knee joint]. Orthopade 1999;28(January (1))26–32. . Available from https://www.ncbi.nlm.nih.gov/pubmed/10081041.

[7] Brittberg M, Winalski CS. Evaluation of cartilage injuries and repair. J Bone Joint Surg Am 2003;85(A Suppl 2):58–69, doi:http://dx.doi.org/10.2106/00004623-200300002-00008.

[8] Aurich M, Albrecht D, Angele P, Becher C, Fickert S, Fritz J, et al. Treatment of osteochondral lesions in the ankle: a guideline from the group "Clinical tissue regeneration" of the German Society of Orthopaedics and Traumatology (DGOU). Z Orthop Unfall 2017;155(February (1)):92–9, doi:http://dx.doi.org/10.1055/s-0042-116330.

[9] Behrens P, Ehlers EM, Kochermann KU, Rohwedel J, Russlies M, Plotz W. New therapy procedure for localized cartilage defects. Encouraging results with autologous chondrocyte implantation. MMW Fortschr Med 1999;141(November 11 (45))49–51. . Available from https://www.ncbi.nlm.nih.gov/pubmed/10795168.

[10] Volz M, Schaumburger J, Frick H, Grifka J, Anders S. A randomized controlled trial demonstrating sustained benefit of Autologous Matrix-Induced Chondrogenesis over microfracture at five years. Int Orthop 2017;41(2017/04/01 (4)):797–804, doi:http://dx.doi.org/10.1007/s00264-016-3391-0.

[11] de Girolamo L, Jannelli E, Fioruzzi A, Fontana A. Acetabular chondral lesions associated with Femoroacetabular Impingement Treated by Autologous Matrix-Induced Chondrogenesis or Microfracture: a comparative study at 8-year follow-up. Arthroscopy 2018;34(11):3012–23, doi:http://dx.doi.org/10.1016/j.arthro.2018.05.035.

[12] Pinski JM, Boakye LA, Murawski CD, Hannon CP, Ross KA, Kennedy JG. Low level of evidence and methodologic quality of clinical outcome studies on cartilage repair of the ankle. Arthroscopy 2016;32(January (1))214–22, doi:http://dx.doi.org/10.1016/j.arthro.2015.06.050 e1.

[13] Ramponi L, Yasui Y, Murawski CD, Ferkel RD, DiGiovanni CW, Kerkhoffs G, et al. Lesion size is a predictor of clinical outcomes after bone marrow stimulation for osteochondral lesions of the talus: a systematic review. Am J Sports Med 2017;45(June (7)):1698–705, doi:http://dx.doi.org/10.1177/0363546516668292.

[14] Chuckpaiwong B, Berkson EM, Theodore GH. Microfracture for osteochondral lesions of the ankle: outcome analysis and outcome predictors of 105 cases. Arthroscopy 2008;24(January (1)):106–12, doi:http://dx.doi.org/10.1016/j.arthro.2007.07.022.

[15] Choi WJ, Park KK, Kim BS, Lee JW. Osteochondral lesion of the talus: is there a critical defect size for poor outcome? Am J Sports Med 2009;37(October (10)):1974–80, doi:http://dx.doi.org/10.1177/0363546509335765.

[16] Polat G, Ersen A, Erdil ME, Kizilkurt T, Kilicoglu O, Asik M. Long-term results of microfracture in the treatment of talus osteochondral lesions. Knee Surg Sports Traumatol Arthrosc 2016;24(April (4)):1299–303, doi:http://dx.doi.org/10.1007/s00167-016-3990-8.

[17] Lambers KTA, Dahmen J, Reilingh ML, van Bergen CJA, Stufkens SAS, Kerkhoffs G. No superior surgical treatment for secondary osteochondral defects of the talus. Knee Surg Sports Traumatol Arthrosc 2018;26(July (7)):2158–70, doi:http://dx.doi.org/10.1007/s00167-017-4629-0.

[18] Niemeyer P, Salzmann G, Schmal H, Mayr H, Sudkamp NP. Autologous chondrocyte implantation for the treatment of chondral and osteochondral defects of the talus: a meta-analysis of available evidence. Knee Surg Sports Traumatol Arthrosc 2012;20(September (9)):1696–703, doi:http://dx.doi.org/10.1007/s00167-011-1729-0.

[19] Gottschalk O, Altenberger S, Baumbach S, Kriegelstein S, Dreyer F, Mehlhorn A, et al. Functional medium-term results after autologous matrix-induced chondrogenesis for osteochondral lesions of the talus: a 5-Year prospective cohort study. J Foot Ankle Surg 2017;56(September-October (5)):930–6, doi:http://dx.doi.org/10.1053/j.jfas.2017.05.002.

[20] Richter M, Zech S, Andreas Meissner S. Matrix-associated stem cell transplantation (MAST) in chondral defects of the ankle is safe and effective - 2-year-followup in 130 patients. Foot Ankle Surg 2017;23(December (4)):236–42, doi:http://dx.doi.org/10.1016/j.fas.2016.05.320.

[21] Richter M, Zech S. Matrix-associated stem cell transplantation (MAST) in chondral lesions at the ankle as part of a complex surgical approach- 5-year-follow-up in 100 patients. Foot Ankle Surg 2019;25(3):264–71, doi:http://dx.doi.org/10.1016/j.fas.2017.11.004.

[22] Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Med Inform Decis Mak 2007;7(June 15):16, doi:http://dx.doi.org/10.1186/1472-6947-7-16.

[23] Agoritsas T, Merglen A, Courvoisier DS, Combescure C, Garin N, Perrier A, et al. Sensitivity and predictive value of 15 PubMed search strategies to answer clinical questions rated against full systematic reviews. J Med Internet Res 2012;14(June 12 (3)):e85, doi:http://dx.doi.org/10.2196/jmir.2021.

[24] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6(July 21 (7))e1000100, doi:http://dx.doi.org/10.1371/journal.pmed.1000100.

[25] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(July 21 (7))e1000097, doi:http://dx.doi.org/10.1371/journal.pmed.1000097.

[26] Moher D, Altman DG, Liberati A, Tetzlaff J. PRISMA statement. Epidemiology 2011;22 (January (1))128, doi:http://dx.doi.org/10.1097/EDE.0b013e3181fe7825 author reply.

[27] Tao KM, Li XQ, Zhou QH, Moher D, Ling CQ, Yu WF. From QUOROM to PRISMA: a survey of high-impact medical journals' instructions to authors and a review of systematic reviews in anesthesia literature. PLoS One 2011;6(11)e27611, doi:http://dx.doi.org/10.1371/journal.pone.0027611.

[28] Richter M, Zech S. Matrix-associated stem cell transplantation (MAST) in chondral defects of foot and ankle is effective. Foot Ankle Surg 2013;19(June (2)):84–90, doi:http://dx.doi.org/10.1016/j.fas.2012.11.005.

[29] Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg 2011;128(July (1)):305–10, doi:http://dx.doi.org/10.1097/PRS.0b013e318219c171.

[30] Coleman BD, Khan KM, Maffulli N, Cook JL, Wark JD. Studies of surgical outcome after patellar tendinopathy: clinical significance of methodological deficiencies and guidelines for future studies. Victorian Institute of Sport Tendon Study Group. Scand J Med Sci Sports 2000;10(February (1)):2–11, doi:http://dx.doi.org/10.1034/j.1600-0838.2000.010001002.x.

[31] Valderrabano V, Miska M, Leumann A, Wiewiorski M. Reconstruction of osteochondral lesions of the talus with autologous spongiosa grafts and autologous matrix-induced chondrogenesis. Am J Sports Med 2013;41(March (3)):519–27, doi:http://dx.doi.org/10.1177/0363546513476671.

[32] Wiewiorski M, Miska M, Kretzschmar M, Studler U, Bieri O, Valderrabano V. Delayed gadolinium-enhanced MRI of cartilage of the ankle joint: results after autologous matrix-induced chondrogenesis (AMIC)-aided reconstruction of osteochondral lesions of the talus. Clin Radiol 2013;68(October (10)):1031–8, doi:http://dx.doi.org/10.1016/j.crad.2013.04.016.

[33] Wiewiorski M, Werner L, Paul J, Anderson AE, Barg A, Valderrabano V. Sports activity after Reconstruction of Osteochondral Lesions of the Talus with Autologous Spongiosa Grafts and Autologous Matrix-Induced Chondrogenesis. Am J Sports Med 2016;44(October (10)):2651–8, doi:http://dx.doi.org/10.1177/0363546516659643.

[34] Thermann H, Becher C, Vannini F, Giannini S. Autologous matrix-induced chondrogenesis and generational development of autologous chondrocyte implantation. Oper Tech Orthop 2014;24(3)210–5, doi:http://dx.doi.org/10.1053/j.oto.2014.05.001 2014/09/01/.

[35] Walther M, Martin K. Scaffold based reconstruction of focal full thickness talar cartilage defects. Clin Res Foot Ankle 2013;1(2):1–5, doi:http://dx.doi.org/10.4172/2329-910X.1000115.

[36] Kubosch EJ, Erdle B, Izadpanah K, Kubosch D, Uhl M, Sudkamp NP, et al. Clinical outcome and T2 assessment following autologous matrix-induced chondrogenesis in osteochondral lesions of the talus. Int Orthop 2016;40(January (1)):65–71, doi:http://dx.doi.org/10.1007/s00264-015-2988-z.

[37] D'Ambrosi R, Maccario C, Ursino C, Serra N, Usuelli FG. The role of bone marrow edema on osteochondral lesions of the talus. Foot Ankle Surg 2018;24(June (3)):229–35, doi:http://dx.doi.org/10.1016/j.fas.2017.02.010.

[38] Baumfeld T, Baumfeld D, Prado M, Nery C. All-arthroscopic AMIC((R)) (AT-AMIC) for the treatment of talar osteochondral defects: a short follow-up case series. Foot (Edinb) 2018;37:23–7, doi:http://dx.doi.org/10.1016/j.foot.2018.07.006 Dec.

[39] D'Ambrosi R, Villafane JH, Indino C, Liuni FM, Berjano P, Usuelli FG. Return to sport after arthroscopic autologous matrix-induced chondrogenesis for patients with osteochondral lesion of the talus. Clin J Sport Med 2019;29(November (6)):470–5, doi:http://dx.doi.org/10.1097/JSM.0000000000000560.

[40] Sadlik B, Kolodziej L, Puszkarz M, Laprus H, Mojzesz M, Whyte GP. Surgical repair of osteochondral lesions of the talus using biologic inlay osteochondral reconstruction: clinical outcomes after treatment using a medial malleolar osteotomy approach compared to an arthroscopically-assisted approach. Foot Ankle Surg 2019;25(August (4)):449–56, doi:http://dx.doi.org/10.1016/j.fas.2018.02.010.

[41] Usuelli FG, D'Ambrosi R, Maccario C, Boga M, de Girolamo L. All-arthroscopic AMIC((R)) (AT-AMIC((R))) technique with autologous bone graft for talar osteochondral defects: clinical and radiological results. Knee Surg Sports Traumatol Arthrosc 2018;26(March (3)):875–81, doi:http://dx.doi.org/10.1007/s00167-016-4318-4.

[42] Schiavone Panni A, Del Regno C, Mazzitelli G, D'Apolito R, Corona K, Vasso M. Good clinical results with autologous matrix-induced chondrogenesis (AMIC) technique in large knee chondral defects. Knee Surg Sports Traumatol Arthrosc 2018;26(April (4)):1130–6, doi:http://dx.doi.org/10.1007/s00167-017-4503-0.

[43] Richter M, Zech S, Geerling J, Frink M, Knobloch K, Krettek C. A new foot and ankle outcome score: questionnaire based, subjective, Visual-Analogue-Scale, validated and computerized. Foot Ankle Surg 2006;12(4)191–9, doi:http://dx.doi.org/10.1016/j.fas.2006.04.001 2006/01/01/.

[44] Steadman JR, Rodkey WG, Singleton SB, Briggs KK. Microfracture technique forfull-thickness chondral defects: technique and clinical results. Oper Tech Orthop 1997;7(4)300–4, doi:http://dx.doi.org/10.1016/S1048-6666(97)80033-X 1997/10/01/.

[45] Case JM, Scopp JM. Treatment of Articular Cartilage Defects of the Knee with Microfracture and Enhanced Microfracture Techniques. Sports Med Arthrosc Rev 2016;24(June (2)):63–8, doi:http://dx.doi.org/10.1097/JSA.0000000000000113.

[46] Benthien JP, Behrens P. Reviewing subchondral cartilage surgery: considerations for standardised and outcome predictable cartilage remodelling: a technical note. Int Orthop 2013;37(November (11)):2139–45, doi:http://dx.doi.org/10.1007/s00264-013-2025-z.

[47] Chen H, Sun J, Hoemann CD, Lascau-Coman V, Ouyang W, McKee MD, et al. Drilling and microfracture lead to different bone structure and necrosis during bone-marrow stimulation for cartilage repair. J Orthop Res 2009;27(November (11)):1432–8, doi:http://dx.doi.org/10.1002/jor.20905.

[48] Walther M, Altenberger S, Kriegelstein S, Volkering C, Roser A. Reconstruction of focal cartilage defects in the talus with miniarthrotomy and collagen matrix.

Oper Orthop Traumatol 2014;26(December (6)):603–10, doi:http://dx.doi.org/10.1007/s00064-012-0229-9.
[49] Dickhut A, Dexheimer V, Martin K, Lauinger R, Heisel C, Richter W. Chondrogenesis of human mesenchymal stem cells by local transforming growth factor-beta delivery in a biphasic resorbable carrier. Tissue Eng Part A 2010;16(February (2)):453–64, doi:http://dx.doi.org/10.1089/ten.TEA.2009.0168.
[50] Niemeyer P, Steinwachs M, Erggelet C, Kreuz PC, Kraft N, Kostler W, et al. Autologous chondrocyte implantation for the treatment of retropatellar cartilage defects: clinical results referred to defect localisation. Arch Orthop Trauma Surg 2008;128(November (11)):1223–31, doi:http://dx.doi.org/10.1007/s00402-007-0413-9.
[51] Steinwachs MR, Gille J, Volz M, Anders S, Jakob R, De Giromlamo L, et al. Systematic review and meta-analysis of the clinical evidence on the use of autologous matrix-induced chondrogenesis in the knee. Cartilage 20191947603519870846, doi:http://dx.doi.org/10.1177/1947603519870846 Sep 11.
[52] Gao L, Orth P, Cucchiarini M, Madry H. Autologous matrix-induced chondrogenesis: a systematic review of the clinical evidence. Am J Sports Med 2019;47(January (1)):222–31, doi:http://dx.doi.org/10.1177/0363546517740575.
[53] Loveday D, Clifton R, Robinson A. Interventions for treating osteochondral defects of the talus in adults. Cochrane Database Syst Rev 2010(August 4 (8)) CD008104, doi:http://dx.doi.org/10.1002/14651858.CD008104.pub2.
[54] Kitaoka HB, Alexander IJ, Adelaar RS, Nunley JA, Myerson MS, Sanders M. Clinical rating systems for the ankle-hindfoot, midfoot, hallux, and lesser toes. Foot Ankle Int 1994;15(July (7)):349–53, doi:http://dx.doi.org/10.1177/107110079401500701.
[55] Richter M, Zech S, Andreas Meissner S. Matrix-associated stem cell transplantation (MAST) in chondral defects of the 1st metatarsophalangeal joint is safe and effective-2-year-follow-up in 20 patients. Foot Ankle Surg 2017;23(September (3)):195–200, doi:http://dx.doi.org/10.1016/j.fas.2016.05.318.
[56] Rothrauff BB, Murawski CD, Angthong C, Becher C, Nehrer S, Niemeyer P, et al. Scaffold-based therapies: proceedings of the international consensus meeting on cartilage repair of the ankle. Foot Ankle Int 2018;39(July (1_suppl)), doi:http://dx.doi.org/10.1177/1071100718781864 41S-7S.