

Osteochondral allograft transplantation for the knee (or other joints)

Systematic Review



Ludwig Boltzmann Institut
Health Technology Assessment

Decision Support Document No. 115
ISSN online: 1998-0469

Osteochondral allograft transplantation for the knee (or other joints)

Systematic Review



Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, March 2019

Project Team

Project leader: Sabine Geiger-Gritsch, Dr. scient.med, Mag. sc.hum, Mag. pharm.

Authors: 1. Author: Thomas Vreugdenburg, BHSc (Hons), PhD
2. Author: Katharina Rosian, BSc, MSc
3. Author: Meegan Vandeppeer, BSc (Hons), PhD
4. Author: Danielle Stringer, BSc, MPH

Project Support

Systematic literature search: Tarquin Mittermayr, BA(Hons), MA

External Review: PD Dr. Gerwin A. Bernhardt, MBA, FACS, University Clinic for Orthopaedics and Traumatology, Medical University Graz, Graz

Internal Review: Sabine Geiger-Gritsch, Dr. scient.med, Mag. sc.hum, Mag. pharm.

Correspondence

Katharina Rosian: Katharina.Rosian@hta.lbg.ac.at

This report should be referenced as follows:

Vreugdenburg T, Rosian K, Vandeppeer M, Stringer D. Allograft transplantation for the knee (or other joints). Decision Support Document No. 115; 2019. Vienna: Ludwig Boltzmann Institute for Health Technology Assessment.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

Disclaimer

The external reviewers did not co-author the scientific report and do not necessarily all agree with its content. Only the LBI-HTA is responsible for errors or omissions that could persist. The final version and the policy recommendations are under the full responsibility of the LBI-HTA.

The HTA Core Model[®], developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. The following version of the Model was used: HTA Core Model Version 4.2. Use of the HTA Core Model does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

CONTENT INFORMATION

Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Wien
<https://hta.lbg.ac.at/page/imprint>

Responsible for content:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisonsgasse 7/20, A-1090 Vienna
<https://hta.lbg.ac.at/>

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at <http://eprints.hta.lbg.ac.at>

Decision Support Document No.: 115

ISSN-online: 1998-0469

© 2019 LBI-HTA – All rights reserved

Contents

Executive summary.....	7
Zusammenfassung	10
1 Scope	15
1.1 PICO question	15
1.2 Inclusion criteria	15
2 Methods	17
2.1 Research questions	17
2.2 Sources.....	18
2.3 Systematic literature search.....	19
2.4 Flow chart of study selection	19
2.5 Analysis	20
2.6 Synthesis.....	20
3 Description and technical characteristics of technology	21
4 Health problem and current use.....	27
5 Clinical effectiveness	31
5.1 Outcomes.....	31
5.2 Included studies.....	32
5.3 Results	34
6 Safety.....	39
6.1 Outcomes.....	39
6.2 Included studies.....	39
6.3 Results	40
7 Quality of evidence	43
8 Discussion	47
9 Recommendation	51
10 References.....	53
Appendix	59
Evidence tables of individual studies included for clinical effectiveness and safety	59
Risk of bias tables and GRADE evidence profile	65
Applicability table	73
List of ongoing trials	74
Literature search strategies.....	75
Search strategy for CRD (DARE, NHS-EED, HTA).....	75
Search strategy for Ovid Medline	75
Search strategy for Embase	76
Search strategy for The Cochrane Library	77

List of figures

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram) 20

Figure 3-1: Intraoperative image of an osteochondral allograft transplant procedure in the knee 21

Figure 3-2: Arthroscopic image of a chondral lesion treated with microfracture. 22

Figure 3-3: Images of a mosaicplasty procedure 22

List of tables

Table 1-1: Inclusion criteria 15

Table 4-1: Classification of cartilage defects by Outerbridge..... 27

Table 4-2: Classification of chondral defects by International Cartilage Repair Society 28

Table 7-1: Summary of findings table of osteochondral allograft transplantation (ankle) 44

Table 7-2: Summary of findings table of osteochondral allograft transplantation (knee) 45

Table 9-1: Evidence based recommendations 51

Table A-1: Osteochondral allograft transplantation: Results from randomised controlled trials (ankle)..... 59

Table A-2: Osteochondral allograft transplantation: Results from observational studies
of osteochondral allograft transplant (knee and ankle) 61

Table A-3: Risk of bias – study level (randomised studies for knee) 65

Table A-4: Risk of bias – study level (case series for knee and ankle)..... 66

Table A-5: Evidence profile: efficacy and safety of osteochondral allograft transplantation (ankle) 68

Table A-6: Evidence profile: efficacy and safety of osteochondral allograft transplantation (knee) 70

Table A-7: Summary table characterising the applicability of a body of studies 73

Table A-8: List of ongoing trials of osteochondral allograft transplantation..... 74

List of abbreviations

ACI.....	Autologous chondrocyte implantation
AdHopHTA.....	Adopting hospital-based HTA in EU
ADL	Activities of daily living
AHRQ	Agency for Healthcare Research and Quality
CE.....	Conformité Européene (European Conformity)
COOP.....	Dartmouth Cooperative Functional Assessment Charts
CRD	Centre for Reviews and Dissemination
DARE.....	Database of Abstracts of Reviews of Effects
EBM	Evidence based medicine
EUTCD.....	European Union Tissue and Cells Directives
FAAM	Foot and Ankle Ability Measure
GRADE.....	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health Technology Assessment
ICRS.....	International Cartilage Repair Society
IHE.....	Institute of Health Economics
IKDC.....	International Knee Documentation Committee
KOOS.....	Knee injury and Osteoarthritis Outcome Score
MACI	Matrix-induced autologous chondrocyte implantation
MCID.....	Minimum clinical important difference
NHS-EED.....	National Health Service-Economic Evaluation Database
NICE.....	National Institute for Health and Care Excellence
OCA.....	Osteochondral allograft transplantation
OLT.....	Osteochondral lesions of the talar dome
POP	Planned and Ongoing Projects database
QoL	Quality of life
RCT.....	Randomised controlled trial
RoB.....	Risk of bias
SF-36	Short Form 36
VAS	Visual analogue scale
WOMAC.....	Western Ontario and McMaster Universities Osteoarthritis Index

Executive summary

Introduction

Health Problem

This systematic review is focussed on patients with articular cartilage defects. Articular cartilage, which covers the ends of bones, decreases friction and provides cushioning in joints. Defects in articular cartilage and subchondral bone can be caused by trauma, cancer, or other arthropathies. Osteochondral defects increase in friction in joints, which can lead to inflammation, swelling, pain and stiffness.

focus on patients with articular cartilage defects

Description of Technology

In theory, osteochondral allograft transplantation (OCA) can be used to treat chondral and osteochondral defects of all sizes, locations and contours; however, it is generally indicated for the treatment of lesions greater than 2cm², and failing conservative management or first-line surgical treatment. It has been mainly used to treat the knee joint but has also been used to treat the ankle, shoulder and elbow. In the absence of OCA, other surgical procedures such as osteochondral autologous transplantation, mosaicplasty, and microfracture may be considered, depending on the size and location of the defect.

osteochondral allograft transplantation (OCA) to treat (osteo)chondral defects in the knee and other joints (ankle, shoulder, elbow)

Research question

Is osteochondral allograft transplantation for the knee or other joints, in comparison to other surgical management, in patients with osteochondral defects, more effective and safe concerning pain, function, quality of life, implant failure and adverse events?

osteochondral allograft transplantation more effective and safe?

Methods

A systematic review was conducted to investigate the safety and effectiveness of OCA. Four biomedical databases (Medline, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination) were searched from inception to 12 December 2018. At least two authors independently conducted the study selection (TV, KR), data extraction (TV, KR, DS), and quality appraisal (TV, KR, DS). Only prospective studies with at least two years of follow-up were considered for inclusion.

literature search in databases, selection, extraction and quality appraisal by at least two authors

Domain effectiveness

Critical outcomes used to evaluate the relative efficacy of OCA included changes in pain scores (e.g. KOOS-Pain, VAS, WOMAC-Pain), changes in disease-specific function scores (e.g. IKDC, WOMAC, KOOS), quality of life, and the necessity for joint replacement.

pain, function, quality of life and necessity for joint replacement for effectiveness

Domain safety

Critical outcomes used to evaluate the relative safety of OCA included procedure-related mortality, adverse events, and transplant failure rates.

mortality, complications and transplant failure for safety

Results

Available evidence

1 RCT (n=40) and
1 case series (n=16)
for ankle joint

4 case series (n=165)
for knee joint

One randomised controlled trial (RCT) was identified (n=40), which investigated OCA to treat ankle defects. In addition, one case series investigating ankle defects (n=16), included for the assessment of safety only, and four case series investigating knee defects (n=165) were identified. No relevant evidence was identified for other joints.

Clinical effectiveness

pain:
ankle – no difference
between groups;
knee – significant
better reduction

There was no difference in *pain* reported across groups in the RCT comparing *ankle OCA* to autologous grafting ($p=0.15$). Pain was measured using three different scales in the case series studies on *knee OCA*, which all showed a statistically significant reduction between pre-operative and post-operative scores. The quality of evidence for this outcome was very low.

function: ankle –
increase in groups;
knee – improvements
between pre- &
post-operative scores

Function increased in both *ankle OCA* and autologous ankle transplant groups in the RCT (n=40), with no significant difference reported between groups ($p=0.25$). *Knee OCA* was reported using a range of scales, including IKDC, WOMAC (function), WOMAC (overall), modified Cincinnati knee-rating score (function), and modified Cincinnati knee-rating score (function). All of the included case series reported statistically significant improvements in function between pre-operative and post-operative scores. The quality of evidence for this outcome was very low.

quality of life:
knee – improvements
between pre- &
post-operative scores

Quality of life was not reported for *ankle OCA*. Improvements were reported by two case series on *knee OCA*, which demonstrated statistically significant improvements between pre- and post-operative KOOS (QoL) scores at 2-years follow-up ($p<0.001$). The quality of evidence for this outcome was very low.

joint replacement:
knee – 3.0-6.6% in
2 case series

Necessity of total joint replacement was not reported for *ankle OCA*. Two case series on *knee OCA* reported progression to arthroplasty, of 3.0% (1/34) over 2 years, and 6.6% (6/91) over a mean of 5.7 years, respectively. The data were too limited to draw meaningful conclusions for this outcome.

Safety

mortality: not reported

No *procedure-related mortality* was reported in any of the included studies for knee and ankle.

complications:
ankle – no difference
between groups;
knee – 4.3-26.5% across
studies

Complication rates were reported variably across the included studies. The RCT (n=40) reported no difference between *ankle OCA* and autologous transplant (RR=0.93, 95% CI 0.24 to 5.60). Reported complications for *knee OCA* ranged from 4.3% to 26.5%. The most common complications included fragmentation of delamination of the graft, fraying, and stiffness requiring manipulation. The quality of evidence for this outcome was very low.

failure rate:
ankle – higher for OCA
compared to autologous
grafts (RCT),
absolute failure rates
ranged from 12.5-29.4%;
knee – 7.0-11.8%

The relative *failure rate* for *ankle OCA* was higher compared to autologous grafts (RR = 1.25, 95% CI 0.20 to 7.92), as reported in one RCT (n=40) with two years of follow-up; however, this study lacked power to detect a significant difference. Failure rates for ankle OCA ranged from 12.5% over 2 years, to 29.4% over a mean of 4.1 years. Failure rates were lower for *knee OCA*, ranging between 7.0% to 11.8% over 2 years. The quality of evidence for this outcome was very low.

Upcoming evidence

There is only one ongoing clinical trial of OCA, which is a single-arm trial with an estimated enrolment of 50 patients and completion date of April 2020. As such, there are currently no ongoing trials that are likely to influence a decision on OCA in the near future.

**only 1 ongoing
single-arm trial**

Reimbursement

Currently, OCA is not reimbursed by the Austrian health care system for treating osteochondral defects in articular cartilage.

**OCA not reimbursed
in Austria**

Discussion

There is a paucity of rigorous, prospective data investigating OCA for treating osteochondral defects. The overall quality of the evidence that was available for ankle and knee indications was low or very low for the reported outcomes.

**low or very low quality
of evidence**

The main limitations in the evidence base were related to small sample sizes, a lack of comparative data, and short follow-up durations. Although a minimum of 24 months was set as inclusion criteria in this review, long-term outcomes such as graft failure require a minimum of four years follow-up to evaluate. None of the available evidence met this criterion. In addition, the only available RCT had a high risk of bias due to inadequate allocation concealment, randomisation and blinding.

**evidence base as
main limitation, only
1 RCT with high risk
of bias included**

Recommendation

The current evidence is not sufficient to prove that OCA for the knee and other joints, for the treatment of osteochondral defects, is more effective and equally safe than other surgical procedures. Furthermore, the prospective single-arm studies had insufficient power to demonstrate treatment efficacy. Based on available evidence, inclusion in the hospital benefit catalogue is not recommended at this time.

**evidence not sufficient

OCA not recommended
for reimbursement**

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

**Fokus auf
PatientInnen mit
Gelenkknorpeldefekten**

Die vorliegende systematische Übersichtsarbeit konzentrierte sich auf PatientInnen mit Gelenkknorpeldefekten. Gelenkknorpel bedecken die Enden der Knochen und verringern somit die Reibung bzw. sorgen für die Dämpfung der Gelenke. Defekte im Gelenkknorpel und im subchondralen Knochen können durch Traumata, Krebs oder andere Arthropathien verursacht werden. Osteochondrale Defekte erhöhen die Reibung in den Gelenken, was zu Entzündungen, Schwellungen, Schmerzen und Steifheit führen kann.

Beschreibung der Technologie

**osteochondrale Allograft
Transplantation (OCA)
zur Behandlung von
(osteo)chondralen
Defekten im Knie und
anderen Gelenken
(Knöchel, Schulter,
Ellbogen)**

Grundsätzlich kann die osteochondrale Allograft Transplantation (OCA) verwendet werden, um chondrale und osteochondrale Defekte jeder Größe, Position und Umgebung zu behandeln. Im Speziellen ist die OCA jedoch für die Behandlung von Läsionen, die größer als 2 cm² sind und nach einem Versagen der konservativen Behandlung oder der chirurgischen Erstlinienbehandlung indiziert. Die OCA wird hauptsächlich zur Behandlung des Kniegelenks, sowie des Knöchel-, Schulter- und Ellbogengelenks eingesetzt. Ist eine OCA nicht indiziert, können abhängig von der Größe und der Lokalisation des Defekts andere chirurgische Verfahren wie osteochondrale autologe Transplantation, Mosaikplastik und Mikrofrakturierung in Betracht gezogen werden.

Wissenschaftliche Fragestellung

Forschungsfrage

Ist bei PatientInnen mit osteochondralen Defekten eine osteochondrale Allograft Transplantation für das Knie oder andere Gelenke im Vergleich zu anderen chirurgischen Maßnahmen wirksamer in Bezug auf Schmerzen, Funktion (der Gelenke), Lebensqualität und der Notwendigkeit eines Gelenkersatzes und sicherer im Hinblick auf unerwünschte Ereignisse?

Methoden

**Literatursuche
in Datenbanken,
Selektion, Extraktion
und Qualitätsbewertung
von mindestens
2 AutorInnen**

Zur Beantwortung der Forschungsfrage wurde am 12. Dezember 2018 eine systematische Literatursuche in vier Datenbanken durchgeführt:

- ✿ Medline,
- ✿ Embase,
- ✿ Cochrane Library,
- ✿ University of York Center for Reviews und Dissemination.

Mindestens zwei AutorInnen führten unabhängig voneinander die Studienauswahl (TV, KR), Datenextraktion (TV, KR, DS) und Qualitätsbewertung (TV, KR, DS) durch. Nur prospektive Studien mit einer Nachbeobachtungszeit von mindestens zwei Jahren wurden in Betracht gezogen.

Klinische Wirksamkeit

Die kritischen Endpunkte, die als Basis für die Bewertung der Wirksamkeit von OCA herangezogen wurden, umfassten:

- ✧ Veränderungen der Schmerzwerte (z. B. mittels KOOS-Pain, VAS, WOMAC-Pain),
- ✧ Veränderungen der krankheitsspezifischen Funktion des Kniegelenks bzw. anderer Gelenke (z. B. mittels IKDC, WOMAC, KOOS),
- ✧ Lebensqualität und
- ✧ Notwendigkeit eines Gelenkersatzes.

entscheidende
Endpunkte für
Wirksamkeit ...

Sicherheit

Die Endpunkte, die für die Ableitung einer Empfehlung zur Sicherheit der OCA herangezogen wurden, umfassten:

- ✧ interventionsbedingte Mortalität,
- ✧ unerwünschte Ereignisse und
- ✧ Versagen des Transplantats.

... und Sicherheit

Ergebnisse

Verfügbare Evidenz

Zur Bewertung der Wirksamkeit konnte lediglich eine randomisierte kontrollierte Studie (RCT) mit 40 PatientInnen identifiziert werden, die die OCA im Vergleich zur autologen Transplantation für die Behandlung von Sprunggelenksdefekten untersuchte.

1 RCT (n=40)
für Sprunggelenk

Darüber hinaus konnten eine prospektive Fallserie zur Untersuchung von Sprunggelenksdefekten (n=16) und vier prospektive Fallserien, die Kniedefekte (n=165) untersuchten, für die Bewertung der Sicherheit identifiziert werden, die den Einschlusskriterien des vorliegenden Berichts entsprachen. Es konnte keine relevante Evidenz für andere Gelenke identifiziert werden. Für prospektive Studien wurde ein Nachbeobachtungszeitraum von mindestens zwei Jahren als Einschlusskriterium festgelegt.

zusätzlich:
1 Fallserie (n=16)
für Sprunggelenk und
4 Fallserien (n=165)
für Kniegelenk

Klinische Wirksamkeit

Es wurde kein Unterschied in der *Veränderung der Schmerzwerte* im RCT berichtet, bei denen die OCA am Sprunggelenk mit der autologen Transplantation verglichen wurde ($p=0.15$). Die Veränderung der Schmerzwerte wurde anhand von drei verschiedenen Skalen in den Fallserien zur Knie-OCA gemessen, die alle eine statistisch signifikante Reduktion zwischen präoperativen und postoperativen Scores zeigten. Die Qualität der Evidenz für dieses Ergebnis war sehr gering.

Schmerzen:
Sprunggelenk – kein
Unterschied zwischen
den Gruppen;
Knie – deutlich
größere Reduktion

Die *krankheitsspezifische Funktionalität* erhöhte sich im RCT (n=40) sowohl in der OCA-Gruppe als auch in der autologen Transplantationsgruppe, wobei zwischen den Gruppen kein signifikanter Unterschied berichtet wurde ($p=0.25$). In den Fallserien für das Kniegelenk wurde der Endpunkt anhand einer Reihe von Skalen gemessen, einschließlich IKDC, WOMAC (Funktion), WOMAC (Gesamt), modifizierter Cincinnati-Kniebewertung (Funktion) und modifizierter Cincinnati Kniebewertungs-Score (Funktion). Alle eingeschlossenen Fallserien berichteten über statistisch signifikante Funktionsverbesserungen zwischen präoperativen und postoperativen Scores. Die Qualität der Evidenz für dieses Ergebnis war sehr gering.

Funktionalität:
Sprunggelenk –
Verbesserung in
beiden Gruppen;
Knie – Verbesserungen
zwischen prä- und
postoperativen Scores

<p>Lebensqualität: Knie – Verbesserungen zwischen prä- und postoperativen Scores</p>	<p>Die Lebensqualität wurde im RCT für Sprunggelenks-OCA nicht berichtet. Verbesserungen in der Lebensqualität wurden in zwei Fallserien zum Kniegelenk berichtet, die statistisch signifikante Verbesserungen zwischen den prä- und postoperativen KOOS-Werten (QoL) nach einer 2-Jahres Nachbeobachtungszeit zeigten ($p < 0.001$). Die Qualität der Evidenz für dieses Ergebnis war sehr gering.</p>
<p>Gelenkersatz: Knie – 3.0-6.6 % in 2 Fallserien</p>	<p>Die Notwendigkeit eines vollständigen Gelenkersatzes wurde im RCT für Sprunggelenks-OCA nicht berichtet. In zwei Fallserien zum Kniegelenk wurde über einen Zeitraum von 2 Jahren ein Fortschreiten der Arthroplastik von 3.0 % (1/34) bzw. 6.6 % (6/91) über einen Zeitraum von 5.7 Jahren berichtet. Die Daten waren allerdings zu limitiert, um aussagekräftige Schlussfolgerungen für diesen Endpunkt ziehen zu können.</p>
<p>Sicherheit</p>	
<p>Mortalität: nicht berichtet</p>	<p>In keiner der eingeschlossenen Studien für das Knie- und Sprunggelenk wurde von einer interventionsbedingten Mortalität berichtet.</p>
<p>Komplikationen: Sprunggelenk – kein Unterschied zwischen den Gruppen; Knie – 4.3-26.5 % über Studien hinweg</p>	<p>Unerwünschte Ereignisse wurden in den eingeschlossenen Studien unterschiedlich berichtet. Das RCT für das Sprunggelenk ($n=40$) identifizierte keinen Unterschied zwischen der OCA und der autologen Transplantation (RR=0.93, 95 % CI 0.24 bis 5.60). Die berichteten unerwünschten Ereignisse für das Kniegelenk lagen zwischen 4.3 % und 26.5 %. Zu den häufigsten Komplikationen zählte die Fragmentierung der Delamination des Transplantats, die Auffaserung sowie Versteifungen, die Bewegung erfordern. Die Qualität der Evidenz für diesen Endpunkt war sehr gering.</p>
<p>Versagensrate: Sprunggelenk – höhere OCA-Werte im Vergleich zu autologer Transplantation (RCT); absolute Versagensrate zwischen 12.5 und 29.4 %; Knie – 7.0-11.8 %</p>	<p>Das relative Versagen des Transplantats wurde im RCT ($n=40$) für das Sprunggelenk berichtet und war nach zweijähriger Nachbeobachtungszeit für die OCA im Vergleich zur autologen Transplantation höher (RR=1,25, 95 % CI 0,20 bis 7,92). Diese Studie war jedoch nicht ausreichend gepowert, um einen statistisch signifikanten Unterschied feststellen zu können. Das Versagen des Transplantats für die Sprunggelenks-OCA lag bei 12.5 % über 2 Jahre und bei 29.4 % über einen Zeitraum von 4.1 Jahren. Die Versagensraten der Transplantate in den Fallserien für die Kniegelenks-OCA waren niedriger und lagen bei einer Nachbeobachtungszeit von 7 Jahren zwischen 7.0 % und 11.8 %. Die Qualität der Evidenz für diesen Endpunkt war sehr gering.</p>
<p>Laufende Studien</p>	
<p>lediglich eine laufende prospektive Fallserie</p>	<p>Aktuell ist nur eine laufende Studie registriert, die die OCA bei osteochondralen Defekten im Kniegelenk untersucht. Es handelt sich dabei um eine unkontrollierte Fallserie mit einer geschätzten Anzahl von 50 PatientInnen und Abschlussdatum im April 2020. Daher gibt es derzeit keine laufenden relevanten Studien, die neue Erkenntnisse bezüglich der Wirksamkeit der OCA im Vergleich zu anderen chirurgischen Verfahren liefern werden.</p>
<p>Kostenerstattung</p>	
<p>derzeit keine Kostenerstattung</p>	<p>Derzeit erfolgt keine Kostenerstattung der OCA zur Behandlung von osteochondralen Gelenksknorpeldefekten durch das öffentliche österreichische Gesundheitssystem.</p>

Diskussion

Es gibt einen Mangel an exakten, prospektiven Daten, die die OCA zur Behandlung von osteochondralen Defekten untersuchen. Insgesamt war die Qualität und Stärke der Evidenz, die für die Beantwortung der Forschungsfrage und für die Indikationen Sprunggelenk und Knie identifiziert wurde, gering oder sehr niedrig.

Die Schwächen der Evidenz lagen vor allem im Design der Studien (z. B. handelte es sich Großteils um Fallserien), in den kleinen Stichprobengrößen, fehlender Vergleichsdaten und den kurzen Nachbeobachtungszeiträumen. Obwohl für die vorliegende systematische Übersichtsarbeit ein Minimum von 24 Monaten Nachbeobachtungszeitraum als Einschlusskriterium festgelegt wurde, ist für die Beurteilung langfristiger Ergebnisse wie Transplantatversagen ein Nachbeobachtungszeitraum von mindestens vier Jahren erforderlich. Keine der eingeschlossenen Studien erfüllte dieses Kriterium. Darüber hinaus hatte das einzige verfügbare RCT ein hohes Bias-Risiko aufgrund unzureichender Randomisierung, Allocation Concealment und Verblindung.

Empfehlung

Auf der Grundlage der verfügbaren Evidenz können keine Schlussfolgerungen gezogen werden, ob das bewertete Verfahren der OCA zur Behandlung von osteochondralen Defekten im Knie oder anderen Gelenken wirksamer und gleichermaßen sicher ist wie andere chirurgische Verfahren. Darüber hinaus hatten die prospektiven einarmigen Studien keine ausreichende Qualität (methodische Mängel), um die Wirksamkeit des Verfahrens nachzuweisen. Auf Basis der verfügbaren Evidenz und in Ermangelung an adäquaten laufenden Studien, wird die Aufnahme in den Erstattungskatalog nicht empfohlen.

geringe bis sehr geringe Evidenzstärke

Schwächen der Evidenz: Studiendesign, fehlende Vergleichsdaten, kleine Stichprobengrößen

lediglich 1 RCT mit hohem Bias-Risiko identifiziert

**Evidenz unzureichend
→ Aufnahme nicht empfohlen**

1 Scope

1.1 PICO question

Is osteochondral allograft transplantation for the knee and other joints in comparison to other surgical management in patients with osteochondral defects more effective and safe concerning pain, function, quality of life, implant failure and adverse events?

PIKO-Frage

1.2 Inclusion criteria

Inclusion criteria for relevant studies are summarized in Table 1-1.

Einschlusskriterien für relevante Studien

Table 1-1: Inclusion criteria

Population	<ul style="list-style-type: none"> ✳ Patients with osteochondral defects in articular cartilage of the knee or other joint who have failed conservative management or primary surgery. ✳ International classification of diseases (ICD)-10-CM code: M94.8 Other specified disorders of cartilage ✳ Contraindications/exclusions: Instability/misalignment of knee joint, late-stage osteoarthritis, rheumatoid disease, multiple cartilage defects, osteonecrosis, tumours ✳ MeSH Terms: Cartilage, Articular/injuries*
Intervention	<ul style="list-style-type: none"> ✳ Fresh or delayed-fresh osteochondral allograft transplantation (OCA) ✳ Product names: Not applicable ✳ MeSH Term: Cartilage/transplantation*, Chondrocytes/transplantation, Allografts
Control	<ul style="list-style-type: none"> ✳ Surgical management; including but not limited to autologous chondrocyte implantation, osteochondral grafting, and microfracture. ✳ MeSH Terms: Not applicable (not used for the search strategy) <p>Rationale: The primary aim of OCA is to improve symptoms of cartilage defects, and to prevent or delay the progression to osteoarthritis and total or partial knee arthroplasty. In this context, patients typically must have failed conservative management to qualify for OCA, therefore the main comparators are other surgical cartilage regeneration or repair procedures.</p>
Outcomes	
Efficacy	<p>Clinical endpoints include changes from pre- to post-treatment measurements of:</p> <ul style="list-style-type: none"> ✳ Decrease in pain, including but not limited to: <ul style="list-style-type: none"> ✳ Visual analogue scale (VAS) ✳ Lysholm Score ✳ International Knee Documentation Committee (IKDC) ✳ Knee Society Knee Score ✳ Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) ✳ Increase in functionality, including but not limited to: <ul style="list-style-type: none"> ✳ Lysholm Score ✳ Tegner activity grading scale ✳ Knee injury and Osteoarthritis Outcome Score (KOOS) ✳ Knee Society Function Score ✳ IKDC ✳ WOMAC

Outcomes/Efficacy (<i>continuation</i>)	<ul style="list-style-type: none"> ✦ Increase in quality of life (QoL), including but not limited to: <ul style="list-style-type: none"> ✦ 36-item Short Form Health Survey Questionnaire (SF-36) ✦ Dartmouth Cooperative Functional Assessment Charts (COOP) ✦ Necessity of total joint replacement ✦ Return to daily/sports/physical activities <p>Rationale: Appropriate clinical outcomes have been informed by systematic reviews [1,2], and the EUnetHTA guidelines [3].</p>
Safety	<p>Relevant safety outcomes include (<i>critical</i> outcomes are highlighted in bold):</p> <ul style="list-style-type: none"> ✦ Procedure-related mortality ✦ Adverse events (peri- and post-operative) ✦ Transplant failure rates ✦ Re-admission ✦ Re-operation/additional surgery <p>Rationale: Appropriate safety outcomes have been informed by recent systematic reviews [1,2], and the EUnetHTA guidelines [4].</p>
Study design	
Efficacy	<ul style="list-style-type: none"> ✦ Randomised controlled trials ✦ Prospective non-randomised comparative study designs ✦ In the absence of comparative evidence, prospective case series with ≥ 15 patients and at least 24 months follow-up will be included. <p>Excluded: conference abstracts, narrative reviews, letter to the editor, author response, case reports, retrospective comparative studies, animal studies, cadaveric studies</p>
Safety	<ul style="list-style-type: none"> ✦ Randomised controlled trials ✦ Prospective non-randomised controlled trials ✦ Prospective case-series with ≥ 15 patients and 24 months follow-up <p>Excluded: conference abstracts, narrative reviews, letter to the editor, author response, case reports, retrospective case series, animal studies, cadaveric studies</p>

Abbreviations *COOP* = Dartmouth Cooperative Functional Assessment Charts; *ICD* = International Statistical Classification of Diseases; *IKDC* = International Knee Documentation Committee; *KOOS* = Knee injury and Osteoarthritis Outcome Score; *SF-36* = 36-item Short Form Health Survey Questionnaire; *VAS* = Visual analogue scale; *WOMAC* = Western Ontario and McMaster Universities Osteoarthritis Index

2 Methods

2.1 Research questions

Description of the technology	
Element ID	Research question
B0001	What are osteochondral allograft transplantation and the comparator(s)?
A0020	For which indications has osteochondral allograft transplantation received marketing authorisation or CE marking?
B0002	What is the claimed benefit of osteochondral allograft transplantation in relation to other surgical procedures?
B0003	What is the phase of development and implementation of osteochondral allograft transplantation and other surgical procedures?
B0004	Who administers osteochondral allograft transplantation and other surgical procedures and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use osteochondral allograft transplantation and other surgical procedures?
B0009	What supplies are needed to use osteochondral allograft transplantation and other surgical procedures?
A0021	What is the reimbursement status of osteochondral allograft transplantation?

Health problem and current use	
Element ID	Research question
A0001	For which health conditions, and for what purposes is osteochondral allograft transplantation used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for osteochondral defects?
A0004	What is the natural course of osteochondral defects?
A0005	What is the burden of disease for the patients with osteochondral defects?
A0006	What are the societal consequences of osteochondral defects?
A0024	How are osteochondral defects currently diagnosed according to published guidelines and in practice?
A0025	How are osteochondral defects currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much is osteochondral allograft transplantation utilised?

Clinical effectiveness	
Element ID	Research question
D0001	What is the expected beneficial effect of osteochondral allograft transplantation on mortality?
A0003	What is the effect of osteochondral allograft transplantation on the mortality due to causes other than osteochondral defects?
D0005	How does osteochondral allograft transplantation affect symptoms and findings (severity, frequency) of osteochondral defects?
D0006	How does osteochondral allograft transplantation affect progression (or recurrence) of the disease or health condition?

Clinical effectiveness	
Element ID	Research question
D0011	What is the effect of osteochondral allograft transplantation on patients' body functions?
D0016	How does the use of osteochondral allograft transplantation affect activities of daily living?
D0012	What is the effect of osteochondral allograft transplantation on generic health-related quality of life?
D0013	What is the effect of osteochondral allograft transplantation on disease-specific quality of life?
D0017	Was the use of osteochondral allograft transplantation worthwhile?

Safety	
Element ID	Research question
C0008	How safe is osteochondral allograft transplantation in comparison to the comparator(s)?
C0002	Are there harms related to dosage or frequency of applying osteochondral allograft transplantation?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of osteochondral allograft transplantation?
C0007	Are osteochondral allograft transplantation and other surgical procedures associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of osteochondral allograft transplantation and other surgical procedures?

2.2 Sources

Quellen:
systematische Suche,
Handsuche sowie
Informationen der
Hersteller und
Einreicher

A range of sources were used to identify relevant literature to answer the research questions relating to the **description of the technology, health problem and current use**, including:

Description of the technology

- ✦ Handsearch in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- ✦ Background publications identified in database search: see Section 2.3
- ✦ Questionnaire completed by the submitting hospitals

Health problem and Current Use

- ✦ Handsearch in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- ✦ Handsearch of clinical guideline databases (AHRQ, EBM guidelines)
- ✦ Background publications identified in database search: see Section 2.3
- ✦ Questionnaire completed by the submitting hospitals

2.3 Systematic literature search

The systematic literature search was conducted on the 12th of December 2018 in the following databases:

- ✧ Medline via Ovid (including PubMed)
- ✧ Embase
- ✧ The Cochrane Library
- ✧ CRD (DARE, NHS-EED, HTA)

The systematic search was limited to articles published in English or German; no other limits were applied to the search strategy. The specific search strategy employed can be found in the Appendix.

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 11th of January 2019, resulting in 75 potentially relevant hits. Of those, 3 may be considered relevant (observational studies) and are included in the Appendix (see Chapter “List of ongoing trials”).

The submitting hospital provided eight publications, all of which were identified in the database searches.

The database searches were supplemented by hand-searches and pearling of identified studies, which resulted in 16 potentially relevant studies.

**systematische
Literatursuche in
4 Datenbanken**

**Suche eingegrenzt
nach Sprache**

**Suche nach laufenden
Studien: 3 Treffer**

**zusätzliche Literatur
von Einreicher & durch
Handsuche**

2.4 Flow chart of study selection

Overall 744 citations were identified through the database searches, and 16 additional citations were identified through targeted handsearching and pearling of identified studies. After deduplication, 582 citations were identified for screening by title and abstract. The references were screened by two independent researchers (TV, KR) and cases of disagreement were resolved through discussion. The selection process is displayed in Figure 2-1.

Relevant studies with appropriate study designs were identified for knee and ankle indications only. No relevant evidence was identified for other joints that may be considered for OCA, such as hips and shoulders.

In total, one RCT and one case series were included for ankle indications, and four case series were included for knee indications. For ankle indications, only the RCT was included for effectiveness outcomes, as this represents the highest level of evidence. Both the RCT and case series were included for safety outcomes.

**Literaturauswahl:
insgesamt
582 Publikationen
identifiziert**

**lediglich Studien zum
Knie- & Sprunggelenk
identifiziert**

**6 Studien
eingeschlossen**

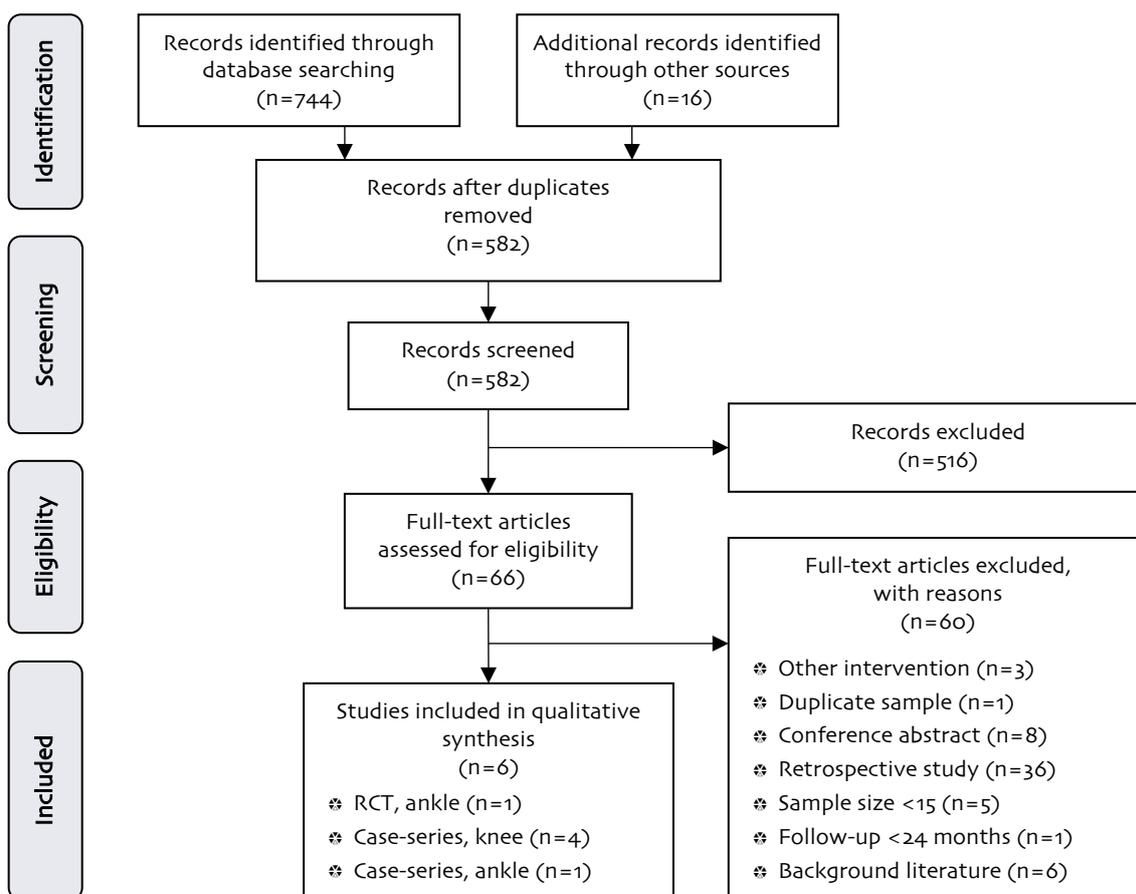


Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.5 Analysis

Bewertung des Bias-Risikos laut Cochrane RoB tool Version 2.0 & IHE Checkliste

Due to the paucity of available evidence, and limited study designs, the safety and effectiveness results are reported narratively. Two independent researchers conducted quality appraisal, including risk of bias assessment, with differences settled via consensus. Quality appraisal was conducted with different tools presented in the Appendix, depending on study design (see Appendix Table A-3 and Table A-4). Randomised controlled trials were appraised using the Cochrane RoB tool Version 2.0 [5]. Single arm case series were evaluated using the Institute of Health Economics (IHE) checklist [6].

2.6 Synthesis

Evidenzsynthese mittels GRADE

The questions were answered in plain text format with reference to Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence tables that are included in Appendix, results were summarized in Table 7-1 and Table 7-2. No quantitative analysis of outcomes was performed, due limited number of relevant comparative trials identified.

3 Description and technical characteristics of technology

Features of the technology and comparators

B0001 – What are osteochondral allograft transplantation and the comparator(s)?

Hyaline cartilage is found in the articular surfaces of bones, where they form joints. Often referred to as articular cartilage, it decreases friction and enables bones to glide smoothly over each other [7].

Fresh or delayed-fresh osteochondral allograft transplantation (OCA) is a technique used to repair both chondral defects (those in which only the articular cartilage is damaged) and osteochondral defects (where there is damage to the articular cartilage and underlying bone) [7, 8]. The procedure involves taking a core of the injured cartilage and underlying bone from the patient and replacing it with a size-matched transplant of mature hyaline cartilage and subchondral bone from a cadaver donor [9, 10]. The theory behind this procedure is that the living cartilage cells (chondrocytes) supplied by the donor transplant support the production of the cartilage matrix indefinitely [11]. Images of an OCA procedure are presented in Figure 3-1.

frische oder verzögert-frische osteochondrale Allograft Transplantation (OCA) dient der Reparatur (osteo)chondraler Defekte mithilfe eines Knorpel-Knochen-Transplantats einer Leichnamsspende

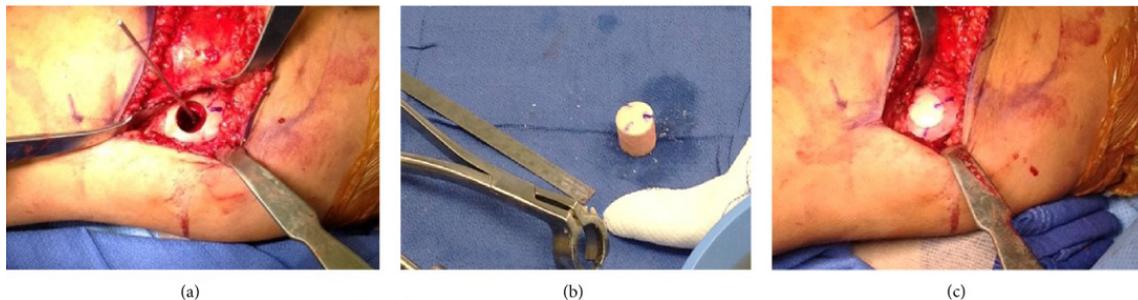


Figure 3-1: Intraoperative image of an osteochondral allograft transplant procedure in the knee, showing (a) marginal excision and preparation of medial femoral condyle, (b) osteochondral allograft preparation, and (c) implantation. Source: Fitzgerald et al. 2014 [12]

In theory osteochondral allograft transplantation can be used to treat chondral and osteochondral defects of all sizes, locations and contours; however, it is generally indicated for treatment of lesions greater than 2 cm². It has been mainly used to treat the knee joint but has also been used to treat the talus of the ankle, shoulder and elbow [8].

für Defekte >2cm², v. a. im Knie-, Sprung-, Schulter- & Ellbogengelenk

Comparators

There are a range of comparator surgical techniques for treatment of osteochondral defects including osteochondral autologous transplantation, microfracture, drilling, mosaicplasty, autologous chondrocyte implantation (ACI) and matrix-induced autologous chondrocyte implantation (MACI). The choice of procedure depends on the size and location of the defect [13].

zahlreiche chirurgische Vergleichsverfahren, abhängig von Defektgröße & Lokalisation ...

... Mikrofrakturierung

Microfracture and drilling involve the creation of small holes into the subchondral bone to create tunnels to the underlying bone marrow. The bleeding caused by this process results in stem cells flowing into the bone and coating the area where the cartilage has been lost. Over time these stem cells develop into a new form of cartilage (fibrocartilage) [14-16]. Images of a microfracture procedure are presented in Figure 3-2.



Figure 3-2:
Arthroscopic image of a chondral lesion treated with microfracture.
Source: Mestrimier et al. 2018 [17]

... osteochondrale Autograft Transplantation

Osteochondral autograft transplantation is used to address small chondral defects which have deep subchondral damage that is untreatable by microfracture or drilling [15]. It is a similar procedure to OCA except it involves the use of viable hyaline cartilage grafts obtained from the patient rather than from a cadaveric donor. As in osteochondral allograft transplantation the graft is a core of cartilage and subchondral bone [15, 18].

... Mosaikplastik

Mosaicplasty is a form of osteochondral autograft transplantation where more than one graft core is used to treat a single cartilage defect. The cores are implanted in a mosaic-like pattern [19]. A visual representation of mosaicplasty is present in Figure 3-3.



Figure 3-3: Images of a mosaicplasty procedure showing (a) arthroscopic measurement of defect size, (b) open procedure, (c) harvesting of autologous osteochondral plugs from lateral supracondylar ridge, (d) insertion of plug through drill guide, (e) harvested osteochondral plugs, and (f) cartilage defect reconstructed with plugs. Source: Seo et al. 2011 [20]

Autologous chondrocyte implantation can treat larger cartilage defects compared to microfracture or mosaicplasty; however, it involves a two-staged procedure [18]. The first procedure involves the harvesting of pieces of the patient's own cartilage and expanding the chondrocytes in a laboratory. In the second procedure the damaged area of cartilage is debrided and the cultured chondrocytes injected into the articular defect [15, 18]. Matrix-induced autologous chondrocyte implantation is an extension of autologous chondrocyte implantation whereby the expanded autologous chondrocytes are implanted on a three-dimensional scaffold which is then inserted into the articular defect [18].

A0020 – For which indications has osteochondral allograft transplantation received marketing authorisation or CE marking?

Osteochondral allografts are not classified as medical devices, and therefore are not subject to CE marking.

Human tissue donation is regulated in the European Union under the European Union Tissue and Cells Directives (EUTCD) 2004/23/EC. The EUTCD outlines the legal framework for the supply of tissues and cells within the EU, to ensure that biological samples meet acceptable safety and quality standards [21]. In this regard, individual suppliers of tissue samples that are licensed to distribute tissue samples under the EUTCD can distribute within the European Union.

Additionally, in Austria tissue donation is regulated under the tissue safety law („Bundesgesetz über die Festlegung von Qualitäts- und Sicherheitsstandards für die Gewinnung, Verarbeitung, Lagerung und Verteilung von menschlichen Zellen und Geweben zur Verwendung beim Menschen – Gewebesicherheitsgesetz“) [22]. Moreover, the principles of tissue and organ donation in Austria is positioned in the „Bundesgesetz über die Transplantation von menschlichen Organen“ (Organtransplantationsgesetz – OTPG) [23].

B0002 – What is the claimed benefit of osteochondral allograft transplantation in relation to other surgical procedures?

Compared with other methods of repair, such as drilling, microfracture and osteochondral autograft transplantation, osteochondral allograft transplantation can repair almost any size osteochondral defect [11]. An additional advantage over drilling and microfracture is that osteochondral allograft transplantation restores the lesion using mature joint cartilage rather than fibrocartilage which has poor biomechanical properties and is less durable [19]. Compared with osteochondral autograft transplantation and mosaicplasty, where grafts are obtained from the patient rather than a donor, there is no graft site related morbidity with osteochondral allograft transplantation [24]. The advantage of osteochondral allograft transplantation compared with ACI and MACI is that it is a single-stage procedure whereas ACI and MACI are two staged-procedures. It can require two to three weeks between the first and second stage to culture the chondrocytes and the second stage requires an arthrotomy [24].

... (Matrix-assistierte) autologe Chondrozyten Implantation ((M)ACI)

kein Medizinprodukt, daher kein CE

Gewebe- und Organspenden in EU über EUTCD geregelt

gesetzliche Verankerung in Österreich über Bundesgesetz „Gewebesicherheitsgesetz“

für Defekte (fast) jeglicher Größe (vs. Mikrofrakturierung), keine transplantatsbezogene Morbidität (vs. Mosaikplastik, Autograft Transplantation), einzeitiges Verfahren (vs. (M)ACI)

<p>Mikrofrakturierung älteste & kosten- günstigste Methode zur Behandlung osteochondraler Defekte</p>	<p>Boo03 – What is the phase of development and implementation of osteochondral allograft transplantation and other surgical procedures?</p>
	<p>The use of osteochondral allograft transplantation and its comparator procedures for the repair of articular cartilage defects have all been extensively evaluated in clinical studies ranging in level of evidence [25].</p>
	<p>Microfracture is reported to be the oldest, most inexpensive and commonly used method for treating osteochondral defects whilst osteochondral autograft transplantation is one of the oldest cartilage transplant procedures for osteochondral defects [15].</p>
<p>osteochondrale Autograft Transplantation ist ältestes Verfahren zur Knorpeltransplantation</p>	<p>The use of osteochondral allograft transplantation around the world varies owing to the different regulatory and logistical issues in each country, as well as the cost of obtaining and processing allografts [26]. Canada and the USA have established programs for fresh osteochondral allografts [27].</p>
<p>Anwendung osteochondraler Allograft Transplantationen variabel, da unterschiedliche Regularien in Ländern</p>	<p>Autologous chondrocyte transplantation for articular cartilage repair developed after osteochondral allograft transplantation. A paper on regulatory approval for autologous human cells and tissue products in the USA, the European Union and Japan noted that as of October 2013 four products derived from autologous chondrocytes for the repair of cartilaginous defects of the femoral condyle were approved by the European Medicines Agency [28].</p>
	<p>Administration, Investments, personnel and tools required to use the technology and the comparator(s)</p>
	<p>Boo04 – Who administers osteochondral allograft transplantation and other surgical procedures and in what context and level of care are they provided?</p>
<p>von orthopädisch chirurgischen SpezialistInnen & qualifiziertem Personal durchzuführen</p>	<p>Boo08 – What kind of special premises are needed to use osteochondral allograft transplantation and other surgical procedures?</p>
	<p>Osteochondral allograft transplantation and its comparator procedures should only be performed by orthopaedic surgeons experienced in cartilage surgery and with specific training in these procedures.</p>
<p>Universitätskliniken, Abteilung für Orthopädie, steriler OP erforderlich</p>	<p>According to the submitting hospitals, osteochondral allograft transplantation and its comparator procedures should be performed in university hospitals/departments for orthopaedics, by orthopaedic surgical specialists and qualified surgical staff. Further, a sterile operation theatre with an anaesthetic workplace is required.</p>
	<p>Boo09 – What supplies are needed to use osteochondral allograft transplantation and other surgical procedures?</p>
<p>präoperative Bildgebung erforderlich</p>	<p>Preoperative imaging using radiographs or magnetic resonance imaging is required prior to osteochondral allograft transplantation to calculate the appropriate allograft size [29, 30].</p>
<p>benötigte chirurgische Hilfsmittel abhängig von zu transplantierenden Oberfläche & verwendeten Operationstechnik</p>	<p>The surgical supplies needed depends on the surface to be grafted and the surgical technique performed (shell or dowel). Dowel allografts involve cylindrically coring out the defect and inserting a matched cylindrical dowel in to the recipient site. If the size of location of the lesion does not permit the use of the dowel technique than the shell graft technique is used. This involves matching donor tissue to the recipient defect using a free-hand approach. The size of the defect is estimated using cannulated, cylindrical sizing guides [8, 31].</p>

Equipment required for the dowel technique includes cutting guides, guide-wire reamers, a padded tamp and cutting guides. Also required is a pressurised pulsed solution to remove residual bone marrow. Additional equipment is required for the shell graft technique including calipers, reamers, depth-gauge, high-speed burr, reciprocating and oscillating saws, bone files and/or rasp owing to the need for measured resection and sculpting of the bone and cartilage [31].

Both techniques require scalpels, prophylactic antibiotics and anaesthesia [30]. Most graft can be fixed in place using pressure applied by the surgeon; however, other options should be available including bioabsorbable pins and/or low-profile interfragmentary screws ($\leq 3\text{mm}$ in diameter) [31]. A tourniquet and leg holder may be used in procedures involving the knee [32].

Fresh grafts must be stored at 4°C . Storage solutions include saline solution, Ringer's lactate or a serum-free media consisting of glucose, salts, amino acids and fetal bovine serum. It is recommended that fresh grafts be used within 28 days of harvesting. Fresh-frozen grafts are stored at -80°C [8,30].

**Skalpelle,
prophylaktische
Antibiotika und
Anästhesie erforderlich**

**Lagerung frischer
Transplantate bei 4°C ,
verzögert-frische bei
 -80°C in Aufbewahrungslösungen**

Regulatory & reimbursement status

A0021 – What is the reimbursement status of osteochondral allograft transplantation?

Currently, OCA for osteochondral defects are not included in the Austrian DRG-system (Leistungsorientierte Krankenanstaltenfinanzierung/LKF). Therefore, the intervention itself is not reimbursed by the Austrian health care system. However, the intervention could be billed with another code, e.g. for arthroscopic operations of the knee or ankle joint (Code NF020 – Arthroscopische Operation des Kniegelenks; NG020 – Arthroscopische Operation des Sprunggelenks).

**aktuell keine Erstattung
der Intervention in
Österreich**

4 Health problem and current use

Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes is osteochondral allograft transplantation used?

Fresh or delayed-fresh osteochondral allograft transplantation has been used to treat chondral and osteochondral lesions in the knee, talus of the ankle, shoulder and elbow [32].

According to the International Cartilage Regeneration and Joint Preservation Society “The most common reasons for performing osteochondral allograft transplantation are:

- ✧ A focal cartilage lesion greater than 2cm²
- ✧ Re-treatment of previous cartilage surgery such as microfracture, autologous osteochondral transplantation or autologous chondrocyte transplantation
- ✧ Severe (type III or IV) osteochondritis dissecans
- ✧ Osteonecrosis
- ✧ Joint reconstruction after a fracture, known as post-traumatic reconstruction [11]”

Contraindications are:

- ✧ Advanced or diffuse degenerative changes
- ✧ Multicompartmental arthrosis [33]

Relative contraindications are:

- ✧ Inflammatory arthropathies
- ✧ Uncorrected joint malalignment and/or ligamentous instability
- ✧ Meniscal insufficiency [33]

In addition to the above contraindications it has been reported that osteochondral allograft transplantation should be avoided in patients who are obese, have altered bone metabolism or are affected by tumours [33].

A0002 – What is the disease or health condition in the scope of this assessment?

The health condition under investigation for this assessment is osteochondral defects. An osteochondral defect is an area of damage to the joints involving the articular cartilage and adjacent subchondral bone [34].

Articular cartilage defects are graded using the International Cartilage Regeneration and Joint Preservation Society and Outerbridge’s classifications [35].

Table 4-1: Classification of cartilage defects by Outerbridge [36]

Grade	Characteristics
0	Normal
1	Softening and swelling of cartilage
2	Fragmentation and fissuring, less than 0.5 inches in diameter
3	Fragmentation and fissuring, greater than 0.5 inches in diameter
4	Erosion of cartilage down to exposed subchondral bone

zur Behandlung (osteo)chondraler Läsionen im Knie-, Sprung-, Schulter- und Ellenbogengelenk

häufigsten Indikationen:

- fokale Knorpelverletzung >2 cm²,
- schwere Osteochondritis dissecans,
- Osteonekrose,
- Gelenkrekonstruktion nach Fraktur

Kontraindikationen:

- fortgeschrittene/ diffuse degenerative Veränderungen,
- Arthrose,
- Entzündungsarthropien,
- unkorrigierte Gelenkfehlstellung/ Bandstabilität,
- Meniskusinsuffizienz,
- Tumore

Fokus auf osteochondrale Defekte

Klassifizierung von Gelenkknorpeldefekten

Table 4-2: Classification of chondral defects by International Cartilage Repair Society [35]

Grade	Characteristics
0	Normal
1	Nearly normal (soft indentation and/or superficial fissures and cracks)
2	Abnormal (lesions extending down to <50% of cartilage depth)
3	Severely abnormal (cartilage defects >50% of cartilage depth)
4	Severely abnormal (through the subchondral bone)

**sportlich aktive
Personen, genetische
Prädisposition,
repetitive Traumata etc.**

A0003 – What are the known risk factors for osteochondral defects?

Osteochondral defects can be caused by a range of factors. Individuals who play sports where traumatic injuries can occur are at risk of acquiring osteochondral defects. Repetitive trauma, a genetic predisposition and abnormal bone development are also associated with the development of osteochondral lesions [37, 38].

**geringes intrinsisches
Heilungsvermögen,
bei Nicht-Behandlung
→ frühzeitige
Gelenksdegeneration
und Osteoarthritis**

A0004 – What is the natural course of osteochondral defects?

Osteochondral lesions have limited ability to self-repair because cartilaginous tissue has no direct blood supply. The lesions may heal by forming fibrous or fibrocartilaginous tissue but this is not as durable as the hyaline cartilage it replaces and eventually fails [35]. Without treatment lesions may get larger and harder to treat over time. Conservative treatments such as non-steroidal anti-inflammatory drugs only delay the progress. If left untreated, articular damage strongly predisposes patients to early joint degeneration and osteoarthritis [13, 39, 40].

Effects of the disease or health condition on the individual and society

**Knorpelläsionen führen
zu Reibungen zwischen
Knochen → verminderte
Lebensqualität,
körperliche
Beeinträchtigungen
bis hin zu Verlust des
Arbeitsplatzes**

A0005 – What is the burden of disease for patients with osteochondral defects?

Articular cartilage lines the end of the bones is responsible for cushioning of the joints and smooth gliding of bones during movement. The loss in cartilage associated with osteochondral lesions means that the joints are no longer cushioned and can rub each other causing pain and inflammation during activities that put pressure on the joint [13, 39]. Other symptoms can include catching, locking and instability [41]. These symptoms have a negative effect on quality of life and a person’s ability to perform daily activities. For very active people, such as professional or amateur athletes or people with jobs involving manual labour, the physical impairment created by an osteochondral lesion has a major impact on their lives including the potential loss of employment [7,42].

**laufende Kosten für
Physiotherapie &
Medikation,
Produktivitätsverlust**

A0006 – What are the societal consequences of osteochondral defects?

Osteochondral defects can result in ongoing costs for physiotherapy and medication. Left untreated, people with osteochondral defects are predisposed to developing osteoarthritis which may require joint replacement. Indirect costs associated with osteochondral defects include loss in time and productivity.

In Austria, 78,277 surgeries of the knee joint and 2,855 surgeries of the ankle joint were performed in 2016 [43]. Out of the surgeries of the knee joint, a total of 37,364 interventions were arthroscopic surgeries [44].

~80.000 OP's am Knie- bzw. ~3.000 am Sprunggelenk in Ö

However, neither information on the number of OCA interventions of the knee or ankle joint performed, nor information regarding the prevalence or incidence of osteochondral defects have been identified.

keine Daten zu OCA Intervention im Knie- bzw. Sprunggelenk

Current clinical management of the disease or health condition

Aoo24 – How are osteochondral defects currently diagnosed according to published guidelines and in practice?

We could not identify published guidelines on the diagnosis of osteochondral defects. A consensus statement on surgical management of symptomatic articular cartilage defects of the knee from the United Kingdom stated, “*History and physical examination alone are not diagnostic, and patients usually undergo plain radiography of the knee to evaluate alignment of the joint, to detect the presence of any radio-opaque loose bodies and determine signs of arthritis*” [41]. They further state that “Magnetic resonance imaging (with or without gadolinium enhancement) can identify and partly quantify articular cartilage defects.” For assessment of lesion size and functional integrity of the surrounding tissue they state that arthroscopy is the gold standard. A practice guideline on management of articular cartilage defects of the knee stated in the introduction that the gold standard for diagnosis of chondral injuries is magnetic resonance imaging [35].

keine Diagnoseleitlinien identifiziert

Konsensus-Statement & Praxisrichtlinie: Arthroskopie als Goldstandard für Beurteilung der Läsionsgröße & Funktionsfähigkeit, sowie MRI für Diagnose chondraler Verletzungen

Aoo25 – How are osteochondral defects currently managed according to published guidelines and in practice?

No evidence-based guidelines for the treatment of osteochondral defects were identified in this review.

keine evidenzbasierten Leitlinien identifiziert

A technology appraisal on autologous chondrocyte implantation for treating symptomatic articular cartilage defects of the knee by the National Institute for Health and Care Excellence (NICE) states that people with articular cartilage defects will first be offered best supportive care. This includes physiotherapy, analgesia, corticosteroid injections and hot or cold application to the joint. Exercise and weight loss is also encouraged. Surgery is only considered in people whose symptoms persist despite best supportive care [42].

lt. NICE: primär Physiotherapie, Analgesie, Gelenkapplikation, Bewegung & Gewichtsreduktion

The NICE guidance on mosaicplasty for symptomatic articular cartilage defects of the knee reported that there is no uniform approach to their management. Treatment choice (such as osteochondral allograft transplantation and comparator techniques listed in B0001) depends on the size of the defect and its location [45].

Operationen nur bei fortbestehen der Symptome

Target population

A0007 – What is the target population in this assessment?

**PatientInnen mit
osteochondralen
Defekten in Gelenken**

The target population includes patients with osteochondral defects (of any joint) who have failed conservative management or primary surgery.

A0023 – How many people belong to the target population?

**keine Daten zu
Prävalenz oder Inzidenz
in Ö identifiziert**

No information on the incidence or prevalence of osteochondral defects in the knee, ankle or shoulder of Austrian or European populations was identified. Moreover, the true incidence is unknown, because not all osteochondral defects cause symptoms.

**9.0 % bis 11.0 % der
PatientInnen, die sich
einer Kniearthroskopie
unterziehen, haben
einen osteochondralen
Defekt**

Studies on large datasets of patients who have undergone knee arthroscopies have estimated the number of patients who might be suitable for cartilage repair procedures using localised full thickness lesions (ICRS grade 3 and 4) as selection criteria. Figures range from 5.3% to 7.0% of all knee arthroscopies when restricted to patients under 40 years of age [46, 47], and 9.0% to 11.0% of all knee arthroscopies in studies that have included all analysed patients regardless of age [47, 48].

A0011 – How much is osteochondral allograft transplantation utilised?

**geschätzte Erbringung
in Gesamtösterreich:
40 Behandlungen
(20 frische &
20 verzögert-frische)**

No data could be identified to estimate the overall size of the population eligible for osteochondral allograft transplantation. Based on the information provided by the submitting hospitals, the estimated annual utilisation of OCA in the submitting hospitals is around 2-5 procedures. In contrast, the annual utilisation in Austria is estimated to be around 40 procedures, of which 20 are fresh and 20 are delayed-fresh OCA.

5 Clinical effectiveness

5.1 Outcomes

The following outcomes were defined as *crucial* for the recommendation:

- ✧ Decrease in pain
- ✧ Increase in functionality
- ✧ Necessity of total joint replacement
- ✧ Increase in quality of life

Symptoms associated with osteochondral defects of the knee and ankle include pain, swelling, catching and locking of the joint [41, 49]. These may impair function, limit a patient's ability to perform their usual activities and have a negative impact upon quality of life. Approaches taken for the management of such defects seek to relieve pain, improving functionality and encouraging the repair of damaged tissue [49, 50].

Decrease in pain was selected as a *crucial* outcome. Pain is a key symptom associated with osteochondral defects; with relief of pain being a common management objective. Various questionnaires are available which elicit an indication of the level of pain experienced by a patient. These may be generic or disease specific.

Both the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) include pain subscales which measure disease-specific *knee* pain [51]. A visual analogue scale (VAS) is a generic tool that is often used to elicit a measure of pain. Minimum clinically important differences (MCID) for WOMAC (pain subscale) have been reported ranging from 22.9 to 36 at two years following knee surgery [52], whereas a change of 19.9 for VAS is clinically relevant for patients with knee pain [53]. MCIDs for KOOS pain subscales have not been calculated in any patient population [52].

Increase in functionality was selected as a *crucial* outcome. Examples of tools that measure functionality and which may be relevant to knee or ankle populations are listed below:

- ✧ The KOOS is a patient-completed questionnaire; eliciting a patient's perception of their knee/knee-problems (specifically, in cases of post-traumatic osteoarthritis or injuries that may lead to posttraumatic osteoarthritis) [51]. It contains 5 domains – pain, symptoms, activities of daily living (ADL), sports and recreational activities, and knee related QoL. The MCID for KOOS physical function scores are 2.2, with a change of 15 representing moderate improvement in patients with knee pain [54].
- ✧ The WOMAC is a self-administered or interview-administered questionnaire designed to assess the course of disease or response to treatment in patients with knee or hip osteoarthritis [51]. It contains 3 subscales – pain, stiffness and function. The MCID for WOMAC has not been calculated for cartilage repair procedures; MCIDs range from 19-33 points at two years following knee replacement [52].
- ✧ The International Knee Documentation Committee (IKDC) questionnaire can be used in patients with a variety of knee conditions to

**entscheidende
Endpunkte für
Wirksamkeit: ...**

**... Verminderung
von Schmerzen**

**... Verbesserung
der Funktionalität**

<p>... Notwendigkeit eines vollständigen Gelenkersatzes</p>	<p>measure changes in symptoms, function and sports activities due to knee impairment [51]. The MCID for IKDC scores is 6.3 at 6 months, and 16.7 at 12 months following cartilage repair [52].</p> <p>✦ The Foot and Ankle Abilities Measure (FAAM) is a self-reported tool which assesses the physical function of patients with musculoskeletal disorders of the leg, foot or ankle [55]. The MCID for FAAM scores ranges from 9 to 77 points (median 32.5) [56].</p>
<p>... Lebensqualität</p>	<p>Necessity of total joint replacement was selected as a <i>crucial</i> outcome. Patients who have suffered an osteochondral defect are at a heightened risk of future osteoarthritis [50].</p> <p>To comprehensively evaluate the ability of OCA to prevent or delay the need for total joint replacement, long-term follow up data is essential.</p> <p>Quality of life (QoL) was selected as a <i>crucial</i> outcome. Reducing symptoms and improving functionality may improve a patient's quality of life, with improved QoL considered the 'final' outcome. Disease specific or generic approaches may be taken to measure QoL. For example, the KOOS, which was introduced above, is a knee-specific measurement tool that contains a QoL subscale [51]. The MCID for KOOS-QoL is change of 8 points in patients with osteoarthritis [54]. The SF-36 is a widely used, non-disease specific measure of QoL. The MCID for SF-36 scores ranges from 7.8 to 17 in patients with knee osteoarthritis [53].</p>
<p>weiterer (nicht entscheidungsrelevanter) Endpunkt: Rückkehr zu täglichen/sportlichen/körperlichen Aktivitäten</p>	<p>Furthermore, the following outcome was considered <i>important</i>, but not <i>crucial</i> to the decision:</p> <p>✦ Return to daily/sports/physical activities</p> <p>The success of treatment in increasing functionality is directly linked to a patient's ability to perform activities of daily living, sports and physical activities. Given this dependence, return to activities of daily living was considered <i>important</i>, though not <i>crucial</i> to the decision-making process.</p>

5.2 Included studies

<p>relevante Studien zu OCA nur zum Knie- & Sprunggelenk identifiziert</p>	<p>Studies evaluating the effect of fresh or delayed-fresh osteochondral allograft transplantation (OCA) for osteochondral defects were considered; however, relevant studies were only identified on patients with defects in the ankle or knee.</p>
<p>Extraktionstabellen im Anhang</p>	<p>Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-6.</p>
<p>1 RCT zum Sprunggelenk</p>	<p>Ankle</p> <p>Only the RCT comparing OCA to another surgical procedure for osteochondral lesions of the ankle was identified. Evidence from this randomised trial was considered when evaluating the effectiveness of OCA to treat osteochondral defects in the ankle.</p>
<p>40 PatientInnen, OCA vs. osteochondraler Autograft Transplantation</p>	<p>The RCT, conducted in the USA, enrolled 40 patients with osteochondral lesions of the talar dome (OLT) [57]. Patients were randomised to receive either an OCA or osteochondral autograft transplantation. These lesions were either recurrent in nature (i.e. had failed initial arthroscopic treatment) or</p>

were of a size 1.5cm² or greater. In both treatment arms, 75% of patients had recurrent OLTs whilst the remaining 25% had large OLTs with no prior surgeries.

The average age and gender distribution of patients in the allograft and autograft groups were similar (40 vs 41 years, 63% vs. 55% male, respectively); as was mean chondral lesion size (1.8cm² vs. 1.6cm²) [57]. Mean follow up times for the intervention and comparator groups were 3.4 and 2.9 years, respectively. Post-operative outcome measures presented are those taken at final follow up.

Amongst those receiving an allograft, 87.5% vs. 80% of OLTs were anterior or central, whilst 12.5% vs. 20% were posteromedial [57].

Patients were eligible so long as their lesion did not involve the medial or lateral shoulder of the talar dome [57]. Four patients in the allograft group were excluded due to significant involvement of the medial or lateral shoulder of the talar dome found intraoperatively. Only the 16 patients who received the appropriate intervention were considered in all analyses. Twenty patients remained in the autograft group for analysis.

Concurrent procedures were not reported. It is possible none occurred however, this was not specified.

Knee

For the indication ‘osteochondral defect in the knee’ no randomised or comparative trials were retrieved thus, we considered prospective case-series with at least 15 patients and at least 24 months follow up when evaluating the effectiveness of OCA to treat osteochondral defects in the knee.

Four single arm, prospective case series were considered; two were conducted in the USA and two in Canada [58-61]. Patient numbers ranged from 17 to 91.

Two studies had 2-year follow-ups, from which two-year, post-operative outcomes measure data could be extracted [58, 59]. Follow-up in the remaining two studies ranged from 1.9 to 4 years, and from 0.3 to 14.5 years. Post-operative outcome data from ‘final follow up’ could be extracted from one of these studies [60]. Relevant outcomes presented by the final study were sparse and did not involve a pre- vs. post-operative comparison [61].

Prior surgeries were reported in three of the four studies [58-60]. Where reported, mean number of prior surgeries per patients varied from 0.7 to 1.7.

Only two studies reported concurrent procedures [58, 60]. These included, non-exhaustively, tibial osteotomy, meniscal transplant, ACL reconstruction and Herbert screw removal.

Two studies specified the transplant location, which included the lateral tibial plateau, lateral femoral condyle and medial femoral condyle [59, 60]. One study specified a femoral condyle location but location on the condyle was not further specified [58]. The final study provided no information of transplant location [61].

Only one study specified the grade of cartilage defect required to be eligible for an OCA. Specifically, this was a grade 4 International Cartilage Repair Society (ICRS) articular cartilage defect [58]. Other studies did not report the grade of cartilage defect.

Ø 40 vs. 41 Jahre,
63 % vs. 55 % männlich,
Ø Defektgröße
1,8 vs. 1,6 cm²,
Ø Nachbeobachtungszeit
3,4 vs. 2,9 Jahre

Einschluss von Pat. nur,
wenn mediale oder
laterale Schulter der
Taluskuettel nicht
betroffen (Ausschluss
4 Pat. mit OCA)

keine kontrollierten
Studien für Kniegelenk

4 prospektive einarmige
Fallserien inkludiert

Nachbeobachtungs-
zeiträume zwischen
0,3 und 14,5 Jahren

Voroperationen in
3 Studien und
Mehrfachbehandlungen
in 2 Studien berichtet

Transplantat-
Lokalisation in 3 Studien

Einschlusskriterium in
1 Studie: Grad 4 ICRS

5.3 Results

Mortality

D0001 – What is the expected beneficial effect of osteochondral allograft transplantation on mortality?

D0003 – What is the effect of osteochondral allograft transplantation on the mortality due to causes other than osteochondral defects of the knee or ankle?

Fragen zur Mortalität im nächsten Kapitel zu Sicherheit beantwortet

Osteochondral defects are not considered life threatening and OCA is not intended to affect patient survival or life expectancy. These research questions are not relevant. Procedure-related mortality was considered as a safety-outcome only.

Morbidity

D0005 – How does osteochondral allograft transplantation affect symptoms and findings (severity, frequency) of osteochondral defects?

Beantwortung Frage anhand Endpunkt „Schmerzen“

The *critical* outcome ‘pain’ was considered when answering this research question.

Ankle

1 RCT: keine Vergleiche im Zeitverlauf

kein statistisch signifikanter (s.s.) Unterschied zwischen Intervention & Kontrolle

A 10-point VAS was used to assess pre- and post-operative pain [57]. The study did not report mean changes in pain score over time. Post-operative pain was compared between the allograft and autograft groups. The difference was not significant (2.7 vs. 2.2, $p=0.15$). Mean pre-operative pain was 7.8 (range 5-10) and 7.9 (range 4-10) for the allograft and autograft groups, respectively. Pre-operative scores were not compared statistically.

Knee

Patient-reported pain in the case series was elicited using knee-specific tools. Pain was directly measured through use of the pain-specific subscales of the KOOS and WOMAC questionnaires.

2 Studien: s.s. Unterschiede zwischen prä- & postoperative Schmerzen

Two studies measured pain via the KOOS-pain domain pre-operatively and two years post-operatively [58, 59]. Both studies found a statistically significant difference between pain pre- and post-operatively (52.5 vs. 79.0, $p<0.001$ and 59 vs. 74, $p=0.028$).

One of these studies also administered the WOMAC questionnaire to patients [59]. The significant improvement in pain observed when using the KOOS was supported by the findings of the WOMAC questionnaire (WOMAC pain subscale score: 91.0 vs. 96.1, $p=0.002$); however, this difference was not clinically important [52].

2 Studien: s.s. Verbesserung der Symptome post-operativ

The PICO considered pain and functionality as the most relevant outcomes to express symptoms, specifying these as outcomes of interest. However, more general measures of patient-reported symptoms are available (measured on the symptom domains of the KOOS and the Modified Cincinnati Knee-Rating System tools). Whilst not directly relevant to the pre-defined outcomes, the results are discussed below for comparative purposes.

1 Studie: statistisch nicht signifikanter Unterschied post-operativ

Amongst the two studies that reported overall KOOS scores, there was variation in the significant/non-significant findings pertaining to improvement in

symptoms post-operatively ($p=0.01$ and $p=0.172$) [58, 59]. A third study which administered a modified Cincinnati Knee-Rating System found a significant difference in symptoms between pre- and post-operative time points (21.9 vs 32.5, $p<0.03$) [60], it is unclear whether this difference is clinically meaningful.

D0006 – How does osteochondral allograft transplantation affect progression (or recurrence) of osteochondral defects?

‘Necessity of total joint replacement’ was the outcome used to inform this research question. Other measures that may be considered relevant include revision, reoperation, and graft failure; these are reported in response to Question C0008. No studies specified this as an outcome measure of interest.

Frage kann nicht beantwortet werden, da keine Evidenz

Ankle

No comparative data was available on this outcome measure. Two patients in each group required a revision surgery (this involved conversion to alternate therapy), although these were due to graft non-unions rather than progression or recurrence of the disease [57].

**1 RCT: 2 Pat. in Interventions- & Kontrollgruppe
→ Revisions-Operation**

Knee

All studies discussed additional procedures required post OCA. In two of the studies, it was reported that at least one patient underwent a subsequent total knee arthroplasty [58, 61]. Across the two studies, a total of 7 of 125 (5.6%, range 3% to 6.6%) patients progressed to a total knee replacement at two years follow-up.

2 Studien: 7 Pat. benötigten Knieendoprothetik

Reliable, long-term follow up data is required if this research question is to be answered robustly.

Function

D0011 – What is the effect of osteochondral allograft transplantation on patients’ body functions?

This question is answered in the subsequent section (D0016 – How does the use of osteochondral allograft transplantation affect activities of daily living?)

Frage mit nachfolgender Frage kombiniert

D0016 – How does the use of osteochondral allograft transplantation affect activities of daily living?

The *critical* outcome ‘functionality’ was considered when answering this research question.

Beantwortung anhand Endpunkt „Funktionalität“

Ankle

Comparative data measured using the Foot and Ankle Ability Measure (FAAM) questionnaire informed the answer to this research question.

1 RCT: kein s.s. Unterschied zwischen Gruppen postoperativ

Pre- and post-operative FAAM scores of each treatment arm were reported however, mean changes in FAAM scores between these time points were not [57].

The difference in postoperative FAAM score between the two groups was found not to be statistically significant (80.7 vs. 85.5, $p=0.25$).

<p>3 Studien verwendeten 4 verschiedene Skalen</p>	<p><i>Knee</i></p> <p>The KOOS, WOMAC, IKDC and Modified Cincinnati knee rating system tools were used interchangeably by three of the four included case series to assess knee function [58-60]. Where possible, function-specific domains have been reported. These include:</p> <ul style="list-style-type: none"> ✧ Function subscales of the WOMAC and Modified Cincinnati knee rating system tools ✧ Activities of daily living (ADL) and sports and recreation domains of the KOOS tool.
<p>2 Studien: s.s. Unterschiede prä- & postoperativ (2 Jahre)</p>	<p>The IKDC is made up of three domains – symptoms, sports and daily activities and knee function however, only an aggregate score is reported.</p> <p><i>KOOS – ADL and sports and recreation domains</i></p> <p>Two studies used the KOOS tool [58, 59]. Both studies reported significant differences between pre- and two-year post-operative measures on the sports and recreation domain (21.2 vs. 54.4, $p=0.002$ and 37 vs. 57, $p=0.005$). There was however discrepancy in significant/non-significant findings on the ADL domain (68.5 vs. 84.8, $p=0.004$ and 69 v 83, $p=0.058$).</p>
<p>1 Studie: s.s. Verbesserung der Funktionalität prä- vs. postoperativ</p>	<p><i>WOMAC – function</i></p> <p>Only one study used the WOMAC questionnaire. A statistically significant change in functionality pre- vs. two years post-operatively, as measured on the function domain, was observed (68.1 vs. 83.1, $p=0.03$) [59]; however, this difference did not fall within the range of MCIDs [52].</p>
<p>2 Studien: s.s. Verbesserung prä- vs. postoperativ (2 Jahre & letztes Follow-Up der Pat.)</p>	<p><i>IKDC</i></p> <p>Two studies used the IKDC questionnaire. Both reported significant changes between baseline and follow-up scores; however, these were below the MCID for a minimum 12 months follow-up after cartilage repair [52]. For Brown et al. (2011), this was between pre-operative and two years post-operative time points, (45 vs. 62, $p<0.001$) [58]. For LaPrade et al. (2009), this was between pre-operative scores and scores taken at last follow-up, the timing of which is uncertain (52 vs. 68.5, $p<0.03$) [60].</p>
<p>1 Studie: s.s. Unterschiede zwischen prä- vs. postoperativ</p> <p>Verbesserung Funktionalität in Studien, ABER kleine Stichproben und nicht-kontrolliertes Studiendesign</p>	<p><i>Modified Cincinnati knee rating system – function</i></p> <p>In addition to the IKDC, LaPrade et al (2009) administered the Modified Cincinnati Knee Rating System [60]. Similar to their findings on the IKDC, significant functionally differences between baseline and follow-up were reported on the function domain (27.3 vs. 36.5, $p<0.01$).</p> <p>Based on the findings of the three prospective case series that provided functionality outcome measures, it would appear OCA leads to significant improvements in functionality. Nonetheless, these results should be interpreted with caution given the relatively small sample sizes ($n=17$ up to $n=34$) and single-centre designs of all studies.</p> <p>Moreover, it is impossible to conclude whether any functional improvement is significantly different from that which would occur when the next best alternative is employed.</p>

Health-related quality of life

D0012 – What is the effect of osteochondral allograft transplantation on generic health-related quality of life?

No generic health related quality of life information was extracted from the included studies.

keine Evidenz

One study did report SF-36 scores; however, only combined scores for knee and shoulder patients were provided. It was not possible to disaggregate the results, therefore; this data was not extracted.

D0013 – What is the effect of osteochondral allograft transplantation on disease-specific quality of life?

Ankle

No comparative data was identified to answer this question for this indication.

**keine Evidenz
zum Sprunggelenk**

Knee

The quality of life subscale of the KOOS questionnaire measures disease-specific quality of life.

Disease specific quality of life was measured preoperatively and 2 years post-operatively in two studies. Both studies reported a significant improvement in health-related quality of life ($p < 0.001$ and $p = 0.001$) [58, 59]. Neither study reported a mean difference; only pre- and post-operative scores, and a p-value.

**2 Studien: s.s.
Verbesserung der
Lebensqualität prä- vs.
postoperativ (2 Jahre)**

Patient satisfaction

D0017 – Was the use of osteochondral allograft transplantation worthwhile?

No data was identified to answer this question for either indication.

keine Evidenz

6 Safety

6.1 Outcomes

The following outcomes were defined as *crucial* to derive a recommendation:

- ✿ Procedure-related mortality
- ✿ Adverse events (peri- and post-operatively)
- ✿ Transplant failure rates

Procedure-related mortality is considered to be a *crucial* safety concern. Any death that occurred during or within 30 days of the procedure, or that could be related directly to OCA implantation, revision or removal were relevant to this outcome. Examples of procedure-related mortality may include infection.

Adverse events specifically related to the intervention (or comparator) were considered a *crucial* safety concern. These may include, for example, disease transmission or an immune response (OCA), and donor site morbidity (autograft)[62].

Transplant failure rate was considered a *crucial* safety outcome. Failure of an allograft may be defined in a number of ways, including ongoing pain and debilitation, failure of graft incorporation or necessity of an alternate surgery following transplantation.

Furthermore, additional outcome measures were considered *important* to inform the decision, although not *crucial*:

- ✿ Re-admission
- ✿ Re-operation/additional surgery

Re-operations/additional surgery and re-admissions associated with the intervention (or comparator) are most likely necessary in the case of an adverse event or a graft failure. Given adverse events and transplant failure rates were defined as *crucial outcomes*, re-operations and re-admissions were considered *important*, but no *crucial* to inform a recommendation.

**entscheidende
Endpunkte für
Sicherheit:**

**eingriffsbezogene
Mortalität**

**unerwünschte
Ereignisse (UEs)**

**Versagensrate bei
Transplantationen**

**weitere (nicht
entscheidungsrelevante)
Endpunkte:**
- wiederholte Kranken-
hauseinweisung
- Re-Operationsrate

6.2 Included studies

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-6.

Ankle

In addition to the RCT, one prospective case series was included in safety analysis for ankle OCA [57, 63]. Follow-up time in the randomised trial ranged from 1 to 6.4 years (mean follow up times for the allograft and autograft groups were 3.4 and 2.9 years, respectively). In the case-series, follow-up time ranged from 2 to 7 years, with mean follow-up of 4.1 years.

The randomised trial has been discussed in detail above (Section 5.2).

**Extraktionstabellen
im Anhang**

**1 RCT (siehe 5.2) &
1 prospektive Fallserie
identifiziert**

**Ø Beobachtungs-
zeitraum: 2,9-4,1 Jahre**

16 Pat. in Fallserie
(17 Knöchel),
Ø 35,8 Jahre alt,
50 % männlich, in
16 Sprunggelenken
bereits Voroperationen

mind. 2 Jahre
Beobachtungszeit,
Defektgrößen &
gleichzeitige
Behandlungen nicht
berichtet

4 Fallserien zum
Kniegelenk (siehe 5.2)

The case-series included 16 patients and a total of 17 ankles undergoing fresh allograft transplantation for a talar lesion [63]. Mean patient age was 35.8 years and 50% were male. Sixteen of the 17 ankles had single or multiple surgeries prior to the allograft transplant. The most common transplant location was the posteromedial talar (64.7%). Transplants also occurred in the medial talar (17.6%), posterolateral talar (11.85) and the anterolateral talar (5.9%). All patients had a least 2 years of follow up data.

The severity/grade of the osteochondral lesion was not reported; however, all except one lesion had at least one dimension greater than 15mm [63].

Concurrent procedures were not reported. It is possible none occurred; however, this was not specified.

Knee

Four case-series informed the safety evaluation of OCA for osteochondral lesions of the knee [58-61]. These studies have been discussed in detail above (Section 5.2).

6.3 Results

Patient safety

Coo08 – How safe is osteochondral allograft transplantation in comparison to other surgical interventions?

Beantwortung Frage
anhand von
2 Endpunkten

The outcomes ‘procedure-related mortality’, ‘adverse events’ and ‘transplant failure rates’ were considered when answering this research question.

None of the included studies, for ankle or knee, reported any cases of procedure-related mortality.

Allograft vs. Autograft (ankle)

1 RCT: am häufigsten:
- schlechte Heilung
des Transplantats
- oberflächliche
Blasenbildung
- Arthrose
- Postoperative
Kniebeschwerden

Only one study provided comparative safety data. This pertained to the use of osteochondral allograft vs. osteochondral autograft transplantation for lesions of the talar dome.

The adverse events reported included painful graft non-unions (18.8% vs. 10.0%), postoperative superficial wound blistering (0.0% vs. 5.0%), anterior ankle arthritis (6.3% vs. 0.0%) and postoperative knee complications (0.0% vs. 30.0%) [57].

Transplantatsversagen:
bei 4 Pat. → Entfernung
des Transplantats

Graft failure rates were not reported explicitly; however, four of the five patients who experienced a graft non-union (12.5% vs. 10.0%) required removal of the graft (RR=1.25, 95% CI 0.20 to 7.92).

Morbidität der
Spenderseite bei
Autograft hoch (30 %)

Notably, there was a relatively high frequency (30%) of donor site morbidity associated with the autograft approach, which is a known disadvantage [62].

Single arm (ankle)

1 Studie:
5/17 Transplantate
versagten

Five (of 17) grafts were considered a failure in the case-series [63]. These grafts had either failed to incorporate post-operatively or failed to relieve symptoms. Two of these ‘failed’ grafts required a subsequent arthrodesis procedure. Another two of the ‘failed’ grafts failed to incorporate post-operatively and one patient withdrew with ongoing symptoms.

An additional 2 grafts were considered 'poor'. These patients required subsequent arthroscopic debridement to reduce ongoing symptoms.

There was one occasion of a malunion of a medial malleolar osteotomy site reported however this did not require additional treatment.

No clear protocol for capturing adverse events was reported in the methods section, therefore, it is possible that not all relevant adverse events have been reported.

Single arm (knee)

Two studies report transplant failure rates of 7% (n=2) and 11.8% (n=2) [58, 59]. In these studies, 'failure' was defined either (1) upon computed tomography scan assessing graft incorporation, and (2) as requiring reoperation due to ongoing symptoms post-operatively.

Adverse events included, non-exhaustively, superficial cellulitis, deep vein thrombosis and pulmonary embolism, fibrosis impinging adjacent meniscus and fragmentation or delamination of the graft.

Where fragmentation or delamination of the graft was identified, this was upon arthroscopic investigation at the time of either (1) a subsequent procedure, or (2) upon defining the graft as a failure due to ongoing pain and debilitation [58, 59].

Only one study specified that patients were monitored for complications [59]. Two of the three remaining studies indicated routine follow-up exams, at specified time points, in their methods sections [58, 60]. Adverse events may have been recorded at these exams however, relying on patient reporting of events leaves open the possibility that not all adverse events were captured.

Co002 – Are there harms related to dosage or frequency of applying osteochondral allograft transplantations?

The available data could not sufficiently answer this research question.

Revision/subsequent operations are reported by all studies however this is rarely a revision/repeat of the OCA surgery itself. Only one study mentioned the occurrence of a 're-transplant', which occurred in three of 91 patients (3.3%) [61].

It is unclear whether a second OCA would commonly be considered upon failure of an initial transplant and whether this would incur any additional risks.

Co004 – How does the frequency or severity of harms change over time or in different settings?

Available data could not sufficiently answer this research question. Whilst adverse events and graft failures may be reported, the timing post transplantation when these occurred is not clearly presented.

Co005 – What are the susceptible patient groups that are more likely to be harmed through the use of osteochondral allograft transplantation?

Ankle

Surgical approach (anterior distal tibial plafondplasty vs. medial malleolar osteotomy)

Ahmad et al. (2016) compared the post-operative outcome scores of patients dependent on the approach that was taken to expose their OLT during surgery (anterior or medial ankle exposure) [57]. No significant differences were found.

2 weitere Transplantate benötigten Arthroskopie

keine eindeutige Erfassung unerwünschter Ereignisse

2 Studien: Transplantatsversagen bei 7-11.8%

UEs: tiefe Venenthrombose, Fibrose, Fragmentierung/ Ablösung des Transplantats

keine eindeutige Erfassung unerwünschter Ereignisse in 2 Studien

keine verlässlichen Informationen

keine verlässlichen Informationen

1 RCT: keine s.s. Unterschiede im chirurgischen Ansatz

Knee

Number of grafts required (single vs. multiple)

große osteochondrale
Läsionen mit
Doppeltransplantaten,
scheinen höheres Risiko
für Transplantatversagen
zu haben

It appears that patients with large osteochondral lesions requiring double grafts may be at a higher risk of graft failure.

The two failures reported by Cinats et al. (2018) occurred in patients who received a double dowel graft [59]. Likewise, the two failures reported by Brown et al. (2011) occurred in patients who had multiple grafts [58].

Region of the knee (weightbearing vs. non-weightbearing zones)

Transplantate im
posterior indirekten
Gewichtsbereich,
scheinen höhere
Versagensrate zu haben

Brown et al. (2011) consider the degree of graft incorporation stratified by region of transplantation [(A) anterior indirect weightbearing region, (B) direct weightbearing region and (C) posterior indirect weightbearing region]. Of note, 8 of 11 (72.7%) of grafts performed in the posterior indirect weightbearing region had <50% incorporation [58]. Moreover, the two failures reported in this study each partially involved this posterior, non-weightbearing zone.

Gender and concurrent procedures

keine s.s. Unterschiede
in Geschlecht &
simultanen
Behandlungen

LaPrade et al. (2009) found no statistically significant differences in functionality outcomes between male and female patients, nor between patients who received a concurrent procedure and those who did not [60].

C0007 – Are osteochondral allograft transplantations or other surgical approaches associated with user-dependent harms?

keine Evidenz

No evidence was identified which could answer this question.

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of osteochondral allograft transplantation and other surgical approaches?

keine Evidenz

Currently there is insufficient evidence to inform the long-term safety of this procedure. Randomised controlled trials with at least 2 years of follow-up, are necessary to determine the relative effectiveness of OCA compared to other surgical procedures. Long-term follow-up studies with outcomes measured at standardised follow-up intervals are necessary to determine long-term failure rates and re-operation rates.

7 Quality of evidence

Risk of bias in the included randomised controlled trial was appraised using the Cochrane RoB tool Version 2.0 [5], and is presented in Table A-3 in the Appendix. The study had a high risk of bias, attributable to inadequate randomisation, allocation concealment, and blinding of both the patients and investigators.

**hohes Bias-Risiko in RCT:
unzureichende
Randomisierung,
fehlende Verblindung**

Risk of bias in the single arm studies was appraised using the IHE appraisal tool for case series studies [64]. The appraisal is presented in Table A-4 of the Appendix.

IHE Tool für Fallserien

The included studies varied in the level of bias attributable to them. Most studies had a moderate risk of bias, one suffered from serious risk of bias and one had a relatively low risk of bias. The main contributors which increased the risk of bias of the studies included single-centre designs (all studies), limited follow-up periods and a failure to provide mean effect changes nor any associated measures of random variability in the data analysis of relevant outcomes.

**niedriges (1 Studie),
moderates (3 Studien)
bis hohes (1 Studie)
Bias-Risiko in Fallserien:
Single-Center-Design,
limitierte Follow-Ups,
fehlende Daten etc.**

The strength of evidence was rated according to the GRADE Scheme for each outcome separately [65]. Each study was rated by two independent researchers. In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [65].

**Qualität der Evidenz
nach GRADE**

GRADE uses four categories to rank the strength of evidence:

- ✧ **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- ✧ **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- ✧ **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- ✧ **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and in the evidence profile in Appendix Table A-5 and Table A-6.

**GRADE Tabellen
nächste Seite**

Overall the strength of evidence for the effectiveness and safety of osteochondral allograft transplantation in ankle joints in comparison to other surgical procedures is low or very low. The strength of evidence for the effectiveness and safety of osteochondral allograft transplantation in knee joints in comparison to other surgical procedures is very low. No evidence was identified for OCA for other joints.

**niedrige bis sehr
niedrige Evidenzstärke
für Sprunggelenk;
sehr niedrige
Evidenzstärke für
Kniegelenk**

Table 7-1: Summary of findings table of osteochondral allograft transplantation (*ankle*)¹

Outcome	Anticipated absolute effects (95% CI)			Relative effect (95% CI)	Number of patients (studies)	Quality	Comments
	Risk with OCA	Risk with osteochondral autograft	Difference				
EFFICACY							
Change in pain score Follow up: 2 years; assessed with: VAS; Scale from: 0 (less pain) to 10 (more pain)	Mean reduction 5.1	Mean reduction 5.7	Mean difference 0.6 (<i>p</i> =0.15)	Not estimable	36 (1 RCT)	⊕⊕○○ LOW ^{2,3}	No significant difference identified, lower scores represent an improvement in pain
Change in function score Follow up: 2 years; assessed with: FAAM; Scale from: 0 (worse function) to 100 (better function)	Mean increase 25.5	Mean increase 31.1	Mean difference 5.6 (<i>p</i> =0.25)	Not estimable	36 (1 RCT)	⊕⊕○○ LOW ^{2,3}	No significant difference identified, higher scores represent an improvement in physical function
Change in quality of life	-	-	-	-	-	-	This outcome was not reported
Total joint replacement	-	-	-	-	-	-	This outcome was not reported
SAFETY⁴							
Procedure-related mortality (RCT) Follow up: 2 years	0%	0%	-	Not estimable	36 (1 RCT)	⊕⊕○○ LOW ^{2,3}	There were no reported cases of procedure-related mortality
Procedure-related mortality (single arm) Follow up: 2 years	0%	-	-	Not estimable	17 (1 case series)	⊕○○○ VERY LOW ^{2,3}	There were no reported cases of procedure-related mortality
Complications (RCT) Follow up: 2 years	18.8% (4.8 to 100)	20.0%	1.4% fewer (15.2 fewer to 92 more)	RR 0.93 (0.24 to 5.60) ⁵	36 (1 RCT)	⊕⊕○○ LOW ^{2,3}	No significant difference identified, duration of follow-up was not adequate for this outcome
Complications (single arm) Follow up: 4.1 (range 2-7) years	5.9% ⁶	-	-	Not estimable	17 (1 case series)	⊕○○○ VERY LOW ^{2,3}	Duration of follow-up was not adequate for this outcome
Transplant failure (RCT) Follow up: 2 years; assessed with: removal or replacement of the graft	12.5% (2 to 79.2)	10.0%	2.5% more (from 8 fewer to 69.2 more)	RR 1.25 (0.20 to 7.92) ⁵	36 (1 RCT)	⊕⊕○○ LOW ^{2,3}	No significant difference identified, duration of follow-up was not adequate for this outcome
Transplant failure (single arm) Follow up: 4.1 (range 2-7) years; assessed with: removal or replacement of the graft	29.4%	-	-	Not estimable	17 (1 case series)	⊕○○○ VERY LOW ^{2,3}	None

Abbreviations *CI* = confidence interval, *FAAM* = foot and ankle disability measure, *OCA* = osteochondral allograft, *RCT* = randomised controlled trials, *RR* = relative risk, *VAS* = visual analogue scale.

Comments

¹ Only RCT data is presented in the summary of findings table, as this represents the highest level of evidence for this indication. Data from the included case series are presented in the appendix.

² There was a serious risk of bias due to inadequate randomization, allocation concealment, and blinding of patients and investigators.

³ Sample size was below the optimal information size.

⁴ In addition to the RCT, one case series was identified that investigated safety outcomes for ankle OCA.

⁵ Calculated using MedCalc® (http://www.medcalc.org/calc/relative_risk.php)

⁶ The reported complication may be underreported. In addition to reported complications, 4 of 17 patients (23.5%) required additional procedures (2 arthroscopic debridement, 2 arthrodesis).

Table 7-2: Summary of findings table of osteochondral allograft transplantation (*knee*)¹

Outcome	Anticipated absolute effects (95% CI)	Relative effect (95% CI)	Number of patients (studies)	Quality	Comments
EFFICACY					
Pain: Change in pain score Follow up: 2 years; assessed with: KOOS – Pain Subscale; Scale from: 0 to 100	Mean reduction in pain ranged from 15 to 26.5 ($p < 0.05$)	Not estimable	51 (2 case series)	⊕○○○ VERY LOW ²	Lower scores indicate improvement in pain
Pain: Change in pain score Follow up: 2 years; assessed with: WOMAC – Pain Subscale; Scale from: 0 to 100	Mean reduction in pain was 5.1 (Pre-op: 91.0 ± 5.7 vs Post-op: 96.1 ± 4.6, $p = 0.002$)	Not estimable	17 (1 case series)	⊕○○○ VERY LOW ²	Lower scores indicate improvement in pain
Pain: Change in pain score Follow up: 2 years; assessed with: Modified Cincinnati knee rating score; Scale from: 0 to 100	Mean reduction in pain was 10.6 (Pre-op: 21.9 vs Post-op: 32.5, $p < 0.03$)	Not estimable	23 (1 case series)	⊕○○○ VERY LOW ²	Lower scores indicate improvement in pain
Function: Change in function score Follow up: range 1.9 to 4 years; assessed with: IKDC; Scale from: 0 to 100	Mean increase in function ranged from 16.5 to 17 ($p < 0.03$)	Not estimable	57 (2 case series)	⊕○○○ VERY LOW ²	Higher scores indicate improvement in physical function
Function: Change in function score Follow up: 2 years; assessed with: WOMAC – Function Subscale; Scale from: 0 to 100	Mean increase in function was 15 (Pre-op: 68.1 ± 23.8 vs. Post-op: 83.1 ± 20.4, $p = 0.03$)	Not estimable	17 (1 case series)	⊕○○○ VERY LOW ²	Higher scores indicate improvement in physical function
Function: Change in function score Follow up: 2 years; assessed with: WOMAC – Overall; Scale from: 0 to 100	Mean increase in function was 17.2 (Pre-op: 65.1 ± 24.8 vs. Post-op: 82.3 ± 19.9, $p = 0.02$)	Not estimable	17 (1 case series)	⊕○○○ VERY LOW ²	Higher scores indicate improvement in physical function
Function: Change in function score Follow up: 1.9 to 4 years; assessed with: Modified Cincinnati Knee Rating Score – Function Subscale; Scale from: 0 to 100	Mean increase in function was 9.2 (Pre-op: 27.3 vs Post-op: 36.5, $p < 0.01$)	Not estimable	23 (1 case series)	⊕○○○ VERY LOW ²	Higher scores indicate improvement in physical function
Function: Change in function score Follow up: 1.9 to 4 years; assessed with: Modified Cincinnati Knee Rating Score – Overall Score; Scale from: 0 to 100	Mean increase in function was 19.8 (Pre-op: 49.2 vs Post-op: 69.0, $p < 0.02$)	Not estimable	23 (1 case series)	⊕○○○ VERY LOW ²	Higher scores indicate improvement in physical function
Function: Change in quality of life Follow up: 2 years; assessed with: KOOS – QoL Subscale; Scale from: 0 to 100	Mean increase in quality of life ranged from 25 to 30.6 ($p < 0.001$)	Not estimable	51 (2 case series)	⊕○○○ VERY LOW ²	Higher scores indicate improvement in quality of life
Necessity of total joint replacement Follow up: 0.3 to 14.5 years ³	Overall 5.6% (7/125)	Not estimable	125 (2 case series)	⊕○○○ VERY LOW ^{2,4}	Limited data to assess this outcome

Outcome	Anticipated absolute effects (95% CI)	Relative effect (95% CI)	Number of patients (studies)	Quality	Comments
SAFETY					
Procedure-related mortality Follow up: range 0.3 to 14.5 years ³	0.0% (0/165)	Not estimable	165 (4 case series)	⊕⊕○○ LOW	There were no reported cases of procedure-related mortality
Complications Follow up: range 0.3 to 14.5 years ³	Overall complications: 12.7% (21/165) (range 4.3% to 26.5%)	Not estimable	165 (4 case series)	⊕○○○ VERY LOW ^{2,4,5}	None
Transplant failure Follow up: 2 years; assessed with: removal or replacement of the graft	Overall transplant failures: 7.8% (4/51) (range 7.0% to 11.8%)	Not estimable	51 (2 case series)	⊕○○○ VERY LOW ^{2,4}	None

Abbreviations *KOOS* = Knee injury and Osteoarthritis Outcome Score, *OCA* = osteochondral allograft, *RCT* = randomised controlled trials, *VAS* = visual analogue scale.

Comments

¹ *P* values should be interpreted with caution due to small sample size without a comparative assessment.

² Sample size was below the optimal information size.

³ A very small proportion of patients in one study had follow-up less than 2 years.

⁴ Follow-up length was insufficient to properly measure the necessity for joint replacement.

⁵ Large degree of variation in reported adverse event rates across studies.

8 Discussion

Osteochondral lesions commonly affect the knee or ankle joint [50]. Typically, these lesions appear following repetitive strain or direct trauma; often owing to a sporting injury.

Symptoms of pain, swelling, catching and locking of the joint may all contribute to debilitation and interfere with one's ability to carry out their activities of daily living. Further, it may cause discomfort, and potentially lead to the progression of osteoarthritis.

Osteochondral allograft transplantation (OCA) is one therapeutic option to treat such defects, including medium to large defects $>3\text{cm}^2$ of the knee or large lesions of the ankle [49, 62]. Surgical treatment of ankle or knee lesion seeks to restore function, relieve pain, induce the healing of bone and damaged cartilage and/or avoid the need for total knee arthroplasty (TKA) in young patients, who respond poorly to TKA [30, 49].

The aim of this systematic review was to evaluate the safety and effectiveness of OCA compared to alternate surgical approaches for patients with an osteochondral lesion who have failed conservative management or primary surgery.

Evidence which met the inclusion criteria for this review was found to pertain exclusively to patients with osteochondral lesions in the knee or ankle.

Interpretation of findings

Study quality, validity and overall level of evidence

Ankle

One included study compared osteochondral allograft to osteochondral autograft transplantation as a treatment for osteochondral lesions of the talar dome [57]. This study was intended to inform the recommendation based on clinical effectiveness however, it was classified as having a high risk of bias and thus all results should be considered with caution.

The RCT reported post-operative pain and functionality scores and provided a p-value for comparison between the two trial arms. Neither pain nor functionality post-operatively was significantly different between groups. The study did not report mean changes between pre- and post-operative scores. It is unclear whether decreases in pain and increases in functionality in either treatment arm were significant.

Neither the efficacy nor comparative effectiveness of OCA is clear from the available evidence. It would appear post-surgical pain and function is comparable between osteochondral allograft and autograft transplants. However, it needs to be established whether there is a significant (statistically or clinically) change in pain and functionality outcomes following surgical intervention and whether this varies between OCA, autograft transplants and other surgical interventions (e.g. autologous chondrocyte implantation or mosaicplasty) [49].

Knie- & Sprunggelenk häufig von osteochondralen Läsionen betroffen → führt zu Schmerzen, Schwellungen etc.

osteochondrale Allograft Transplantation (OCA) für Defekte $>3\text{cm}^2$

Ziel: Bewertung Wirksamkeit & Sicherheit von OCA

1 RCT für Wirksamkeit: Allograft vs. Autograft; hohes Bias-Risiko

keine s.s. Unterschiede zwischen Gruppen bei Schmerzen & Funktionalität

keine eindeutigen Ergebnisse zur Wirksamkeit (Allograft & Autograft scheinen ähnlich wirksam zu sein)

Notwendigkeit einer Re-Operation ähnlich in beiden Gruppen; Morbidität Spenderseite nur unter Autograft

Again, the RCT provided the only comparative safety data for OCA relative to an appropriate comparator (i.e. osteochondral autograft transplant). The need for revision operations due to graft non-unions was similar regardless of treatment assignment. Of note, 30% of the autografts led to donor site morbidity (i.e. knee complications). Such complications were avoided in the OCA group.

zusätzlich 1 Fallserie für Sicherheit: hohe Versagensrate der Transplantate

An additional, case-series was included in the safety assessment; however, this study was identified as having a moderate risk of bias. Five of 17 grafts were considered a 'failure', and a further 2 were considered 'poor' due to the need for post-transplant arthroscopic debridement.

rezenter Review: Versagensrate, Re-Operationen, Revisionen sei relativ hoch

A recently published systematic review drew the conclusion that OCA may improve functional status in patients with large lesions of the talus however, the associated risk of failure, re-operation, or revision surgery is relatively high [66]. This review, however, relied solely on small ($n \leq 38$), prospective case series.

Sicherheit OCA vs. andere Interventionen ungewiss

The comparative safety of OCA to all relevant comparators remains uncertain.

Knee

lediglich 4 Fallserien für Wirksamkeit

No comparative studies comparing OCA to a relevant comparator for osteochondral defects of the knee were retrieved. Four prospective case-series were included to inform the effectiveness recommendation for OCA therapy for defects of the knee [58-61].

3 Studien enthielten Daten zu Schmerzen, Funktionalität & Lebensqualität; 1 Studie nur zu Anzahl totaler Kniearthroskopien

Knee-specific measurement tools were used by three of the four studies to elicit patient-reported measures of pain, functionality and quality of life outcomes. The remaining study, which was identified as having a severe risk of bias, provided no patient-reported outcome measures. It did, however, report known number of subsequent total knee arthroscopies undergone which was of relevance.

OCA scheint (s.s.) Wirkung auf Schmerz, Funktionalität & Lebensqualität zu haben

Based on the available evidence it would seem OCA has significant (statistically) effect of pain, functionality and quality of life; however, this observation should be considered cautiously given it is based solely on small, prospective case series and provides no comparative assessment.

ähnliches Ergebnis in Reviews (retrospektive Studien eingeschlossen)

Recent systematic reviews support the notion that clinical outcomes improve following OCA surgery; however, a significant portion of the evidence informing the conclusions drawn in these reviews is retrospective [1, 2, 67].

gleichen 4 Fallserien für Sicherheit: umfassendes Sicherheitsprofil von OCA fraglich

The same four case series referred to for the effectiveness evaluation of OCA in knee patients also informed the safety evaluation. Adverse events are reported; however, it is difficult to judge whether this provides a comprehensive safety profile of OCA. Namely because only one study specified that complications were monitored.

Relevance of the outcomes assessed to the potential patient-relevant benefits

Wirksamkeitsergebnisse umfassen Schmerzen, Funktionalität, Lebensqualität, Aktivitäten des täglichen Lebens, Notwendigkeit eines Gelenkersatzes

Effectiveness outcomes assessed during this review include pain, functionality, quality of life, activities of daily living/sport and necessity of total joint replacement. This suite of outcomes was thought sufficient to capture patient-relevant benefits of OCA.

Effectiveness in ankle patients in the single RCT was measured using the FAAM for overall functionality and a 10-point VAS to measure patient-perceived pain.

Various knee-specific, patient-reported tools were employed to measure symptoms, functionality and quality of life outcomes. These included the KOOS, the WOMAC, the IKDC and the Modified Cincinnati Knee Rating System. Some of these tools are measured with patient-completed questionnaires, which involve a level of subjectiveness. The applicability of the included studies, including population, interventions, comparators and outcomes, is outlined in the Appendices (See Appendix Table A-7).

The responsiveness of the IKDC and the WOMAC to changes following surgical interventions has been demonstrated [51].

Both the KOOS and the WOMAC capture disaggregated component scores, which is of benefit when interpreting results [51]. The KOOS sports and recreation subscale may not be applicable for less physically active patients, although it is commonly active individuals at risk of OCAs. However, the function scale of the WOMAC may not be comprehensive for physically active patients as it lacks difficult functional tasks.

The Cincinnati Knee Rating system has been shown reliable in both uninjured patients and those seeking treatment for knee-related problems however, a “modified” scale was used by the included study in this report which may not be appropriately reflective of the original scale [68].

Evidence gaps and ongoing studies

This systematic review identified a lack of comparative data for OCA. Considering this sparsity, it remains difficult to comprehensively understand the benefits and risks associated with OCA.

A single RCT, restricted to osteochondral lesions of the talar dome was retrieved. This study had a high risk of bias, and an overall sample size of only 40 patients. Moreover, it was necessary to rely solely on prospective, single-arm studies to inform a recommendation for the use of OCA for osteochondral knee defects despite the knee being a common site of such defects.

In addition, there are no registered, active, ongoing trials that intend to compare OCA to a relevant comparator (see Appendix Table A-8).

Greater comparative evidence for OCA relative to both autografts and other potential surgical approaches, and across both ankle and knee populations is essential to reach a better-informed recommendation.

Limitations in the report

This report encountered limitations regarding the available evidence base. As outlined in the pre-defined PICO criteria, only the highest level of evidence was considered for each indication. For ankle lesions, this meant a single RCT formed the evidence based to inform the effectiveness recommendation. Prospective case-series were included to inform the safety recommendation, however, only one additional study was retrieved. For knee lesions, only prospective case-series studies were identified. For both indications, there was a distinct lack of prospective, comparative data. The studies that were identified had small sample sizes, or follow-up times that were too short to detect important effects. Further, effectiveness outcomes were reported by different scoring systems, thereby limiting the ability to compare data across studies. Finally, five studies were excluded based on small sample size ($n < 15$) [69-73]. These studies reported relevant safety outcomes, but did not identify any complications not already identified in the included studies.

**Anwendung
verschiedener Tools
in einzelnen Studien,
teilweise äußerst
subjektiv**

große Lücken in Evidenz

**lediglich 1 RCT zum
Sprunggelenk**

**keine adäquaten
laufenden Studien**

**umfangreichere,
vergleichende Evidenz
notwendig**

**ausschließlich höchste
verfügbare Evidenzstufe
eingeschlossen
(1 RCT zum
Sprunggelenk,
5 Fallserien
≥ 15 PatientInnen)**

**ausschließlich
prospektive Studien**

Ausschluss retrospektiver Studien (Unklarheit über umfassende Erhebung relevanter Endpunkte, Nachbeobachtungszeiträume variieren stark)

The exclusion of retrospective study designs limited the evidence base obtained in this review; however, this decision was justified given the validity concerns of retrospective designs. Retrospective studies were excluded from this review for several reasons. First, it is unclear whether all relevant outcomes were collected (e.g. failures, adverse events), or if they were recorded comprehensively in clinical databases. Some patients may have left the care of the institution and had a failure or adverse event elsewhere that may not be captured in these studies. Second, follow-up times vary greatly between patients in retrospective trials, and results are often reported at last follow-up. This is particularly problematic for reported graft survival rates, whereby the last-observation-carried-forward method has been used to extrapolate survival findings of all patients to the longest follow-up time in the study [74]; for example, the majority of patients had a follow-up of only 2 years, but graft survival was extrapolated over 22 years of follow-up based on the longest-treated patient, thereby presenting distorted estimates of graft survival rates. For these reasons, only prospective studies were included in this review.

gegenwärtige Evidenz erlaubt keine gesicherten Aussagen zu Wirksamkeit und Sicherheit von OCA im Vergleich zu anderen Interventionen

Conclusion

A comprehensive understanding of the comparative risks and benefits of OCA compared to other forms of surgical management for osteochondral defects of the knee or ankle joint is not possible based on the currently available evidence. Very little comparative data was found, and where it was available, this was a single study, and was limited to patients with osteochondral lesions of the talar dome. Single-arm studies made up much of the evidence based available upon which to build a recommendation. At this stage, the comparative clinical effectiveness and safety of OCA relative to other surgical approaches remains unclear.

9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 9-1: Evidence based recommendations

	The inclusion in the catalogue of benefits is recommended .
	The inclusion in the catalogue of benefits is recommended with restrictions .
	The inclusion in the catalogue of benefits is currently not recommended .
X	The inclusion in the catalogue of benefits is not recommended .

Reasoning:

The current evidence is insufficient to prove that the assessed technology is at least as effective and safe than the comparators for knee and other joints. New study results will potentially influence the effect estimate considerably; however, there does not appear to be any ongoing clinical trials that will add further information in the near future.

On the basis of the limited evidence demonstrating a benefit of OCA in comparison to osteochondral autograft transplantation for knee and other joints, as well as the lack of ongoing trials, the inclusion in the hospital benefit catalogue is not recommended.

**keine ausreichend
robuste Evidenz**

**Aufnahme
nicht empfohlen**

10 References

- [1] Assenmacher AT, Pareek A, Reardon PJ, Macalena JA, Stuart MJ, Krych AJ. Long-term Outcomes After Osteochondral Allograft: A Systematic Review at Long-term Follow-up of 12.3 Years. *Arthroscopy* 2016; 32: 2160-8.
- [2] Chahla J, Sweet MC, Okoroha KR, Nwachukwu BU, Hinckel B, Farr J, et al. Osteochondral Allograft Transplantation in the Patellofemoral Joint: A Systematic Review. *Am J Sports Med* 2018: [Epub ahead of print].
- [3] European Network for Health Technology Assessment. Endpoints used for Relative Effectiveness Assessment: Clinical endpoints. 2015. [cited 18.12.2018]; Available from: http://www.eunethta.eu/sites/default/files/WP7-SG3-GL-clin_endpoints_amend2015.pdf.
- [4] European Network for Health Technology Assessment. Endpoints used in Relative Effectiveness Assessment: SAFETY. 2015. [cited 18.12.2018]; Available from: http://www.eunethta.eu/sites/default/files/sites/5026.fedimbo.belgium.be/files/WP7-SG3-GL-safety_amend2015.pdf.
- [5] Higgins JP, Sterne JA, Savovic J, Page M, Hróbjartsson A, Boutron I, et al. A revised tool for assessing risk of bias in randomized trials. *Cochrane Database Syst Rev* 2016; 10 (Suppl 1): 29-31.
- [6] Moga C, Guo B, Schopflocher D, Harstall C. Development of a quality appraisal tool for case series studies using a modified Delphi technique. 2012. [cited 28.01.2019]; Available from: <http://www.ihe.ca/advanced-search/development-of-a-quality-appraisal-tool-for-case-series-studies-using-a-modified-delphi-technique>.
- [7] Medical Services Advisory Committee. Matrix-induced autologous chondrocyte implantation and autologous chondrocyte implantation. 2011. [cited 14.01.2019]; Available from <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1140-public>.
- [8] Torrie AM, Kesler WW, Elkin J, Gallo RA. Osteochondral allograft. *Curr Rev Musculoskelet Med* 2015; 8: 413-22.
- [9] University of Wisconsin Sports Medicine. Rehabilitation Guidelines Following Osteochondral Allograft or Autograft Transplantation. 2017. [cited 14.01.2019]; Available from: https://www.uwhealth.org/files/uwhealth/docs/pdf2/SM_rehab_oats.pdf.
- [10] Washington University Physicians. Osteochondral Autograft and Allograft. 2017. [cited 14.01.2019]; Available from: <https://www.ortho.wustl.edu/content/Patient-Care/2894/Services/Sports-Medicine/Overview/Knee/Osteochondral-Autograft-Allograft.aspx>.
- [11] International Cartilage Regeneration & Joint Preservation Society. Allograft. 2018. [cited 15.01.2019]; Available from: <https://cartilage.org/patient/about-cartilage/cartilage-repair/allograft/>.
- [12] Fitzgerald J, Broehm C, Chafey D, Treme G. Chondroblastoma of the knee treated with resection and osteochondral allograft reconstruction. *Case Rep Orthop* 2014; 2014: 543959.
- [13] International Cartilage Regeneration & Joint Preservation Society. Cartilage Repair Techniques. 2018. [cited 15.01.2019]; Available from: <https://cartilage.org/patient/about-cartilage/cartilage-repair/>.
- [14] Gracitelli GC, Moraes VY, Franciozi CE, Luzo MV, Belloti JC. Surgical interventions (microfracture, drilling, mosaicplasty, and allograft transplantation) for treating isolated cartilage defects of the knee in adults. *Cochrane Database Syst Rev* 2016; 9: Cd010675.
- [15] Ihejirika R. Will Biologic Treatment for Cartilage Restoration Become the Standard of Care? 2018. [cited 14.01.2019]; Available from: <https://www.aaos.org/AAOSNow/2018/Jan/Research/research02/>.
- [16] Stanford Health Care. Chondral/Osteochondral Defect. 2018. [cited 15.01.2019]; Available from: <https://stanfordhealthcare.org/medical-conditions/bones-joints-and-muscles/chondral-osteochondral-defect.html>.
- [17] Mestriner AB, Ackermann J, Gomoll AH. Patellofemoral Cartilage Repair. *Curr Rev Musculoskelet Med* 2018; 11: 188-200.

- [18] Medvedeva EV, Grebenik EA, Gornostaeva SN, Telpuhov VI, Lychagin AV, Timashev PS, et al. Repair of Damaged Articular Cartilage: Current Approaches and Future Directions. *Int J Mol Sci* 2018; 19.
- [19] International Cartilage Regeneration & Joint Preservation Society. Mosaicplasty. 2018. [cited 15.01.2019]; Available from: <https://cartilage.org/patient/about-cartilage/cartilage-repair/mosaicplasty/>.
- [20] Seo SS, Kim CW, Jung DW. Management of focal chondral lesion in the knee joint. *Knee Surg Relat Res* 2011; 23: 185-96.
- [21] European Commission. Mapping of More Stringent Tissues and Cells Donor Testing Requirements – Mapping Exercise 2015. 2015. [cited 14.02.2019]; Available from: https://ec.europa.eu/health/blood_tissues_organs/key_documents/testing_cellsdonors_mapping_en.
- [22] Rechtsinformationssystem des Bundes (RiS). Bundesgesetz über die Festlegung von Qualitäts- und Sicherheitsstandards für die Gewinnung, Verarbeitung, Lagerung und Verteilung von menschlichen Zellen und Geweben zur Verwendung beim Menschen (Gewebesicherheitsgesetz-GSG). 2019. [cited 14.02.2019]; Available from: <https://www.ris.bka.gv.at/GeltendeFassung.wxe?Abfrage=Bundesnormen&Gesetzesnummer=20005698>.
- [23] Bundeskanzleramt Österreich. Bundesgesetz über die Transplantation von menschlichen Organen (Organtransplantationsgesetz – OTPG). 2018. [cited 28.02.2019]; Available from: <https://www.ris.bka.gv.at/GeltendeFassung.wxe?Abfrage=Bundesnormen&Gesetzesnummer=20008119>.
- [24] Melton JT, Cossey AJ. Techniques for cartilage repair in chondral and osteochondral defects of the knee. *Acta Orthop Belg* 2011; 77: 152-9.
- [25] Camp CL, Stuart MJ, Krych AJ. Current concepts of articular cartilage restoration techniques in the knee. *Sports Health* 2014; 6: 265-73.
- [26] Farr J, Gomoll AH. 2016 barriers to cartilage restoration. *J Clin Orthop Trauma* 2016; 7: 183-6.
- [27] Tirico LE, Demange MK, Santos LA, de Rezende MU, Helito CP, Gobbi RG, et al. Development of a Fresh Osteochondral Allograft Program Outside North America. *Cartilage* 2016; 7: 222-8.
- [28] Yano K, Watanabe N, Tsuyuki K, Ikawa T, Kasanuki H, Yamato M. Regulatory approval for autologous human cells and tissue products in the United States, the European Union, and Japan. *Regenerative Therapy* 2015; 1: 45-56.
- [29] Bugbee W. Osteochondral Allograft Transplantation. Clinical Outcome and Return to Sport. *Aspetar Sports Medicine Journal* [Internet]. 2016; 5:[246-51 pp.]. [cited 14.02.2019]; Available from: <http://www.aspetar.com/journal/viewarticle.aspx?id=316#.XEUxrGcUlwk>.
- [30] Pisanu G, Cottino U, Rosso F, Blonna D, Marmotti AG, Bertolo C, et al. Large Osteochondral Allografts of the Knee: Surgical Technique and Indications. *Joints* 2018; 6: 42-53.
- [31] Sechriest II VF, Bole BJ, Bugbee W. Osteochondral Allograft Transplantation. In: Sgaglione NA, Lubowitz JH, Provencher MT, editors. *The Knee: AANA Advanced Arthroscopic Surgical Techniques: Slack Incorporated and Advanced Arthroscopic Surgical Techniques*; 2016. p. 243-55.
- [32] Turtel A. Osteochondral Grafting of Articular Cartilage Injuries. 2017. [cited 16.01.2019]; Available from: <https://emedicine.medscape.com/article/1252755-overview#a11>.
- [33] Chui K, Jeys L, Snow M. Knee salvage procedures: The indications, techniques and outcomes of large osteochondral allografts. *World J Orthop* 2015; 6: 340-50.
- [34] Knipe H, Gaillard F. Osteochondral defect. [cited 16.01.2019]; Available from: <https://radiopaedia.org/articles/osteochondral-defect>.
- [35] Vaish A, Vaishya R, Vijay V, Agarwal AK. Practice guidelines for approaching articular cartilage defects of the knee. *Apollo Medicine* 2017; 14: 17-20.
- [36] Outerbridge RE. The etiology of chondromalacia patellae. *J Bone Joint Surg Br* 1961; 43-b: 752-7.
- [37] American Orthopaedic Foot & Ankle Society. Osteochondral lesion. [cited 16.01.2019]; Available from: <http://www.aofas.org/footcaremd/conditions/ailments-of-the-ankle/Pages/Osteochondral-Lesion.aspx>.

References

- [38] Cedars-Sinai. Osteochondral Lesions/Osteochondritis Desiccans. 2018. [cited 16.01.2019]; Available from: <https://www.cedars-sinai.edu/Patients/Health-Conditions/Osteochondral-Lesions-Osteochondritis-Desiccans.aspx>.
- [39] Makris EA, Gomoll AH, Malizos KN, Hu JC, Athanasiou KA. Repair and tissue engineering techniques for articular cartilage. *Nature Reviews Rheumatology* 2015; 11: 21-34.
- [40] Lyman S, Nakamura N, Cole BJ, Erggelet C, Gomoll AH, Farr J, 2nd. Cartilage-Repair Innovation at a Standstill: Methodologic and Regulatory Pathways to Breaking Free. *J Bone Joint Surg Am* 2016; 98: e63.
- [41] Biant LC, McNicholas MJ, Sprowson AP, Spalding T. The surgical management of symptomatic articular cartilage defects of the knee: Consensus statements from United Kingdom knee surgeons. *Knee* 2015; 22: 446-9.
- [42] National Institute for Health and Care Excellence. Autologous chondrocyte implantation for treating symptomatic articular cartilage defects of the knee. 2017. [cited 22.01.2019]; Available from <https://www.nice.org.uk/guidance/ta477>.
- [43] Statistik Austria. Jahrbuch der Gesundheitsstatistik 2016. 2018. [cited 14.02.2019]; Available from: http://statistik.at/web_de/services/publikationen/4/index.html?includePage=detailedView§ionName=Gesundheit&pubId=495.
- [44] Bundesministerium für Arbeit Soziales Gesundheit und Konsumentenschutz B. Medizinische Leistungen bei stationären Aufenthalten nach Kapiteln des Leistungskatalogs 2017. 2018. [cited 14.02.2019]; Available from: http://www.kaz.bmg.gv.at/fileadmin/user_upload/Leistungen/1_T_Leistungen_nach_Kapitelstruktur.pdf.
- [45] National Institute for Health and Care Excellence. Mosaicplasty for symptomatic articular cartilage defects of the knee. 2018. [cited 22.01.2019]; Available from: <https://www.nice.org.uk/Guidance/IPG607>.
- [46] Hjelle K, Solheim E, Strand T, Muri R, Brittberg M. Articular cartilage defects in 1,000 knee arthroscopies. *Arthroscopy* 2002; 18: 730-4.
- [47] Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: study of 25,124 knee arthroscopies. *Knee* 2007; 14: 177-82.
- [48] Aroen A, Loken S, Heir S, Alvik E, Ekeland A, Granlund OG, et al. Articular cartilage lesions in 993 consecutive knee arthroscopies. *Am J Sports Med* 2004; 32: 211-5.
- [49] Rungprai C, Tennant JN, Gentry RD, Phisitkul P. Management of Osteochondral Lesions of the Talar Dome. *Open Orthop J* 2017; 11: 743-61.
- [50] Ondresik M, Oliveira JM, Reis RL. Advances for Treatment of Knee OC Defects. *Adv Exp Med Biol* 2018; 1059: 3-24.
- [51] Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care Res (Hoboken)* 2011; 63 Suppl 11: S208-28.
- [52] Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of Knee Function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis care & research* 2011; 63: S208-S28.
- [53] Katz NP, Paillard FC, Ekman E. Determining the clinical importance of treatment benefits for interventions for painful orthopedic conditions. *Journal of orthopaedic surgery and research* 2015; 10: 24.

- [54] Singh JA, Luo R, Landon GC, Suarez-Almazor M. Reliability and Clinically Important Improvement Thresholds for Osteoarthritis Pain and Function scales: A Multicenter study. *The Journal of rheumatology* 2014; 41: 509-15.
- [55] Martin RL, Irrgang JJ, Burdett RG, Conti SF, Van Swearingen JM. Evidence of validity for the Foot and Ankle Ability Measure (FAAM). *Foot Ankle Int* 2005; 26: 968-83.
- [56] Hung M, Baumhauer JF, Licari FW, Voss MW, Bounsanga J, Saltzman CL. PROMIS and FAAM Minimal Clinically Important Differences in Foot and Ankle Orthopedics. *Foot Ankle Int* 2019; 40: 65-73.
- [57] Ahmad J, Jones K. Comparison of Osteochondral Autografts and Allografts for Treatment of Recurrent or Large Talar Osteochondral Lesions. *Foot Ankle Int* 2016; 37: 40-50.
- [58] Brown D, Shirzad K, Lavigne SA, Crawford DC. Osseous Integration after Fresh Osteochondral Allograft Transplantation to the Distal Femur: A Prospective Evaluation Using Computed Tomography. *Cartilage* 2011; 2: 337-45.
- [59] Cinats D, Miller S, Abusara Z, Heard SM, Hutchison C, Schachar N, et al. Evolution of a Novel Tissue Preservation Protocol to Optimize Osteochondral Transplantation Outcomes. *Cartilage* 2018: [Epub ahead of print].
- [60] LaPrade RF, Botker J, Herzog M, Agel J. Refrigerated osteoarticular allografts to treat articular cartilage defects of the femoral condyles. A prospective outcomes study. *J Bone Joint Surg Am* 2009; 91: 805-11.
- [61] Mahomed MN, Beaver RJ, Gross AE. The long-term success of fresh, small fragment osteochondral allografts used for intraarticular post-traumatic defects in the knee joint. *Orthopedics* 1992; 15: 1191-9.
- [62] Bentley G, Bhamra JS, Gikas PD, Skinner JA, Carrington R, Briggs TW. Repair of osteochondral defects in joints--how to achieve success. *Injury* 2013; 44 Suppl 1: S3-10.
- [63] Haene R, Qamirani E, Story RA, Pinsker E, Daniels TR. Intermediate outcomes of fresh talar osteochondral allografts for treatment of large osteochondral lesions of the talus. *J Bone Joint Surg Am* 2012; 94: 1105-10.
- [64] Moga C, Guo B, Schopflocher D, Harstall C. Development of a quality appraisal tool for case series studies using a modified Delphi technique. In: (IHE) IoHE, editor. 2012.
- [65] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction- GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; 64: 383-94.
- [66] VanTienderen RJ, Dunn JC, Kusnezov N, Orr JD. Osteochondral Allograft Transfer for Treatment of Osteochondral Lesions of the Talus: A Systematic Review. *Arthroscopy* 2017; 33: 217-22.
- [67] Familiari F, Cinque ME, Chahla J, Godin JA, Olesen ML, Moatshe G, et al. Clinical Outcomes and Failure Rates of Osteochondral Allograft Transplantation in the Knee: A Systematic Review. *Am J Sports Med* 2018; 46: 3541-9.
- [68] Barber-Westin SD, Noyes FR, McCloskey JW. Rigorous statistical reliability, validity, and responsiveness testing of the Cincinnati knee rating system in 350 subjects with uninjured, injured, or anterior cruciate ligament-reconstructed knees. *Am J Sports Med* 1999; 27: 402-16.
- [69] Adams SB, Dekker TJ, Schiff AP, Gross CP, Nunley JA, Easley ME. Prospective Evaluation of Structural Allograft Transplantation for Osteochondral Lesions of the Talar Shoulder. *Foot & Ankle International* 2018; 39: 28-34.
- [70] Berlet GC, Hyer CF, Philbin TM, Hartman JF, Wright ML. Does fresh osteochondral allograft transplantation of talar osteochondral defects improve function? *Clinical Orthopaedics & Related Research* 2011; 469: 2356-66.
- [71] Karataglis D, Learmonth DJ. Management of big osteochondral defects of the knee using osteochondral allografts with the MEGA-OATS technique. *Knee* 2005; 12: 389-93.
- [72] Kosashvili Y, Raz G, Backstein D, Lulu OB, Gross AE, Safir O. Fresh-stored osteochondral allografts for the treatment of femoral head defects: surgical technique and preliminary results. *International Orthopaedics* 2013; 37: 1001-6.

References

- [73] Locht RC, Gross AE, Langer F. Late osteochondral allograft resurfacing for tibial plateau fractures. *Journal of Bone & Joint Surgery – American Volume* 1984; 66: 328-35.
- [74] Briggs D, Sadr KN, Pulido P, Bugbee W. The use of osteochondral allograft transplantation for primary treatment of cartilage injuries in the knee. *Orthopaedic Journal of Sports Medicine* 2015; 3.
- [75] European Network for Health Technology Assessment. Internal validity (of randomized controlled trials). 2013. [cited 18.12.2019]; Available from: https://www.eunetha.eu/wp-content/uploads/2018/01/16_WP7-SG3-GL-int_val_RCTs_amend2015.pdf.

Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Osteochondral allograft transplantation: Results from randomised controlled trials (*ankle*)

Author, year	Ahmad et al 2016
Country	USA
Sponsor	None
Intervention/Product	OCA
Comparator	Osteochondral autograft
Study design	RCT
Number of pts	40 (I: 20 vs C: 20) ¹
Inclusion criteria	Recurrent OLT that failed initial arthroscopic treatment or large ($\geq 1.5\text{cm}^2$) OLT, Failed recent nonoperative treatment, with a minimum 4 weeks NWB immobilisation, OLT does not involve the (medial or lateral) shoulder of the talar dome, Amenable to operative treatment with osteochondral plugs
Age of patients (yrs) [mean (range)]	I: 39.7 (17-60) C: 41.3 (14-63)
Gender, male %	I: 62.5%* C: 55.0%*
Number of prior surgeries per patient	NR
Indication (%)	Osteochondral lesions of the talar dome (OLT) 100%
Concurrent procedures (%)	NR
Mean graft storage time, days	NR
Chondral lesion size (range)	I: 1.8cm ² (0.7-4.2) C: 1.6 cm ² (0.7-2.4)
Transplanted location (%)	I: Anterior or central OLT (87.5%*) Posteromedial (12.5%*) C: Anterior or central OLT (80.0%*) Posteromedial (20.0%*)
Follow-up, years (range)	I: 3.4 (1.2-6.4)* C: 2.9 (1-5.4)*
Loss to follow-up, n (%)	I: 4 (20%*) ² C: 0 (0%)

¹ Total number randomised. An ITT study design was not employed; number of patients used when reporting patient characteristics and in subsequent analyses was 36 (I:16 vs. C: 20)

² Four patients in the intervention arm were excluded intra-operatively as they were discovered to have significant involvement of either the medial or lateral shoulder of the talar dome.

Author, year	Ahmad et al 2016
Outcomes	
Efficacy	
Decrease in pain	
* VAS mean (range)	I vs. C Preoperative 7.8/10 (5-10) vs. 7.9/10 (4-10) Post-operative 2.7/10 (1-8) vs. 2.2/10 (0-8) $p=0.15$
Increase in functionality	
* FAAM mean (range)	I vs. C Preoperatively 55.2/100 (36.9-82.1) vs. 54.4/100 (31.0-88.1) Postoperatively 80.7/100 (56.0-95.2) vs. 85.5/100 (56.0-97.6) $p=0.25$
Increase in quality of life	NR
Necessity of total joint replacement	NR
Return to daily/sports/physical activities	NR
Safety	
Procedure-related mortality	0 (0%)
Adverse events n (%)	I vs. C graft nonunion 3 (18.8%) vs. 2 (10.0%) postoperative superficial wound blistering 0 (0%) vs 1 (5.0%) postoperative knee complications 0 (0%) vs. 6 (30.0%) anterior ankle arthritis 1 (6.3%) vs. 0 (0%)
Transplant failure rates	I vs. C graft nonunion requiring removal ³ 2 (18.8%) vs. 2 (10.0%)
Re-admission	NR
Re-operation/additional surgery	I vs. C Conversion to alternate treatment ³ 2 (12.5%) vs. 2 (10.0%)

Abbreviations *OCA* = osteochondral allograft transplantation, *OLT* = osteochondral lesion of the talar dome, *RCT* = randomised controlled trial, *FAAM* = foot and ankle ability measure, *VAS* = visual analogue scale.

Notes *calculations made during extraction

³ Two patients in the intervention arm had their allograft converted to an autograft as revision operative treatment; two patients in the comparator arm had their autograft converted to talar allograft plugs as revision operative treatment. At six months post-revision surgery, all patients had achieved full osteochondral healing on radiographic and CT imaging.

Table A-2: Osteochondral allograft transplantation: Results from observational studies of osteochondral allograft transplant (*knee and ankle*)

Author, year	Brown et al 2011	Cinats et al 2018	LaPrade et al 2009	Mahomed et al 1992	Haene et al 2012 ⁴
Country	USA	Canada	USA	Canada	Canada
Sponsor	AlloSource Inc., Centennial, Colorado	Calgary Health Trust	None	NR	None
Intervention/Product	OCA	OCA	OCA	OCA	OCA
Comparator	N/A	N/A	N/A	N/A	N/A
Study design	Prospective case series	Prospective case series	Prospective case series	Prospective case series	Prospective case series ⁵
Number of pts	34	17 ⁶	23	91	16
Transplant for knee or ankle	Knee	Knee	Knee	Knee	Ankle
Inclusion criteria	Grade 4 International Cartilage Repair Society (ICRS) articular cartilage defects	Age 18-50, presence of 80% meniscus, no inflammatory arthropathy, no osteoarthritis, no Workers Compensation Board cases	Symptomatic full-thickness articular cartilage defect of >3cm ² , no so-called kissing lesion of the corresponding articular cartilage surface, less than minor peripheral osteophytes or joint-space narrowing, no ligamentous instability, no malalignment, presence of >50% of the meniscus in the ipsilateral compartment	Posttraumatic osteoarticular defect of the knee joint	Undergoing fresh allograft transplantation for a talar lesion
Age of patients, yrs (range)	34.5 (15-61)	33 (17-45)	30.9 (16.4-46.9)	41.9 (17-75)	35.8 (15-53)
Gender, male %	74.0%	47.1%	56.5%*	56.0%*	50.0%
Number of prior surgeries per patient	0.7	1.2* ⁷	1.7	NR	16 of 17 ankles had undergone single or multiple surgeries

⁴ Haene et al. (2012) included for safety data only as an RCT for ankle patients was available.

⁵ Potentially retrospective, although given the ambiguity this was left in.

⁶ Three patients with shoulder transplants were excluded from the data extraction.

Data pertaining to outcome measures reported for knee and shoulder patients combined was not extracted (VAS and SF-36 scores).

⁷ Calculated, 20 procedures from 17 knee patients

Author, year	Brown et al 2011	Cinats et al 2018	LaPrade et al 2009	Mahomed et al 1992	Haene et al 2012 ⁴
Indication (%)	Avascular necrosis (5.0%) Osteochondritis dissecans (31.0%) Focal osteoarthritis defects (64.0%) ⁸	NR	Localized osteochondral lesion due to a dislodged osteochondritis dissecans lesion of the femoral condyle (60.9%*) Localized full-thickness chondral defects (39.1%*)	Posttraumatic osteoarticular defect of the knee joint (100%)	Talar lesion (100%)
Concurrent procedures (%)	Anterior cruciate ligament reconstruction (2.9%*) Tibial realignment osteotomy (14.7%*) Medial patellofemoral ligament reconstruction (2.9%*) Meniscus transplant (5.9%*) ⁹	NR	Proximal tibial osteotomy (30.4%*) Meniscal transplant (13.0%*) Partial posterior horn medial meniscectomy (4.3%*) Concurrent Herbert screw removal (4.3%*) Concurrent revision anterior cruciate ligament reconstruction additional to meniscal transplant (4.3%*)	NR	NR
Mean graft storage time, days (range)	21.1 (16-26)	10.6 (3-18)	20.3 (15-25)	NR	NR
Chondral lesion size (range)	5.7 (1.5-15) cm ²	2.6* (2.0-3.4) cm diameter	4.8 (3.1-9.6) cm ²	NR	At least one dimension >15mm ¹⁰
Transplanted location (%)	Femoral condyle (100%)	Lateral tibial plateau (17.6%*) Lateral femoral condyle (41.2%*) Medial femoral condyle (41.2%*)	Medial femoral condyle (82.6%*) Lateral femoral condyle (13.0%*) Both medial and lateral (4.3%*)	NR	Posteromedial talar (64.7%*) Medial talar (17.6%*) Posterolateral talar (11.8%*) Anterolateral talar (5.9%*)
Follow-up, years mean, (range)	2	2	3 (1.9 to 4) ¹¹	5.7* (0.3 - 14.5*) ¹²	4.1 (2-7)
Loss to follow-up, n (%)	10 (29.4%) ¹³	0 (0%)	0 (0%)	28 (30.8%*) ¹⁴	0 (0%)

⁸ Information presented in the written text and table differed. Indications reported in the written text were extracted,

⁹ Information presented in the written text and in the table differed. Concurrent procedures reported in the written text were extracted. Total number of patients receiving concurrent interventions (n=9) was the same in both the written text and the table. Percentages calculated using patient number (n=34) as denominator.

¹⁰ For all except one lesion, whose diameter was between 10-15mm and which had failed prior autograft transplantation

¹¹ Three patients did not have 2-year follow-up data however, all three reported their knees felt normal so did not want to return for a follow-up exam.

¹² It is unclear how many patients had a follow-up of less than 2 years,

¹³ Applies for a follow-up period of 2-years. 3 patients moved, 1 was converted to a total knee arthroplasty and 6 were lost for unknown reasons.

¹⁴ 23 patients could not be contacted by phone, 5 patients died due to causes unrelated to the procedure.

Author, year	Brown et al 2011	Cinats et al 2018	LaPrade et al 2009	Mahomed et al 1992	Haene et al 2012 ⁴
Outcome					
Efficacy					
Decrease in pain					
⊛ KOOS (pain)	Baseline vs. 2-year follow-up 59 (± 17) vs. 74 (± 22) <i>p=0.028</i>	Preoperative vs. 2-years postoperative 52.5 (± 24.3) vs. 79.0 (± 20.53) <i>p<0.001</i>	NR	NR	
⊛ WOMAC (pain)	NR	Preoperative vs. 2-years postoperative 91.0 (± 5.7) vs. 96.1 (± 4.6) <i>p=0.002</i>	NR	NR	
⊛ Modified Cincinnati knee-rating score (symptoms)	NR	NR	Baseline vs. follow-up ¹⁵ 21.9 vs 32.5 <i>p<0.03</i>	NR	
Increase in functionality					
⊛ IKDC Questionnaire	Baseline vs. 2-year follow-up 45 (± 11) vs. 62 (± 20) <i>p<0.00157</i>	NR	Baseline vs. follow-up ¹⁵ 52.0 vs. 68.5 <i>p<0.03</i>	NR	
⊛ WOMAC (function)	NR	Preoperative vs. 2-years postoperative 68.1 (± 23.8) vs. 83.1 (± 20.4) <i>p=0.03</i>	NR	NR	
⊛ WOMAC (overall)	NR	Preoperative vs. 2-years postoperative 65.1 (± 24.8) vs. 82.3 (± 19.9) <i>p=0.02</i>	NR	NR	
⊛ Modified Cincinnati knee-rating score (function)	NR	NR	Baseline vs. follow-up ¹⁵ 27.3 vs. 36.5 <i>p<0.01</i>	NR	
⊛ Modified Cincinnati knee-rating score (overall)	NR	NR	Baseline vs. follow-up ¹⁵ 49.2 vs 69.0 <i>p<0.02</i>	NR	

¹⁵ Data collected at final clinical follow-up was compared to preoperative data. No specified post-operative data collection interval is specified.

Author, year	Brown et al 2011	Cinats et al 2018	LaPrade et al 2009	Mahomed et al 1992	Haene et al 2012 ⁴
Increase in quality of life					
* KOOS (QoL)	Baseline vs. 2-year follow-up 23 (± 17) vs. 48 (± 22) <i>p</i> <0.001	Preoperative vs. 2-years postoperative 20.6 (± 15.4) vs. 51.2 (± 31.1) <i>p</i> =0.001	NR	NR	
Necessity of total joint replacement (n)	n=1	NR	NR	n=6	
Return to daily/sports/physical activities					
* KOOS (activities of daily living)	Baseline vs. 2-year follow-up 69 (± 21) vs. 83 (± 23) <i>p</i> =0.058	Preoperative vs. 2-years postoperative 68.5 (± 24.3) vs. 84.8 (± 19.9) <i>p</i> =0.004	NR	NR	
* KOOS (sports and recreation)	Baseline vs. 2-year follow-up 37 (± 26) vs. 57 (± 30) <i>p</i> =0.005	Preoperative vs. 2-years postoperative 21.2 (± 22.0) vs. 54.4 (± 31.9) <i>p</i> =0.002	NR	NR	
Safety					
Procedure-related mortality	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Adverse events * peri- and post-operative, n(%)	<i>On arthroscopic investigation.</i> ¹⁶ Fibrosis impinging adjacent meniscus (n=1) ICRS grade 2/3 changes in transplanted graft cartilage (n=2) Fragmentation or delamination of the graft with associated loose bodies (n=3) Minimal fraying (n=3)	DVT and pulmonary embolism: n=1 (5.9%*) Edema, fragmentation at the interpositional interface with delamination of the articular cartilage. ¹⁷ n=2 (11.8%)	Superficial cellulitis: n=1 (4.3%*)	Stiffness requiring manipulation (n=3) Reflex sympathetic dystrophy (n=1) Wound hematoma (n=1) Rupture of the patellar tendon (n=1) Respiratory (n=2) ¹⁸	Malunion of a medial malleolar osteotomy site (n=1) ¹⁹

¹⁶ In patients who had a subsequent procedure, transplanted grafts were evaluated arthroscopically. 14 patients had a subsequent procedure, 9 of which were directly related to the OCA transplant.

¹⁷ Found on MRI and secondary arthroscopy in the 2 patients whose grafts were considered 'failures' (i.e. ongoing pain and debilitation).

¹⁸ Number only, no %, reported. Calculations were not made as it was unclear what the denominator should be.

¹⁹ This did not require additional treatment.

Author, year	Brown et al 2011	Cinats et al 2018	LaPrade et al 2009	Mahomed et al 1992	Haene et al 2012 ⁴
Transplant failure rates, n(%)	n=2 ²⁰ (7%)	n=2 (11.8%*)	NR	NR ²¹	5 of 17 ankles (29.4%*)
Re-admission	NR	NR	NR	NR	NR
Re-operation/additional surgery	Procedure directly related to OCA: (n=9) Procedure unrelated to OCA: (n=5)	Second arthroscopy (after transplant failure): n=2 (11.8%*)	Removal of symptomatic hardware from a concurrent proximal tibial opening n=3 (13.0%) Diagnostic arthroscopy (after valgus twisting injury) n=1 (4.3%*) Lateral patellotibial ligament reconstruction n=1 (4.3%*)	Total knee arthroplasty (n=6) Arthrodesis (n=3) Re-transplant (n=3) Curettage and drilling: (n=1) ²²	Arthroscopic debridement 2 of 17 ankles (11.8%*) Arthrodesis 2 of 17 ankles (11.8%*)

Abbreviations *FAAM* = foot and ankle ability measure, *ICRS* = International Cartilage Repair Society, *IKDC* = International Knee Documentation Committee, *KOOS* = Knee injury and osteoarthritis outcome score, *N/A* = not applicable, *NR* = not reported, *OCA* = osteochondral allograft, *OCT* = osteochondral lesion of the talar dome, *VAS* = visual analogue scale, *WOMAC* = Western Ontario and McMaster Universities Osteoarthritis index.

* Own calculations.

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found randomised comparative trial can be found from the Cochrane Collaboration [5] and in the Guidelines of EUnetHTA [75]. Single arm studies were appraised according to the IHE appraisal tool for case series studies [6].

Table A-3: Risk of bias – study level (randomised studies for knee), see [5]

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating Physician			
Ahmad et al, 2016 [57]	No	No	No	No	Yes	Yes	High

²⁰ This number is based on 30 patients who were evaluated by CT scan.

²¹ % successful transplants at 5, 10- and 14-years post transplantation was presented however, it is unclear how many patients were included in the calculations at each time point. The information presented was considered very misleading and was therefore not extracted.

²² Presented as number of patients only, not %, as it was unclear at what stage in follow up these occurred i.e. what the denominator should be (original sample, or exclude those lost to follow up)

Table A-4: Risk of bias – study level (case series for knee and ankle), see [6]

Study reference/ID	Brown et al 2011	Cinats et al 2018	LaPrade et al 2009	Mahomed et al 1992	Haene et al 2012
Study objective					
1. Was the hypothesis/aim/objective of the study clearly stated in the abstract, introduction or methods section?	Yes	Yes	Yes	Yes	Yes
Study design					
2. Was the study conducted prospectively?	Yes	Yes	Yes	Unclear ²³	Yes
3. Were the cases collected in more than one centre?	No	No	No	No	No
4. Were patients recruited consecutively?	Unclear	Unclear	Yes	Unclear	Unclear
Study population					
5. Were the characteristics of the patients included in the study described?	Yes	Yes	Yes	Partial ²⁴	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	No ²⁵	Yes	Yes	No ²⁶	No ²⁷
7. Did patients enter the study at a similar point in the disease? ²⁸	Yes	Yes	Yes ²⁹	Unclear	Yes
Intervention and co-intervention					
8. Was the intervention of interest clearly described?	Yes	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described? ³⁰	Yes	No	Yes	No	No

²³ Patients receiving fresh osteochondral allografts via the Bone Bank Program have been prospectively followed since 1972. Mahomed et al. (1992) report outcomes for a subgroup of patients (i.e. those whose osteochondral defect is due to trauma) in whom, on review of the first 100 cases. There is a possibility this is a post-hoc analysis

²⁴ Previous surgeries undergone are not reported.

²⁵ Exclusion criteria (i.e. ineligibility for an allograft transplant) not specified.

²⁶ Inclusion/exclusion criteria for the Blood Bank Program (from which patients are taking part in) is not reported.

²⁷ Exclusion criteria (i.e. ineligibility for a fresh allograft transplant) not specified.

²⁸ Grade of cartilage defect. Where this was not reported, lesion size was then considered.

²⁹ All lesions were symptomatic full-thickness articular cartilage defects of >3cm².

³⁰ Concurrent procedures were considered when answering this question.

Study reference/ID	Brown et al 2011	Cinats et al 2018	LaPrade et al 2009	Mahomed et al 1992	Haene et al 2012
Outcome measures					
10. Were relevant outcome measures established a priori?	Yes	Yes	Yes	Yes	Yes
11. Were the relevant outcomes measured using appropriate objective/subjective methods? ³¹	Yes	Yes	Yes	No ³²	Yes
12. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Unclear ³³	Yes
Statistical Analysis					
13. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	No ³⁴	Yes
Results and Conclusions					
14. Was follow-up long enough for important events and outcomes to occur? ³⁵	No	No	No	Yes	Yes
15. Were losses to follow-up reported?	Yes	Yes	Yes	Yes	Yes
16. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	No ³⁶	No ³⁷	No	No	No
17. Were the adverse events reported?	Yes	Yes	Yes	Yes	
18. Were the conclusions of the study supported by results?	Yes	Yes	Yes	Unclear ³⁸	Yes
Competing interests and sources of support					
19. Were both competing interests and sources of support for the study reported?	Yes	Yes	Yes	No	Unclear ³⁹
Overall Risk of bias	Moderate	Moderate	Low	Serious	Moderate

Notes with regard to the number of yes responses: 1-7 was considered indicative of serious risk of bias, 8-14 of moderate risk and 15-19 of low.

³¹ Where routine follow-ups were specified in the methods section, it was assumed that the intent was to monitor both outcomes and complications at these visits.

³² The method for capturing complications was not adequately reported in the methods section.

³³ Pre-surgical assessment is not explicitly described, although failure is described as an increment in the post-operative knee score, implying a comparison to a pre-operative score.

³⁴ Survivorship analysis extrapolating follow-up of all patients to the longest follow up time of a single patient, does not account for censoring correctly.

³⁵ Mean follow-up of 4 years was considered reasonable.

³⁶ Variability in the mean difference was not reported, only a p-value.

³⁷ Variability in the mean difference was not reported, only a p-value.

³⁸ Many conclusions are summarised at the closure of the article. These are not all supported by, or relevant to, the results presented.

³⁹ Potential conflict of interest noted, although the conflicting party not identified (in the available disclosure statement).

Table A-5: Evidence profile: efficacy and safety of osteochondral allograft transplantation (*ankle*)

Quality assessment							Summary of findings				
							Number of patients		Effect		Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OCA	Autologous autograft	Relative (95% CI)	Absolute (95% CI)	
Efficacy											
Pain: change in pain score (Follow up: 2 years; assessed with: VAS; Scale from: 0 (less pain) to 100 (more pain))											
1	RCT	serious ¹	N/A (only one trial)	not serious	serious ²	none	16	20	-		⊕⊕○○ LOW
Function: Change in function score (follow up: 2 years; assessed with: FAAM; Scale from: 0 (worse function) to 100 (better function))											
1	RCT	serious ¹	N/A (only one trial)	not serious	serious ²	none	16	20	-		⊕⊕○○ LOW
Function: Change in quality of life (outcome not reported)											
-	-	-	-	-	-	-	-	-	-	-	-
Necessity of total joint replacement (outcome not reported)											
-	-	-	-	-	-	-	-	-	-	-	-
Safety											
Procedure-related mortality (follow up: 2 years)											
1	RCT	serious ¹	N/A (only one trial)	not serious	serious ²	Follow-up duration too short	0/16	0/20	not estimable	-	⊕⊕○○ LOW
Procedure-related mortality (follow up: 2 to 7 years)											
1	Case series	serious ³	N/A (only one trial)	not serious	serious ²	Follow-up duration too short	0/16	-	-	-	⊕○○○ VERY LOW
Complications (follow up: 2 years)											
1	RCT	serious ¹	N/A (only one trial)	not serious	serious ²	Follow-up duration too short	3/16 (18.8%)	4/20 (20.0%)	RR 0.93 (0.24 to 5.60)	14 fewer per 1,000 (from 152 fewer to 920 more)	⊕⊕○○ LOW
Complications (follow up: 2 to 7 years)											
1	Case series	serious ³	N/A (only one trial)	not serious	serious ²	Follow-up duration too short	1/17 ankles (5.9%)	-	-	-	⊕○○○ VERY LOW
Transplant failure (follow up: 2 years; assessed with: removal or replacement of the graft)											
1	RCT	serious ¹	N/A (only one trial)	not serious	serious ²	Follow-up duration too short	2/16 (12.5%)	2/20 (10.0%)	RR 1.25 (0.20 to 7.92)	25 more per 1,000 (from 80 fewer to 692 more)	⊕⊕○○ LOW

Quality assessment							Summary of findings				
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients		Effect		Quality
							OCA	Autologous autograft	Relative (95% CI)	Absolute (95% CI)	
Transplant failure (follow up: 2 to 7 years; assessed with: removal or replacement of the graft)											
1	Case series	Serious ³	N/A (only one trial)	not serious	serious ²	Follow-up duration too short	5/17 ankles (29.4%)	-	-	-	⊕⊕⊕⊕ VERY LOW
Re-admission (outcome not reported)											
-	-	-	-	-	-	-	-	-	-	-	-
Re-operation (Follow up: 2 years; assessed with: any follow-up procedure on the treated joint)											
1	RCT	serious ¹	N/A (only one trial)	not serious	serious ²	Follow-up duration too short	2/16 (12.5%)	2/20 (10.0%)	RR 1.25 (0.20 to 7.92)	25 more per 1,000 (from 80 fewer to 692 more)	⊕⊕⊕⊕ LOW
Re-operation (follow up: 2 to 7 years; assessed with: any follow-up procedure on the treated joint)											
1	Case series	Serious ³	N/A (only one trial)	not serious	serious ²	Follow-up duration too short	4/17 ankles (23.5%)	-	-	-	⊕⊕⊕⊕ VERY LOW

Abbreviations *CI* = confidence interval, *N/A* = not applicable, *OCA* = osteochondral allograft transplantation, *RCT* = randomized controlled trial, *RR* = relative risk.

Comments

¹ There was a serious risk of bias due to inadequate randomization, allocation concealment, and blinding of patients and investigators.

² Sample size is below optimal information size.

³ Eligibility criteria were unclear, additional co-interventions were not reported, no estimates of random variability were reported, method for capturing complications were not reported.

Table A-6: Evidence profile: efficacy and safety of osteochondral allograft transplantation (*knee*)

Quality assessment							Summary of findings				
							Number of patients		Effect		Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OCA	Other surgical procedure	Relative (95% CI)	Absolute (95% CI)	
Efficacy											
Pain: change in pain score (follow up: 2 years; assessed with: VAS; Scale from: 0 (less pain) to 100 (more pain))											
2	Case series	not serious	not serious	not serious	serious ¹	none	51	-	-	Mean reduction in pain ranged from 15 to 26.5 ($p < 0.05$)	⊕○○○ VERY LOW
Pain: Change in pain score (follow up: 2 years; assessed with: WOMAC – Pain Subscale; Scale from: 0 (less pain) to 100 (more pain))											
1	Case series	not serious	N/A (only one trial)	not serious	serious ¹	none	17	-	-	Mean reduction in pain was 5.1 (Pre-op: 91.0 ± 5.7 vs Post-op: 96.1 ± 4.6, $p = 0.002$)	⊕○○○ VERY LOW
Pain: Change in pain score (follow up: 2 years; assessed with: Modified Cincinnati knee rating score; Scale from: 0 (less pain) to 100 (more pain))											
1	Case series	not serious	N/A (only one trial)	not serious	serious ¹	none	23	-	-	Mean reduction in pain was 10.6 (Pre-op: 21.9 vs Post-op: 32.5, $p < 0.03$)	⊕○○○ VERY LOW
Function: Change in function score (follow up: 2 years; assessed with: FAAM; Scale from: 0 (worse function) to 100 (better function))											
2	Case series	not serious	not serious	not serious	serious ¹	none	57	-	-	Mean increase in function ranged from 16.5 to 17 ($p < 0.03$)	⊕○○○ VERY LOW
Function: Change in function score (follow up: 2 years; assessed with: WOMAC – Function Subscale; Scale from: 0 (worse function) to 100 (better function))											
1	Case series	not serious	N/A (only one trial)	not serious	serious ¹	none	17	-	-	Mean increase in function was 15 (Pre-op: 68.1 ± 23.8 vs. Post-op: 83.1 ± 20.4, $p = 0.03$)	⊕○○○ VERY LOW
Function: Change in function score (follow up: 2 years; assessed with: WOMAC – Overall; Scale from: 0 (worse function) to 100 (better function))											
1	Case series	not serious	N/A (only one trial)	not serious	serious ¹	none	17	-	-	Mean increase in function was 17.2 (Pre-op: 65.1 ± 24.8 vs. Post-op: 82.3 ± 19.9, $p = 0.02$)	⊕○○○ VERY LOW

Quality assessment							Summary of findings				
							Number of patients		Effect		Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OCA	Other surgical procedure	Relative (95% CI)	Absolute (95% CI)	
Function: Change in function score (follow up: 1.9 to 4 years; assessed with: Modified Cincinnati Knee Rating Score – Function Subscale; Scale from: 0 (worse function) to 100 (better function))											
1	Case series	not serious	N/A (only one trial)	not serious	serious ¹	none	23	-	-	Mean increase in function was 9.2 (Pre-op: 27.3 vs Post-op: 36.5, $p < 0.01$)	⊕○○○ VERY LOW
Function: Change in function score (follow up: 1.9 to 4 years; assessed with: Modified Cincinnati Knee Rating Score – Overall Score; Scale from: 0 (worse function) to 100 (better function))											
1	Case series	not serious	N/A (only one trial)	not serious	serious ¹	none	23	-	-	Mean increase in function was 19.8 (Pre-op: 49.2 vs Post-op: 69.0, $p < 0.02$)	⊕○○○ VERY LOW
Return to activities of daily living (follow up: 2 years; assessed with KOOS activities of daily living sub-scale; Scale from 0 (worse) to 100 (better))											
2	Case series	not serious	Not serious	not serious	serious ¹	none	51	-	-	Mean increase ranged from 14 to 16.3 ($p = 0.048$, $p = 0.004$)	⊕○○○ VERY LOW
Return to activities of daily living (follow up: 2 years; assessed with KOOS sports and recreation sub-scale; Scale from 0 (worse) to 100 (better))											
2	Case series	not serious	Not serious	not serious	serious ¹	none	51	-	-	Mean increase ranged from 20 to 33.2 ($p = 0.005$, $p = 0.002$)	⊕○○○ VERY LOW
Function: Change in quality of life (follow up: 2 years; assessed with: KOOS – QoL Subscale; Scale from: 0 (worse WoL) to 100 (better QoL))											
2	Case series	not serious	not serious	not serious	serious ¹	none	51	-	-	Mean increase in quality of life ranged from 25 to 30.6 ($p < 0.001$)	⊕○○○ VERY LOW
Necessity of total joint replacement (follow-up: 0.3 to 14.5 years) ²											
2	Case series	not serious	not serious	not serious	Serious	none	125	-	-	Overall 5.6% (7/125)	⊕○○○ VERY LOW
Safety											
Procedure-related mortality (follow up: 0.3 to 14.5 years) ²											
4	Case series	not serious	not serious	not serious	not serious	none	0/165	-	-	0%	⊕⊕○○ LOW

Quality assessment							Summary of findings				
							Number of patients		Effect		Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OCA	Other surgical procedure	Relative (95% CI)	Absolute (95% CI)	
Complications (follow up: 12 months)											
4	Case series	serious ³	serious ⁴	not serious	serious ¹	none	21/165	-	-	Overall complications: 12.7% (range 4.3% to 26.5%)	⊕○○○ VERY LOW
Transplant failure (follow up: 2 years; assessed with: removal or replacement of the graft, or progression to arthroplasty) ²											
2	Case series	serious ³	not serious	not serious	serious ¹	none	4/51	-	-	Overall transplant failures: 7.8% (range 7.0% to 11.8%)	⊕○○○ VERY LOW
Re-admission (outcome not reported)											
-	-	-	-	-	-	-	-	-	-	-	-
Re-operation (Follow up: 2 years; assessed with: any follow-up procedure on the treated joint) ²											
4	Case series	serious ³	not serious	not serious	serious ¹	none	34/165	-	-	Overall re-operation rate: 20.6% (range 11.8% to 41.2%)	⊕○○○ VERY LOW

Abbreviations *CI* = confidence interval, *N/A* = not applicable, *OCA* = osteochondral allograft transplantation.

Comments

¹ Sample was below the optimal information size.

² A very small proportion of patients in one study had follow-up less than 2 years.

³ Follow-up length was insufficient to properly measure the outcome.

⁴ Large degree of variation in reported adverse event rates across studies.

Applicability table

Table A-7: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	<p>The target population for osteochondral allograft transplantation in clinical practice is patients with osteochondral defects who have failed conservative management or primary surgery; however, relevant data was only identified for knee and ankle joints.</p> <p>Ankle: the RCT explicitly states that patients must have failed non-operative treatment (and initial arthroscopic treatment if the lesion is <1.5cm²) to be eligible. The majority of ankles in the case-series (94.1%) had undergone at least one prior surgery.</p> <p>Knee: no included case-series specified failure of non-surgical or primary surgical approaches as an inclusion criteria. Where reported (or where possible to calculate) mean number of prior surgeries varied from 0.7 to 1.7. One case-series specified the grade of cartilage defect (Grade 4 ICRS) of included patients.</p> <p>Osteochondral defects are often trauma-induced and often appear following a sporting injury, suggesting that active, younger patients are at a heightened risk. The mean age of patients across included studies fell between 30.9 to 41.9 years.</p> <p>All lesions of the ankle in included studies were located on the talar or talar dome. Lesions of the knee were mostly located on the femoral condyle. A small percentage (17.6%) in one study were located on the lateral tibial plateau.</p>
Intervention	<p>The intervention of interest is fresh or delayed-fresh osteochondral allograft transplantation.</p> <p>Ankle</p> <p>Ankle transplants were performed under general anesthetic, and a thigh tourniquet was used. They were either press fit into the OLT site without internal fixation (randomised trial) or fixed with herbert screws or bioabsorbable pins (case-series). Weight-bearing commenced 6-12 weeks post-operatively. Grafts in the RCT were used within 7 days of their release. Graft storage time in the case-series is unclear. Neither study reported any concomitant interventions occurring. It is possible that none were performed.</p> <p>Knee</p> <p>Knee transplants were press-fit into the site. Only one study reported that fixation was required [61]. Post-surgical non weight-bearing periods varied from immediate weight bearing, to non weight-bearing periods for 8 weeks, to partial weight-bearing for 1 year.</p> <p>Three studies reported graft storage time, which ranged from 3 to 26 days. Only two studies explicitly reported concomitant interventions. It is unclear how reflective the concomitant interventions reported are of clinical practice.</p>
Comparators	<p>Typically, patients must have failed conservative management (or primary surgery) to be eligible for OCA thus the relevant comparators were identified as other surgical management options.</p> <p>The comparator used in the randomised trial (specifically for lesions of the ankle) was an osteochondral autograft plug. The autograft was harvested from patients' own knees (the ipsilateral superolateral distal femoral condyle).</p> <p>This is one possible alternate surgical approach to treat lesions of the ankle however, others also exist (e.g. autologous chondrocyte implantation or mosaicplasty) [49].</p> <p>No comparative data of OCA compared to relevant comparator to treat lesions of the knee were identified.</p> <p>The evidence available does not include sufficient comparison to (all) possible comparators available in a clinical setting.</p>
Outcomes	<p>Ankle</p> <p>The randomised trial reported pain and functionality outcomes. The exact timing of post-operative measures presented is unclear; results from last follow-up were considered (mean follow-up times were 3.4 and 2.9). Two of the most important clinical outcomes/objectives of surgical treatment were captured however, necessity of total joint replacement is another <i>crucial</i> outcome that was not reported. It is possible that no cases occurred considering the limited follow-up.</p> <p>Adverse events were well-reflected in the RCT, subsequent procedures were well-reflected in both the RCT and the case-series, transplant failure was reported in the case-series.</p>

Outcomes (continuation)	Knee The single-arms studies of knee patients reported to varying degrees some or all of the crucial/important effectiveness outcomes using various, knee-specific measurement tools. Only two studies clearly presented outcome results taken 2-years post-operatively. A third presented results from last follow-up (mean follow-up time was 3 years). Relevant outcomes presented by the final study were sparse; pertaining to adverse events, necessity of total knee arthroscopy and subsequent procedures. Overall, transplant failure rates and subsequent/revision surgeries were captured. Only one of the case-series specified that complications were monitored – it is possible that adverse events were not adequately reported, given the reliance on patient reporting at follow-up appointments.
Setting	The included randomised study was conducted in a single centre in the USA. The included case series (included for both effectiveness and safety outcomes in knee patients, and safety outcomes exclusively for ankle patients) were conducted in single centres in either the USA or Canada. The settings of the studies reflect the clinical setting in which the technology is intended to be used in an appropriate way. No applicability issues are expected from the geographical setting.

Abbreviations *ICRS* = International Cartilage Repair Society, *OCA* = osteochondral allograft transplantation, *OLT* = osteochondral lesions of the talus, *RCT* = randomised controlled trial.

List of ongoing trials

Table A-8: List of ongoing trials of osteochondral allograft transplantation

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT00263432 * unknown status	Cartilage injury of the knee 18-65 years Enrollment: 10	Fresh allogenic chondrocyte implant	N/A	Healing of the cartilage injuries	July 2015	University Hospital, Ghent. University Ghent.
NCT02430558 * unknown status	Knee osteo- chondral lesions 18-55 years Enrollment: 40	Osteochondral allografts (OD- PHOENIX2)	N/A	IKDC, KOOS Recellularisation and integration of tissue	December 2016	TBF Genie Tissulaire
NCT02503228 * active, not recruiting	Osteochondral Defect of the femoral condyle Female ≥18 years Enrollment: 50	Missouri Osteochondral Allograft Preservation System -Preserved Cartilage	N/A	IKDC Tegner Activity Scale Patient-Reported Outcomes Measurement Information System survey Standard of Care Diagnostic Imaging Non-standard of care magnetic resonance imaging Blood and Urine Samples	April 2020	University of Missouri- Columbia Musculoskeletal Transplant Foundation

Abbreviations *IKDC* = International Knee Documentation Committee, *KOOS* = Knee injury and Osteoarthritis Outcome Score, *N/A* = not applicable.

Literature search strategies

Search strategy for CRD (DARE, NHS-EED, HTA)

Search Date: 12/12/2018	
#1	MeSH DESCRIPTOR Cartilage, Articular EXPLODE ALL TREES
#2	(osteochondral NEAR (defect* or injur* or lesion* or fracture* or rupture* or tear* or damage*))
#3	#1 OR #2
#4	MeSH DESCRIPTOR Allografts EXPLODE ALL TREES
#5	MeSH DESCRIPTOR Transplantation, Homologous EXPLODE ALL TREES
#6	(allogeneic transplant*)
#7	MeSH DESCRIPTOR CARTILAGE EXPLODE ALL TREES WITH QUALIFIER TR
#8	MeSH DESCRIPTOR CHONDROCYTES EXPLODE ALL TREES WITH QUALIFIER TR
#9	(allograft*)
#10	(osteochondral)
#11	(chondrocyt* NEAR (allograft* OR allogeneic))
#12	(OCA)
#13	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14	#3 AND #13
Total:36 Hits	

Search strategy for Ovid Medline

Database: Ovid MEDLINE(R) <1946 to November Week 5 2018>, Ovid MEDLINE(R) Epub Ahead of Print <December 10, 2018>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 206, 2018>, Ovid MEDLINE(R) Daily Update <December 06, 2018>	
Search Strategy:	
1	exp *Cartilage, Articular/in [injuries] (1744)
2	(osteochondral adj5 (defect* or injur* or lesion* or fracture* or rupture* or tear*)).mp. (3473)
3	1 or 2 (4901)
4	exp Allografts/ (6271)
5	exp Transplantation, Homologous/ (83779)
6	allogeneic transplant*.mp. (4548)
7	exp *CARTILAGE/tr [Transplantation] (4021)
8	exp *CHONDROCYTES/tr [Transplantation] (1231)
9	7 or 8 (5173)
10	(allograft* or allogeneic).mp. (118237)
11	9 and 10 (747)
12	(osteochondral allograft* adj5 (transplant* or implant*)).mp. (275)
13	OCA.ti,ab. (1003)
14	(chondrocyt* adj5 (allograft* or allogeneic)).mp. (222)
15	4 or 5 or 6 or 11 or 12 or 13 or 14 (92353)
16	3 and 15 (291)
17	remove duplicates from 16 (291)
Search date: 11/12/2018	

Search strategy for Embase

No.	Query Results	Results	Date
#30	#12 AND #29	303	12 Dec 2018
#29	#13 OR #14 OR #24 OR #25 OR #26 OR #27 OR #28	16,842	12 Dec 2018
	'allograft'/mj	5,112	12 Dec 2018
#27	'allograft'/mj	9,421	12 Dec 2018
#26	(chondrocyt* NEAR/5 (allograft* OR allogeneic)):ti,ab,de	382	12 Dec 2018
#25	oca:ti,ab	1,502	12 Dec 2018
#24	#18 AND #23	916	12 Dec 2018
#23	#19 OR #20 OR #21 OR #22	212,883	12 Dec 2018
#22	allograft*:ti,ab,de OR allogeneic:ti,ab,de	189,704	12 Dec 2018
#21	(allogeneic NEAR/5 (transplant* OR implant*)):ti,ab,de	61,221	12 Dec 2018
#20	'allograft'/exp	35,376	12 Dec 2018
#19	'allograft'/exp	38,789	12 Dec 2018
#18	#15 OR #16 OR #17	5,271	12 Dec 2018
#17	'chondrocyte* transplant*':ti,ab,de	689	12 Dec 2018
#16	'cartilage transplantation'/exp	3,975	12 Dec 2018
#15	'chondrocyte implantation'/exp	889	12 Dec 2018
#14	('osteochondral allograft*' NEAR/5 (transplant* OR implant*)):ti,ab,de	362	12 Dec 2018
#13	'osteochondral allograft transplantation'/exp	59	12 Dec 2018
#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	4,435	12 Dec 2018
#11	(osteochondral NEAR/5 (defect* OR injur* OR lesion* OR fracture* OR rupture* OR tear* OR damage* OR degenerat*)):ti,ab,de	4,353	12 Dec 2018
#10	'articular cartilage degeneration'/exp	13	12 Dec 2018
#9	'articular cartilage damage'/exp	13	12 Dec 2018
#8	'articular cartilage injury'/exp	24	12 Dec 2018
#7	'articular cartilage defect'/exp	43	12 Dec 2018
#6	'osteochondral fracture'/exp	82	12 Dec 2018
#5	'osteochondral lesions of the talus'/exp	12	12 Dec 2018
#4	'osteochondral lesion of the talus'/exp	52	12 Dec 2018
#3	'osteochondral lesion'/exp	111	12 Dec 2018
#2	'osteochondral injury'/exp	31	12 Dec 2018
#1	'osteochondral defect'/exp	151	12 Dec 2018

Search strategy for The Cochrane Library

Search Date: 12/12/2018	
ID	Search
#1	MeSH descriptor: [Cartilage, Articular] explode all trees and with qualifier(s): [injuries – IN]
#2	((osteocondral OR cartilage* OR chondrocyte*) NEAR (defect* OR injur* OR lesion* OR fracture* or rupture* or tear* OR damage*)) (word variations have been searched)
#3	(osteocondral): ti,ab,kw (word variations have been searched)
#4	(chondrocyte*): ti,ab,kw (word variations have been searched)
#5	#1 OR #2 OR #3 OR #4
#6	MeSH descriptor: [Allografts] explode all trees
#7	(allograft*): ti,ab,kw (word variations have been searched)
#8	(allgeneic): ti,ab,kw (word variations have been searched)
#9	("allogeneic transplant*"): ti,ab,kw (word variations have been searched)
#10	(chondrocyt* NEAR (allograft* OR allgeneic)) (word variations have been searched)
#11	MeSH descriptor: [chondrocytes] explode all trees and with qualifier(s): [transplantation – TR]
#12	MeSH descriptor: [cartilage] explode all trees and with qualifier(s): [transplantation – TR]
#13	MeSH descriptor: [Transplantation, Homologous] explode all trees
#14	(osteocondral allograft* NEAR (transplant* or implant*)) (word variations have been searched)
#15	(OCA): ti,ab,kw (word variations have been searched)
#16	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17	#5 AND #16
Total: 114 Hits	



Ludwig Boltzmann Institut
Health Technology Assessment