



Evidence Review:

Autologous chondrocyte implantation for osteocondral lesions of the talus (adults)

NHS England

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1. Introduction

Osteochondral lesions (OCLs) are areas of joint damage involving the articular hyaline cartilage and the underlying subchondral bone. These defects can cause pain, clicking, grinding or functional instability of the joint, and may lead to osteoarthritis and serious disability. The defects or lesions are thought to be caused by an ischaemic event affecting the joint, for example as a result of trauma or injury, or spontaneously, a condition called osteochondritis dissecans. Cartilage lacks blood and nerve supplies, and therefore has a limited potential for self-repair.

The ankle joint consists of three bones: the tibia, the fibula and the talus. The talus lies above the calcaneus and supports the weight of the body at the ankle. Osteochondral defects of the talus occur predominantly on the talar dome, which is the uppermost part of the talus. Patients with an osteochondral defect often have unresolved ankle pain.

Patients presenting with symptomatic osteochondral defects are first treated with either surgical debridement (alone or in combination with Kirschner-wire drilling or microfracture of the subchondral bone) or bone grafting. If the first surgery does not resolve the symptoms, patients may be referred to specialist orthopaedic centres for a resurfacing procedure.

Autologous chondrocyte implantation (ACI) is one type of resurfacing procedure, developed in the late 1980s to treat areas of cartilage damage in the knee. However, ACI has also been used rarely in other joints, such as the ankle. Second and third generation approaches have evolved over the years, but all ACI's are two-stage procedures. ACI involves harvesting the patient's own chondrocytes from the joint (either healthy articular cartilage taken from a non-articulating area or from the defect itself) during arthroscopic surgery. Chondrocytes are then cultured in a laboratory to increase their number. Chondrocytes can be cultured traditionally ('traditional ACI') or by using biomarkers to select cells most likely to produce hyaline cartilage; these cells are called characterised chondrocytes. Finally, the chondrocytes are implanted into the area of damaged cartilage during a second surgical procedure, in the hope that they will repair the damaged area. The aim is to repair the damaged area by resurfacing with defect with new hyaline cartilage.

In first generation ACI, the implanted cultured chondrocytes are covered with a cap made from periosteum (ACI-P), fibrous tissue that covers bones. In second generation ACI the cap is made from collagen (ACI-C). The third generation of ACI involved seeding the chondrocytes onto a porcine collagen membrane (ACI-M) to avoid chondrocytes leaking around the cap.

Chondroelect (Sobi) is currently licensed in the UK for repair of symptomatic cartilage defects of the knee. A number of other commercial ACI products are in clinical trials for knee repair. MACI (Vericel) was approved by the EMA but is no longer available commercially.

2. Summary of results

Osteochondral lesions (OCLs) of the talus, also known as osteochondritis dissecans, are areas of joint damage involving the articular hyaline cartilage and underlying subchondral bone.

Autologous chondrocyte implantation (ACI), is a two-stage procedure involving a first surgery to harvest cartilage cells, or chondrocytes, and a second surgery to implant the cells into the damaged area with the intention of resurfacing the defect with new cartilage.

Bone marrow derived chondrocyte transplantation (BMDCT) - an emerging procedure where a scaffold loaded with mesenchymal stem cells derived from the bone marrow is transplanted in the lesion to promote healing and repair.

Different metrics have been used to assess recovery and clinical effectiveness of OCL treatments in the studies reviewed. The most widely-used outcome scales include: (i) American Orthopaedic Foot and Ankle Society (AOFAS) score in which pain, function and alignment scores are assessed by the physician; (ii) the Visual Analogue Scale (VAS), which is a self-reported ten-point scale for pain; (iii) the Tegner scale, which is a self-reported measure of physical activity and performance, and (iv) the magnetic resonance observation of cartilage repair tissue (MOCART) score, which uses different variables to describe the constitution of the cartilage repair tissue and the surrounding structures.

This review of current evidence for autologous chondrocyte implantation was undertaken to answer the following questions:

Is ACI (first, second and third generation) clinically effective in adult patients with symptomatic osteochondral lesions of the talus?

Is ACI (first, second and third generation) cost effective in adult patients with symptomatic osteochondral lesions of the talus?

The body of evidence for this review comprises two systematic reviews, two case control studies and nine case series. Majority of findings in this are from smaller size retrospective single studies which could be particularly susceptible to bias, especially patient selection. In addition there is heterogeneity in terms of study design, patient characteristics, management methods and outcome assessment. The two systematic reviews included suffer from significant limitations in the methodology and lack of good quality studies available for review. In summary, there is low level and inconclusive evidence for clinical effectiveness of ACI in adult patients with symptomatic osteochondral lesions of the talus. The current evidence is unable to establish the superiority of ACI to existing treatment options currently available for these patients. There is no evidence available on cost effectiveness of ACI.

1. Is ACI (first, second and third generation) clinically effective in adult patients with symptomatic osteochondral lesions of the talus?

Niemeyer et al., (2012) systematically reviewed 16 retrospective studies to conclude an overall clinical success rate of 89.9% with limited clarity on the basis of this finding. Giannini et al. (2014), a retrospective case study with 46 patients, reported overall success rate was 93.5% at 7 years follow up with significant improvements in AOFAS from a mean pre-operative score of 57.2 ± 14.3 to 86.8 ± 13.4 at the 12-month follow up, and results continued to improve after three and seven years. A prospective case series with 18 patients, reported (50.3% +/- 13.2%) improvement in all clinical scores (FFI, AOFAS, MOCART and AAOS) 21 months after matrix-associated chondrocyte implantation (MACI) (Aurich et al., 2011).

Another recent retrospective case series (Kwak et al. 2014) reported the clinical outcomes of first generation ACI from 32 consecutive patients who had previously failed bone marrow stimulation, supporting the claim that ACI produced significant improvements in AOFAS score, Tegner activity score, and the Finsen score over a 70-month follow-up period. Magnan et al. (2012) investigated the effectiveness of MACI in a case series of 30 patients operated by a single surgeon, reporting significant improvement in AOFAS and VAS scores after 3 years follow-up.

Severe limitations of the studies including in the review especially potential for patient selection bias, lack of a comparator arm and heterogeneity of the study populations, are likely to significantly impact replication of these findings in real –world setting.

While studies included in this review suggest that autologous chondrocyte implantation (ACI) is clinically effective in the treatment of talus OCL, the extent of ACI's clinical effectiveness only becomes meaningful in the context of existing treatments or emerging technologies. Zengerink et al., 2010 included 52 studies in a systematic review of all OCL of talus treatments, totalling 1361 patients. In this study, ACI had an overall success rate of 76%. However, the authors reported better overall success rates for OATS (87%) and BMS (85%). The statistical significance of the reported difference was not reported. Heterogeneity across the studies and patient population was not addressed. A smaller retrospective case control study of 20 patients study reported that MACT and microfracture (bone marrow stimulation) were both equally effective without any significant differences in clinical outcomes. (Apprigh et al., 2012)

A recent retrospective case-control study reporting comparable levels of effectiveness when ACI and bone marrow derived cells transplantation (BMDCT), were used to treat a homogenous patient sample (n=40 for each subgroup) with isolated osteochondral lesions of the talar (Buda et al., 2015). Both treatments were reported to produce excellent AOFAS scores postoperatively, which was further supported by clinical and radiological evaluation (e.g. using Magnetic Resonance Observation of Cartilage Repair Tissue scoring system (MOCART) scores). However, neither of these treatments are currently considered standard interventions for OCLs of the talus.

In summary, the current evidence for clinical effectiveness of ACI in adult patients with symptomatic osteochondral lesions of the talus is inconclusive.

2. Is ACI (first, second and third generation) cost effective in adult patients with symptomatic osteochondral lesions of the talus?

The review did not identify any relevant studies on cost effectiveness of ACI used in the treatment of osteochondral lesions of the talus compared to existing treatments. In some studies, authors have expressed opinion that ACI may not be more cost effective compared to other treatments (Zengerink et al., 2010, Apprich et al., 2012, Magnan et al., 2012). However, these views are yet to be substantiated with a robust, statistically-backed evidence base.

3. Research questions

Is ACI (first, second and third generation) clinically effective in adult patients with symptomatic osteochondral lesions of the talus?

Is ACI (first, second and third generation) cost effective in adult patients with symptomatic osteochondral lesions of the talus?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

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Appendix One

Grade	Study design and intervention			Outcomes					Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
4	Systematic	Total 213 patients. Mean 13 patients/study (range 2 - 46)	Autologous chondrocyte implantation (ACI)	Clinical effectiveness of the intervention	Clinical success rate and Mean Coleman Methodology Score	Overall clinical success rate was 89.9%. Mean Coleman Methodology Score (CMS) was 65 points	-	-	Niemeyer, Philipp; Salzmann, Gian; Schmal, Hagen; Mayr, Hermann; Südkamp, Norbert P.. 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(9):1696-1703.	-	-	Evidence concerning the use of ACI for osteochondral and chondral defects of the talus is still elusive. Although clinical outcome from currently available studies seems promising, it is difficult to establish whether ACI is superior or inferior to other treatment methods such as osteochondral transplantation or microfracturing due to the lack of randomised controlled studies. All identified studies were single arm case series which may suffer from patient selection bias. In retrospective cases, not only is there risk of inconsistent patient selection criteria, treatment procedures could also differ due to the surgeon's decisions. The methodology behind results reported is unclear. The percentage of "good" and "excellent" results was considered "success rate", but this seems to be largely based on the author's opinion on the studies and were not backed by proper statistical analysis.

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3	Systematic	1361	ACI	Clinical effectiveness of the intervention compared to existing interventions	Study size weighted success rates. Based on 'good-excellent' scores on AOFAS, Hannover score VAS etc.	Overall success rates for intervention: 1. ACI: 45/59 patients = 76%; 2. Rest: 39/86 patients = 45%; 3. Cast: 44/83 patients = 53%; 4. Excision: 32/59 patients = 54%; 4. Excision and curettage: 199/259 = 77%; 5. Excision, curettage and BMS: 329/386 patients = 85%; 6. Excision, curettage and autogenous bone graft: 45/74 patients = 61%; 7. Antegrade (transmalleolar drilling: 26/41 patients = 63% 8. Osteochondral transplantation (OATS); 212/243 patients = 87%; 9. Retrograde drilling: 37/42 patients = 88%; 10. Fixation: 24/27 patients = 89%. BMS was identified as the treatment of choice, because it is both clinically effective and cost effective (based on?), compared to newer techniques such as OATS and ACI.	-	-	Zengerink, Maartje; Struijs, Peter A. A.; Tol, Johannes L.; van Dijk, Cornelis Niek. Treatment of osteochondral lesions of the talus: a systematic review. Knee Surg Sports Traumatol Arthrosc 2010;18(2):238-246.	-	-	All patients had osteochondral lesions of the talus. The systematic review was limited by the paucity of high quality studies that could provide evidence for OATS and ACI. Also, the last available study dates back to 2006; over the last nine years, the costs of performing ACI could be lower due to improvement in technology and surgical methods. Importantly, the patient sample size for BMS procedures was 386 patients whereas for ACI it was only 59. This asymmetry strongly suggests that in order to reduce statistical bias, more patients who have undergone ACI are required so that a more accurate assessment can be made. It is not clear if the reported difference is statistically significant. Also, there was no attempt to address patient heterogeneity in the subgroups.
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2-	Case-control	80 patients. ACI (n=40), BMDCT (n=40)	ACI performed arthroscopically with a hyaluronic acid membrane	Clinical effectiveness of the intervention compared to existing interventions	1. AOFAS scores 2. Clinical and radiological evaluation, using MRI Mocart score and T2 mapping sequence	Clinical results were similar for both interventions at 48 months. No statistically significant influence was reported after evaluation of all the pre-operative parameters. 1. Both the techniques achieved excellent results, with a mean final AOFAS at 48 months of 90.5±12.0 points (ACI range 41–100; BMDCT range 66–100). 2. The X-ray projections taken at every follow-up showed no signs of joint degeneration in every patient of both groups MRI Mocart score was similar in both groups. 3. The T2 values of the repair tissue were in the range compatible with hyaline cartilage in 85 % of the BMDCT and in 75 % of the ACI, highlighting a higher presence of hyaline like values in the BMDCT group, and lower incidence of fibrocartilage as well.	Rate of return to sporting activity	ACI and BMDCT clusters achieved the same rate of return to sport (69 %) at the final follow-up of 48 months. The rate of return to sport activity showed slightly better results for BMDCT than ACI.	Buda, Roberto; Vannini, Francesca; Castagnini, Francesco; Cavallo, Marco; Ruffilli, Alberto; Ramponi, Laura; Pagliuzzi, Gherardo; Giannini, Sandro. Regenerative treatment in osteochondral lesions of the talus: autologous chondrocyte implantation versus one-step bone marrow derived cells transplantation. Int Orthop 2015;39(5):893-900.	-	-	Patients had focal, isolated osteochondral lesions of the talar dome. The OLT were all classified as type II or IIA (>1.5 cm ² in area and/or >5 mm deep, respectively). This study showed ACI and BMDCT to be effective regenerative techniques for the treatment of OLT. The study is limited by its retrospective design, which could introduce patient selection bias. Also, the two groups analysed had different rates of associate procedures which did not influence the outcome.
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3	Case series	32 consecutive patients, of which 29 patients were available for follow-up	First generation ACI	Clinical effectiveness of the intervention	1. AOFAS score 2. Tegner activity score 3. Finsen score 4. Clinical assessments with the simplified symptomatology evaluation (SSE) 5. Lysholm knee scores International	1. Mean AOFAS improved from 50.1 to 85.9 2. Mean Tegner score improved from 1.6 to 4.3 3. The Finsen score improved from 13.7 to 5.1 4. Preoperative: 26 rated their ankle as "poor" and 3 as "fair". Final follow-up: 9 ankles were rated as "excellent," 14 as "good," 5 as "fair", 1 as "poor" 5. Lysholm knee score from the donor knees: average 96.2 (range, 78-100) at final follow-up	Patient reported outcomes (informal verbal feedback)	90% of patients reported that they were satisfied with the procedure, and 93% said they would undergo the operation again.	Kwak, Steve K.; Kern, Brian S.; Ferkel, Richard D.; Chan, Keith W.; Kasraeian, Sina; Applegate, Gregory R.. Autologous chondrocyte implantation of the ankle: 2- to 10-year results. Am J Sports Med 2014;42(9):2156-2164.	-	-	The study included consecutive patients. Patients who had failed bone marrow stimulation techniques for osteochondral lesions of the talus. Patients had focal, contained, unipolar lesions greater than 1 cm2 to 2 cm2 in size; pain unresponsive to nonoperative management; persistent pain after previous drilling and/or microfracture; and magnetic resonance imaging (MRI) evidence of a cartilage defect and subchondral irregularity. The main weakness of this paper was the lack of a control or comparator arm, so while clinical effectiveness can be established, it cannot be compared to an existing intervention to assess superiority of clinical effectiveness. Although the selection criteria clearly stated the only patients who had failed previous surgery and underwent first generation ACI were included, this means that a key limitation of the study was that only first generation ACI was evaluated. Third generation procedures (MACI) have now generally replaced first generation ACI.
3	Case series	46	ACI	Clinical effectiveness of the intervention	Postoperative AOFAS	Mean pre-operative AOFAS score: 57.2 ± 14.3. AOFAS at the 12-month follow-up: 86.8 ± 13.4 (p = 0.0005); AOFAS at 36 months after surgery: 89.5 ± 13.4 (p = 0.0005); AOFAS at final follow-up of 87.2 ± 14.5 months: 92.0 ± 11.2 (p = 0.0005). The overall scores at the final follow-up were rated as 29 excellent, 9 good, 3 fair and 1 poor. Overall success rate was 93.5% at 7 years follow up.	-	-	Giannini, Sandro; Buda, Roberto; Ruffilli, Alberto; Cavallo, Marco; Pagliuzzi, Gherardo; Bulzamini, Maria Chiara; Desando, Giovanna; Luciani, Deianira; Vannini, Francesca. Arthroscopic autologous chondrocyte implantation in the ankle joint. Knee Surg Sports Traumatol Arthrosc 2014;22(6):1311-1319.	-	-	Patients had a lesion with a mean size of 1.6 cm2 (range 1.0–4.0). This study confirmed the ability of arthroscopic ACI to repair osteochondral lesions in the ankle joint with satisfactory clinical results after a 7 year follow-up. The key limitation of the study is the small patients size (48), which may impact the representativeness of study population and retrospective design, which is likely to introduce significant patients selection bias. Its key strength is the long duration (7 years) of follow-up, which allows statistical anomalies to be evened out.

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3	Case series	22	Matrix associated autologous chondrocyte implantation (MACI). Patients with osteochondritis dissecans also received an autologous bone graft	Clinical effectiveness of the intervention	1. American Orthopaedic Foot and Ankle Society (AOFAS) score 2.10-point visual analogue scale (VAS) 3. Tegner score Magnetic Resonance Observation of Cartilage Repair Tissue scoring system (MOCART)	1. The AOFAS score improved significantly from 70.1 to 87.9/92.6/93.5/95.0/95.5 and 95.3 points at three, six, 12, 24, 36 and 63.5 months, respectively 2. On a visual analogue scale, pain intensity decreased from 5.7 (± 2.6) to 0.9 (± 0.8) while subjective function increased from 5.3 (± 2.3) to 8.9 (± 0.9) at final follow-up (each $p < 0.001$). 3. The Tegner score rose significantly from 2.4 (± 1.2) to 4.7 (± 0.6). 4. The MOCART score improved from 62.6 (± 19.4) at three months to 83.8 (± 9.4) at final follow-up. Authors conclude that matrix associated autologous chondrocyte implantation (MACI) is capable of significant and stable long-term improvement of pain and functional impairment caused by focal full-thickness chondral and osteochondral talus	-	-	Anders, Sven; Goetz, Juergen; Schubert, Thomas; Grifka, Joachim; Schaumburger, Jens. Treatment of deep articular talus lesions by matrix associated autologous chondrocyte implantation-- results at five years. Int Orthop 2012;36(11):2279-2285.	-	-	This article analysed patients with full-thickness chondral or osteochondral lesions of the talus. The study lasted for an average of 63.5 months, which allows statistical anomalies and errors to even out over time. The biggest limitations are chiefly in the study design, which is a prospective case-series. the lack of a randomised control makes it difficult to assess the extent to which recovery was a result of the treatment. Furthermore, it is not possible to conclude that MACI is superior over other new or existing treatment options based on this study alone. The sample size is 22 patients, which is not large, but acceptable for this condition.
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3	Case series	30	MACI	Clinical effectiveness of the intervention	-	AOFAS: preoperative: 36.9 ± 6.6, follow-up: 83.9 ± 13.6 VAS: 141.1 ± 35.6 COUGHLIN: 3.1 ± 0.8 MOCART: preoperative: 6.3 ± 0.8, follow-up: 3.8 ± 0.9 We obtain excellent results in 17 patients (56,7%) out of 30, good results in 11 patients (36,7%) out of 30, and insufficient results in 2 cases (6,6%). Authors conclude that the results of this study support ACI/MACI as an effective procedure, but do not support any superiority of ACI/MACI over other techniques such as microfracture and microdrilling or OATS, regardless of the size of the lesions.	-	-	Magnan, B.; Samaila, E.; Bondi, M.; Vecchini, E.; Micheloni, G. M.; Bartolozzi, P.. Three-dimensional matrix-induced autologous chondrocytes implantation for osteochondral lesions of the talus: midterm results. Adv Orthop 2012;2012(0):9421-74.	-	-	Inclusion criteria in this study were patients affected by a posttraumatic and non traumatic osteochondritis dissecans, aged more than 16 years old and less than 50, osteochondral lesions sized more than 1.5 cm² and less than 4 cm². This study had several strengths. A single surgeon performed all the surgeries, hence reducing operator bias. Although it was a case series, which means it lacks a randomised control, it had a prospective design with clearly defined inclusion criteria such as age, condition and size of lesion.
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2-	Case-control	20 patients (MACT (n=10), MFX (n=10))	Matrix-associated autologous chondrocyte transplantation (MACT)	Clinical effectiveness of the intervention compared to existing interventions	1. Postoperative AOFAS score (an AOFAS score of 100e90 points as excellent, 89e80 as good, 79e70 as fair, and below 69 as poor results) 2. Morphological and clinical scoring	The mean AOFAS score improved significantly ($P < 0.001$) for both groups (MACT: from preoperatively 48.8 +/-20.4 to post-operatively 83.6 +/- 9.7; MFX: pre-operatively 44.3 +/-16.5 to post-operatively 77.6 +/-13.2). No differences in the AOFAS ($P = 0.327$) and MOCART ($P = 0.720$) score were observed between MACT and microfracture postoperatively. The study concludes that MACT and microfracture are both effective, and do not show significant differences in clinical outcomes. At a mean duration of 4 years after MACT, 70% of our patients were rated as excellent and good, whereas 30% were rated as fair and poor. Microfracture patients yielded excellent and good results in 60% and fair or poor results in 40% of cases at a mean follow-up of nearly 5 years	-	-	Apprich, S.; Trattng, S.; Welsch, G. H.; Noebauer-Huhmann, I. M.; Sokolowski, M.; Sokolowski, M.; Hirschfeld, C.; Stelzeneder, D.; Domayer, S.. Assessment of articular cartilage repair tissue after matrix-associated autologous chondrocyte transplantation or the microfracture technique in the ankle joint using diffusion-weighted imaging at 3 Tesla. Osteoarthr. Cartil. 2012;20(7):703-711.	-	-	The MACT patient group consisted of six females and four males (mean age 31 6.5 years; BMI 25.1 4.2 kg/m2; postoperative interval 48 21.5 months; mean defect size 1.21 0.6 cm2) (mean SD). The study was limited by a relatively small number of patients in both groups and the difference in follow-up time points - i.e. a large albeit statistically insignificant span of follow-up times. The patients were consecutive, but authors included clear inclusion criteria and performed an unpaired Student's t test for age, BMI and post-operative interval to minimise patient selection bias. Despite the precautions taken, the patient subgroups included in the study are likely to be highly selected and hence may not fully represent the actual patient population for ACI. The study was of good quality since the MACT treatment group was compared to a control group receiving microfracturing (MFX).
3	Case series	27	Matrix-associated chondrocyte implantation (MACI)	Clinical effectiveness of the intervention	1. AOFAS score 2. Tegner score 3. University of California lower extremity activity scale	Most patients report a significant improvement in symptoms with full return to activities of daily living. However, 36% of those under 40 years of age and 78% of those over 40 years of age reported restricted recreational activity. In addition, 54% of patients over 40 continue to have moderate or severe pain	-	-	Dixon, Sean; Harvey, Leigh; Baddour, Edward; Janes, Greg; Hardisty, Gerard. Functional outcome of matrix-associated autologous chondrocyte implantation in the ankle. Foot Ankle Int 2011;32(4):368-374.	-	-	This review is based on the study abstract. The full text of the article was not available online. Therefore the results need to be interpreted with caution in the absence of a detailed appraisal of the study methodology and results.

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3	Case series	20	ACI	Clinical effectiveness of the intervention	1. AOFAS score 2. MOCART score	1. The AOFAS score increased from 59 ± 16 preoperatively to 84 ± 18 at follow-up ($P < 0.0005$) Results were rated, respectively, as excellent in 9 (45%) patients, good in 7 (35%); fair in 3 (10%), and poor in 2 (10%). 2. Non-significant correlations of the Mocar score were found with the clinical score. The authors concluded that the study supported ACI as an effective methodology in the treatment of osteochondral lesions of the talus. The most satisfactory results were observed with time; namely in patients with more than 4 years' follow-up.	-	-	Battaglia, Milva; Vannini, Francesca; Buda, Roberto; Cavallo, Marco; Ruffilli, Alberto; Monti, Carlo; Galletti, Stefano; Giannini, Sandro. Arthroscopic autologous chondrocyte implantation in osteochondral lesions of the talus: mid-term T2-mapping MRI evaluation. Knee Surg Sports Traumatol Arthrosc 2011;19(8):1376-1384.	-	-	Studied patients with osteochondral lesion of the talus, aged 35 ± 8 years. The biggest limitation of the study is the patient sample size ($n=20$). However, the authors noted that this was, to their knowledge, the largest study reporting clinical, MRI morphological outcomes for arthroscopic ACI.
3	Case series	38	ACI	Clinical effectiveness of the intervention	1. MOCART score 2. second look arthroscopy	For patients with a pre-operative AOFAS score of < 73.4 points, the post operative AOFAS score was 41.6 ± 8.9 . For patients whose preoperative AOFAS scores were > 73.4 points, the postoperative AOFAS score was 38.6 ± 12.2	-	-	Lee, K. T.; Lee, Y. K.; Young, K. W.; Park, S. Y.; Kim, J. S.. Factors influencing result of autologous chondrocyte implantation in osteochondral lesion of the talus using second look arthroscopy. Scand J Med Sci Sports 2012;22(4):510-515.	-	-	The patient's age and the size of the lesion were factors affecting cartilage repair as observed through a second look arthroscopy 1 year after ACI for the repair of an OLT. The study was limited in that it did not have a randomised control. Also, 38 patients is not a large number, but for this treatment method (ACI), it is an acceptable sample size.

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3	Case series	17	Autologous chondrocyte transplantation (ACT) (n=4) or Matrix-associated autologous chondrocyte transplantation (MACT) (n=13)	Clinical effectiveness of the intervention	(AOFAS), a modified Cincinnati score, and a subjective ankle-hindfoot score (AHS)	The AOFAS improved from 50.0 to 87.3, the Ankle hindfoot score (AHS) improved from 43.8 to 84.1, and the modified Cincinnati score from 2.9 to 6.9. MRI data demonstrated good defect filling, and T2 mapping results indicated that the collagen and water content of the repair tissue was comparable to adjacent cartilage	-	-	Nehrer, Stefan; Domayer, S. E.; Hirschfeld, Clemens; Stelzeneder, David; Trattinig, Siegfried; Dorotka, Ronald. Matrix-Associated and Autologous Chondrocyte Transplantation in the Ankle: Clinical and MRI Follow-up after 2 to 11 Years. Cartilage 2011;2(1):81-91.	-	-	Patients selected had chronic symptomatic cartilage defects in the ankle. The mean size of the defects was 1.5 ± 0.7 cm ² . This study was designed as a prospective case series, which makes it subject to patient selection bias. The lack of a control or comparator makes it difficult to show the extent to which recovery was because of the surgery, or to assess effectiveness as compared to new or existing treatments for OCLs of the talus. Additionally, the very small patient sample size of 17 patients lends the study little statistical weight.
3	Case series	18	MACI	Clinical effectiveness of the intervention compared to existing interventions	1. Foot Function Index (FFI), 3. American Orthopaedic Foot & Ankle Society (AOFAS) scale Core Scale of the Foot and Ankle Module of 4. American Academy of Orthopaedic Surgeons (AAOS) Lower Limb Outcomes Assessment Instruments, 5. Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score	A significant improvement (50.3% +/- 13.2%) in all clinical scores was noted. 1. FFI pain before MACI: 5.5 +/- 2.0, after MACI: 2.8 +/- 2.2; 2. FFI disability module before MACI: 5.0 +/- 2.3, after MACI: 2.6 +/- 2.2 3. AOFAS before MACI: 58.6 +/- 16.1, after MACI: 80.4 +/- 14.1; 4a. AAOS standardised mean before MACI: 59.9 +/- 16.0, after MACI: 83.5 +/- 13.2; 4b. AAOS normative score before MACI: 23.0 +/- 13.0, after MACI: 42.2 +/- 10.7). According to the AOFAS Hindfoot score, 64% were rated as excellent and good, whereas 36% were rated fair and poor. 5. The mean MOCART score was 62.4 +/- 15.8 points Authors concluded that The study showed that MACI had modest improvements on clinical outcomes after an average follow-up of 21 months.	-	-	Aurich, Matthias; Bedi, Harvinder S.; Smith, Peter J.; Rolauffs, Bernd; Mückley, Thomas; Clayton, James; Blackney, Mark. Arthroscopic treatment of osteochondral lesions of the ankle with matrix-associated chondrocyte implantation: early clinical and magnetic resonance imaging results. Am J Sports Med 2011;39(2):311-319.	-	-	Patients had OCLs in the ankle classified as chronic type II (0-5 mm deep) or IIA (0.5 mm deep). The study is limited by the relatively short follow-up period of 21.4 months (mean), since MACI is a substantial surgery and recovery time alone takes around 12 months. Also, this study lacked a randomised control group and had a small patient size of 18, introducing bias and difficulty in the assessment of MACI over other new or existing interventions in the treatment of OCLs.

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Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	n/a
Updated search terms - Population	talus OR ankle OR talar
Updated search terms - Intervention	autologous chondrocyte* implantation OR autologous cartilage implantation OR autologous chondrocyte* transplantation OR autologous cartilage transplantation OR autologous cultured chondrocyte* OR ACI OR ACI-C OR ACI-P OR ACI-P OR ACI-M OR ACT OR MACI OR matrix-based autologous OR matrix based autologous OR matrix-associated autologous OR matrix associated autologous OR matrix-associated chondrocyte* OR matrix associated chondrocyte* OR matrix-induced autologous OR matrix induced autologous OR matrix-applied autologous OR matrix applied autologous OR matrix-applied characterised autologous OR matrix applied characterised autologous OR matrix-assisted autologous OR matrix assisted autologous OR chondron OR ChondroCelect OR Carticel OR Novocart
Updated search terms - Comparator	n/a
Updated search terms - Outcome	n/a
Inclusion criteria	General inclusion criteria
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	n/a

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Exclusion criteria	General exclusion criteria
	Studies with the following characteristics will be excluded:
	1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist) 7. Narrative / non-systematic reviews (relevant referenced studies to be included)
	Specific exclusion criteria
	n/a