Meniscal allograft transplantation for post-meniscectomy syndrome

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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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).

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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.

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Content

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List of Abreviations

ACL ..... Anterior cruciate ligament
CE ..... Communauté Européenne
CRD ..... Centre for Reviews and Dissemination
CT ..... Controlled trial (non-randomised)
EU ..... European Union
EUTCD ..... European Union Tissue and Cells Directives
EUnetHTA ..... European network for Health Technology Assessment
GRADE ..... Grading of Recommendations Assessment, Development and Evaluation
ICRS ..... International Cartilage Repair Society
IHE ..... Institute of Health Economics
IKDC ..... International Knee Documentation Committee
KOOS ..... Knee injury and Osteoarthritis Outcome Score
KOOS-ADL ..... Knee injury and Osteoarthritis Outcome Score – Activities of daily living subscale
KOOS-QoL ..... Knee injury and Osteoarthritis Outcome Score – Quality of Life subscale
LBI-HTA ..... Ludwig Boltzmann Institute for Health Technology Assessment
MAT ..... Meniscal allograft transplantation
MeSH ..... Medical Subject Heading
MRI ..... Magnetic resonance imaging
QoL ..... Quality of life
RCT ..... Randomised controlled trial
TKA ..... Total knee arthroplasty
WOMAC ..... Western Ontario and McMaster Universities Osteoarthritis Index
VAEV ..... Verwaltung von Änderungs- und Ergänzungsvorschlägen zum Leistungskatalog
VAS ..... Visual analogue scale

Executive Summary

Introduction

Health problem

This systematic review is focussed on patients with post-meniscectomy syndrome. A meniscus is a crescent-shaped piece of cartilage in the knee that provides load distribution, shock absorption and lubrication between the thigh (femur) and shin (tibia) bones. Post-meniscectomy syndrome is broadly characterised by intractable pain following the partial or total removal of a meniscus. Removal of a meniscus can lead to joint instability, increased risk of osteoarthritis, and eventually total joint replacement.

focus on patients with post-meniscectomy syndrome

persistent pain after meniscectomy

Description of technology

Meniscal allograft transplantation (MAT) involves the transplant of a cadaveric meniscal allograft into the knee of a patient who has had a prior (sub)total meniscectomy. The transplanted allograft is intended to be permanent, and aims to restore the load bearing and shock absorption function provided by the meniscus. In theory, MAT is proposed to relieve the pain and swelling associated with post-meniscectomy syndrome, lower the risk of progression to osteoarthritis, and prolong the need for a total knee replacement and associated revisions.

meniscal allograft transplantation (MAT) from cadaver, to relieve pain, lower risk of osteoarthritis

In the absence of a clear surgical alternative to MAT in post-meniscectomy patients, conservative management is proposed as the main treatment alternative. There are no clear guidelines for what constitutes conservative management in the context of post-meniscectomy syndrome; however, the main treatment aims of conservative management include symptom control via analgesics and injections, stabilisation of the joint via muscle strengthening, and behaviour modification.

conservative management is main treatment alternative

Research question

In patients with post-meniscectomy syndrome, is meniscus allograft transplantation more effective concerning changes in pain, changes in function, and necessity of total joint replacement, and as safe concerning complications and transplant failure in comparison to conservative management?

meniscus allograft transplantation more effective and as safe?

Methods

The research question was investigated through a systematic review of the current literature on MAT. Four biomedical databases (Medline, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination) were searched from inception to 22 December 2017. Two authors (TV, SF) independently conducted the study selection, data extraction, and quality appraisal.

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

Domain effectiveness

The outcomes used as evidence to derive a recommendation on the relative efficacy of MAT included: changes in pain scores (KOOS-Pain), changes in disease-specific function scores (IKDC, Lysholm, Tegner, KOOS), and the necessity for total knee arthroplasty (TKA).

pain, function, and necessity of knee arthroplasty for effectiveness

Domain safety

complications and transplant failure for safety

The outcomes used as evidence to derive a recommendation on the relative safety of MAT included: procedure-related complications, and transplant failure.

Results

Available evidence

one comparative study with 36 patients

Only one non-randomised comparative study with 36 patients was identified to derive a recommendation on the comparative effectiveness of MAT compared to conservative management.

additionally 5 case series

In addition, five prospective case series with a total of 308 patients were included in order to inform the recommendation on safety.

Clinical effectiveness

pain: significantly better improvement with MAT

The change in patient-reported pain was significantly improved in the MAT group compared to conservative management at 12 months (MD 15.1, 95% CI 2.4 to 27.8, p=0.021).

function: partly significantly better improvements with MAT

Regarding function, the mean difference in the change in scores was not statistically significant for Lysholm, IKDC or KOOS-Sports scores; however, KOOS-Composite and KOOS-ADL scores demonstrated significant increases, favouring MAT.

quality of life: significant increases with MAT

Quality of life demonstrated both clinically important and statistically significant increases in the MAT group.

Safety

no significant differences in complications

The relative risk of complications for MAT was 6.92 (95% CI 0.91 to 285.8, p>0.05) compared to conservative management. The overall complication rate for MAT across all studies was 22.9% (range 0.0% to 38.5%).

nearly all complications with MAT required re-operations

All but one complication related to MAT required re-operation, typically with arthroscopy. No complications required re-intervention in the conservative management group.

4.6% failure rate

The overall failure rate of MAT was 4.6% (range 1.7% to 7.7%) with a mean follow-up time of 46 months (range 13 to 120).

Upcoming evidence

2 ongoing trials, both single arm studies

There are currently two registered clinical trials investigating MAT for the treatment of post-meniscectomy syndrome. Both trials are single arm studies (n=120 and 119), and as such will not provide additional certainty around the comparative efficacy of MAT in relation to conservative management.

Reimbursement

MAT not reimbursed in Austria

Currently, MAT is not reimbursed by the Austrian health care system for the treatment post-meniscectomy syndrome.

Discussion

The overall quality of evidence identified for this review was very low for all of the reported outcomes.

very low quality of evidence

The main limitations in the evidence base were in relation to the level of evidence (i.e. primarily case series), high risk of bias, and small sample sizes. In addition, interpreting the literature on MAT is complicated by the large number of concomitant procedures reported, varying techniques used to fix allografts, the number of prior procedures received by patients, poor reporting of complications, and the varied time-points at which outcomes were reported.

no (proper) randomisation, high risk of bias, small sample sizes

The current evidence is not sufficient to prove that MAT, for the treatment of post-meniscectomy syndrome, is more effective and equally safe than conservative management.

evidence not sufficient

Recommendation

On the basis of the limited evidence demonstrating a benefit of MAT relative to the main comparator, as well as the lack of ongoing trials, inclusion in the hospital benefit catalogue is not recommended.

MAT not recommended for reimbursement

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Fokus auf Postmeniskektomie-Syndrom

Die vorliegende systematische Übersichtsarbeit konzentrierte sich auf PatientInnen mit Postmeniskektomie-Syndrom. Ein Meniskus ist ein halbmondförmiges Knorpelstück im Knie, das eine Lastenverteilung, Stoßdämpfung und Schmierung zwischen den Knochen des Oberschenkels (Femur) und des Schienbeins (Tibia) gewährleistet. Das Postmeniskektomie-Syndrom ist weitgehend durch persistierende Schmerzen nach der teilweisen oder vollständigen Entfernung eines Meniskus gekennzeichnet. Die Entfernung des Meniskus ist vorrangig bei inoperablen Rissen indiziert und kann zu Gelenkinstabilität, erhöhtem Risiko für Osteoarthritis und schließlich zu totalem Gelenkersatz führen.

Entfernung Meniskus bei inoperablen Rissen, jedoch bleibende Schmerzen möglich

Beschreibung der Technologie

Meniskustransplantation zur Schmerzreduktion und langfristig zur Vermeidung von Knieendoprothese

Bei der Meniskustransplantation wird ein passender Spendermeniskus von verstorbenen Menschen in das Knie von PatientInnen eingesetzt, die zuvor einer (sub)totalen Meniskektomie unterzogen wurden. Der transplantierte Meniskus soll dauerhaft im Knie verbleiben und soll die vom Meniskus bereitgestellte Belastungs- und Stoßabsorptionsfunktion wiederherstellen. So soll eine Meniskustransplantation die, mit dem Postmeniskektomie-Syndrom verbundenen, Schmerzen und Schwellungen lindern, das Risiko einer möglichen Gonarthrose verringern und die Notwendigkeit eines totalen Knieersatzes (Knieendoprothese) und damit einhergehende Revisionen vermeiden oder zumindest hinauszögern.

konservative Therapie als vorrangige Behandlungsalternative

Aufgrund einer fehlenden eindeutigen chirurgischen Alternative zur Meniskustransplantation bei Postmeniskektomie-PatientInnen wird eine konservative Behandlung als Hauptbehandlungsalternative vorgeschlagen. Jedoch gibt es keine klaren Richtlinien für die konkreten Inhalte eines konservativen Behandlungsansatzes im Rahmen des Postmeniskektomie-Syndroms. Die wichtigsten Behandlungsziele des konservativen Managements umfassen jedoch die Symptomkontrolle über Medikamente und Injektionen, die Stabilisierung des Gelenks durch Muskelstärkung (Physiotherapie) und Verhaltensmodifikation.

Wissenschaftliche Fragestellung

Meniskustransplantation wirksamer und zumindest genauso sicher?

Ist bei PatientInnen mit Postmeniskektomie-Syndrom die Meniskustransplantation im Vergleich zu konservativem Management wirksamer bezüglich Schmerzen, Funktion (des Kniegelenks) und der Notwendigkeit einer Knieendoprothese und zumindest gleich sicher im Hinblick auf Komplikationen und Transplantatversagen?

Methoden

Literatursuche in Datenbanken, Selektion, Extraktion und Qualitätsbewertung von zwei Autoren

Zur Beantwortung der Forschungsfrage wurde am 22. Dezember 2017 eine systematische Literatursuche in vier Datenbanken (Medline, Embase, Cochrane Library, Center for Reviews and Dissemination of the University of York) durchgeführt. Zwei Autoren (TV, SF) führten unabhängig voneinander die Studienauswahl, Datenextraktion und Qualitätsbewertung durch.

Klinische Wirksamkeit

Die kritischen Endpunkte, die als Basis für eine Bewertung der Wirksamkeit der Meniskustransplantation herangezogen wurden, umfassten: Veränderungen der Schmerzen (mittels KOOS-Pain), Veränderungen der krankheitsspezifischen Funktion des Kniegelenks (mittels IKDC, Lysholm, Tegner, KOOS) und die Notwendigkeit einer totalen Knieendoprothese.

Wirksamkeitsendpunkte: Schmerzen, Funktion und Notwendigkeit Knieersatz

Sicherheit

Die Endpunkte, die für die Ableitung einer Empfehlung zur Sicherheit der Meniskustransplantation herangezogen wurden, umfassten: interventionsbedingte Komplikationen und Versagen des Transplantates.

Sicherheitsendpunkte: Komplikationen und Versagen Transplantat

Ergebnisse

Verfügbare Evidenz

Zur Bewertung der Wirksamkeit konnte lediglich eine nicht-randomisierte kontrollierte Studie mit 36 PatientInnen identifiziert werden, die die Meniskustransplantation mit einem konservativen Behandlungsansatz verglich.

eine Vergleichsstudie mit 36 PatientInnen

Zusätzlich konnten noch fünf prospektive Fallserien mit insgesamt 308 PatientInnen für die Bewertung der Sicherheit identifiziert werden.

zusätzlich 5 Fallserien

Klinische Wirksamkeit

Die, von den PatientInnen berichteten, Schmerzen konnten 12 Monate nach dem Eingriff mittels Meniskustransplantation – im Vergleich zur konservativen Behandlung – signifikant verbessert werden (mittlere Differenz 15,1, 95 % Konfidenzintervall 2,4 bis 27,8; p=0,021).

Schmerzen: signifikante Verbesserung mit Meniskustransplantation

Die Funktion (des Kniegelenks) konnte mittels Meniskustransplantation – im Vergleich zur konservativen Behandlungsmethode – nicht signifikant verbessert werden, wenn diese mittels Lysholm, IKDC oder KOOS-Sport gemessen wurden. Wurde die Funktion jedoch mit dem KOOS-Composite und dem KOOS-ADL (ADL steht für „activities of daily life“) gemessen, dann konnten signifikante Verbesserungen der Funktion mittels Meniskustransplantation festgestellt werden.

Funktion: teilweise signifikante Verbesserungen mit Meniskustransplantation im Vergleich zu konservativer Therapie

Die Lebensqualität konnte mittels Meniskustransplantation sowohl klinisch relevant als auch statistisch signifikant verbessert werden – im Vergleich zur konservativen Therapie.

Lebensqualität: signifikante Verbesserungen mit Meniskustransplantation

Sicherheit

Das relative Risiko für Komplikationen einer Meniskustransplantation, im Vergleich zur konservativen Therapie, lag bei 6,92 (95 % Konfidenzintervall von 0,91 bis 28,8; p>0,05). Die Komplikationsrate der Meniskustransplantation aller Studien lag durchschnittlich bei 22,9 % (in den einzelnen Studien lag die Rate zwischen 0 und 38,5 %).

keine signifikanten Unterschiede bei Komplikationen

Mit Ausnahme einer Studie, bedurften alle, durch die Meniskustransplantation bedingten, Komplikationen einer Reoperation, meist mittels Arthroskopie.

fast alle Komplikationen bedurften Reoperation

Insgesamt versagten 4,6 % der Transplantate (in den einzelnen Studien lag die Rate zwischen 1,7 und 7,7 %), bei einer durchschnittlichen Nachbeobachtung von 46 Monaten.

Transplantatsversagen in 4,6 % der Fälle

Laufende Studien

2 laufende Studien, beides Fallserien

Aktuell sind zwei laufende Studien registriert, die die Meniskustransplantation zur Behandlung des Postmeniskektomie-Syndroms untersuchen. Bei beiden Studien handelt es sich um unkontrollierte Fallserien (eine Studie mit 120 und die andere mit 119 PatientInnen). Daher werden diese Studien keine neuen Erkenntnisse bezüglich der Wirksamkeit der Meniskustransplantation im Vergleich zur konservativen Therapie liefern.

Kostenerstattung

derzeit keine Kostenerstattung

Derzeit erfolgt keine Kostenerstattung der Meniskustransplantation zur Behandlung des Postmeniskektomie-Syndroms durch das öffentliche österreichische Gesundheitssystem.

Diskussion

sehr geringe Evidenzstärke

Insgesamt war die Qualität und Stärke der Evidenz, die für die Beantwortung der Forschungsfrage identifiziert wurde, sehr gering.

fehlende Randomisierung in Studien, hohes Bias-Risiko, kleine Studiengrößen

Die Schwächen der Evidenz lagen vor allem im Design der Studien (z. B. handelte es sich Großteils um Fallserien), im hohen Bias-Risiko und in den kleinen Studiengrößen. Außerdem wurden die Komplikationen zum Teil unzureichend beschrieben und die Zeitpunkte der Outcome-Messung variierten mitunter erheblich, was die Vergleichbarkeit der Studienergebnisse stark beeinträchtigt. Darüber hinaus bleibt unklar, inwieweit die zahlreichen begleitenden Interventionen (z. B. Kreuzbandplastiken), die verschiedenen OP-Techniken zur Fixierung der Transplantate und die Anzahl vorangegangener Interventionen die Ergebnisse in den Studien beeinflussen oder beeinflusst haben.

Evidenz nicht ausreichend

Die derzeit verfügbare Evidenz ist nicht ausreichend, um zu klären, ob die Meniskustransplantation zur Behandlung des Postmeniskektomie-Syndroms wirksamer als, und zumindest genauso sicher ist, wie ein konservativer Therapieansatz.

Empfehlung

Erstattung Meniskustransplantation nicht empfohlen

Auf Basis der mangelnden Evidenz, die einen Vorteil der Meniskustransplantation zur hauptsächlichen Vergleichsintervention – der konservativen Therapie – demonstriert und in der Ermangelung an adäquaten laufenden Studien, wird die Aufnahme in den Erstattungskatalog nicht empfohlen.

1 Scope

1.1 PICO question

PIKO-Frage

In patients with post-meniscectomy syndrome, is meniscus allograft transplantation more effective concerning changes in pain, changes in function, and necessity of total joint replacement, and as safe concerning complications and transplant failure in comparison to conservative management?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

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

Table 1-1: Inclusion criteria

Population	❁ Patients with post-meniscectomy syndrome (i.e. pain, swelling and restricted movement after sub(total) meniscectomy). ❁ **Contraindications/exclusions**: Significant articular cartilage wear. Significant articular cartilage wear is defined as Outerbridge Grade < III [1], or Ahlbäck Grade ≤ II [2]. ❁ International classification of diseases **(ICD)-10-CM code**: M23.3 Other meniscus derangements ❁ **MeSH Terms**: Tibial Meniscus Injuries [C26.558.781], Menisci, Tibial [A02.165.308.538, A10.165.382.350.163], Meniscectomy [E04.555.490] **Rationale**: International guidelines on the recommended use of meniscal allograft transplantation are not currently available. Therefore, the population has been defined based on the suggested indications in the reimbursement application, and informed by recent systematic reviews.[3-6]
Intervention	❁ Meniscal allograft transplantation (MAT) ❁ **Product names**: Not applicable ❁ **MeSH Terms**: Menisci, Tibial/transplantation* [A02.165.308.538.500, A02.835.583.475.590, A10.165.382.350.163.500]
Control	❁ Conservative management; including but not limited to physiotherapy, cortisone injections, pain management, bracing, activity modification, and weight loss. ❁ No therapy/no treatment. **Rationale**: International guidelines on the recommended use of MAT are not currently available. The primary purpose of meniscal allograft transplant in the context of post-meniscectomy syndrome is symptom control and to delay the need for total knee arthroplasty. In this context, alternative treatment options are limited.

Outcomes	

Efficacy	Relevant clinical endpoints for efficacy include changes from pre- to post-treatment measurements of (*critical* outcomes are highlighted in bold):
	• **Decrease in pain**, including but not limited to:
	  • Visual analogue scale (VAS)
	  • International Knee Documentation Committee (IKDC)
	  • Knee injury and Osteoarthritis Outcome Score (KOOS)
	• **Increase in function**, including but not limited to:
	  • Lysholm Score
	  • Tegner Score
	  • KOOS
	  • IKDC
	• **Prolonged or prevented total joint replacement**
	• Increase in quality of life (QoL), including but not limited to:
	  • 36-item Short Form Health Survey Questionnaire
	  • KOOS-QoL
	• Return to daily activities
	Rationale: Appropriate clinical outcomes have been informed by systematic reviews [3, 6-9] and the EUnetHTA guidelines.[10]

Safety	Relevant safety outcomes include (*critical* outcomes are highlighted in bold): • **Complications** • **Transplant failure/time to failure** • Re-operation/additional surgery • Procedure-related mortality **Rationale:** Appropriate safety outcomes have been informed by a recent systematic review [3, 6] and the EUnetHTA guidelines.[11]
Study design	
Efficacy	• Randomised controlled trials • Prospective non-randomised controlled trials • In the absence of comparative evidence, prospective case series will be included **Excluded**: narrative reviews, letter to the editor, author response, case reports.
Safety	• Randomised controlled trials • Prospective non-randomised controlled trials • Prospective case-series ($n \geq 40$) **Excluded**: conference abstracts, narrative reviews, letter to the editor, author response, case reports, retrospective case series.

Abbreviations: *ICD = International classification of diseases; IKDC = International Knee Documentation Committee; KOOS = Knee injury and Osteoarthritis Outcome Score; MAT = meniscal allograft transplantation; QoL = Quality of life; VAS = Visual analogue scale.*

2 Methods

2.1 Research questions

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

Health problem and Current Use	
Element ID	**Research question**
A0001	For which health conditions, and for what purposes is meniscal allograft transplant used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for post-meniscectomy syndrome?
A0004	What is the natural course of post-meniscectomy syndrome?
A0005	What is the burden of disease for patients with post-meniscectomy syndrome?
A0006	What are the consequences of post-meniscectomy syndrome for society?
A0024	How is post-meniscectomy syndrome currently diagnosed according to published guidelines and in practice?
A0025	How is post-meniscectomy syndrome 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 are meniscal allograft transplant utilised?

Clinical Effectiveness	
Element ID	**Research question**
D0001	What is the expected beneficial effect of meniscal allograft transplant on mortality?
D0003	What is the effect of meniscal allograft transplant on the mortality due to causes other than post-meniscectomy syndrome?
D0005	How does meniscal allograft transplant affect the symptoms and findings (severity, frequency) of post-meniscectomy syndrome?
D0006	How does meniscal allograft transplant affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of meniscal allograft transplant on patients' body functions?
D0016	How does the use of meniscal allograft transplant affect activities of daily living?
D0012	What is the effect of meniscal allograft transplant on generic health-related quality of life?
D0013	What is the effect of meniscal allograft transplant on disease-specific quality of life?
D0017	Was the use of meniscal allograft transplant worthwhile?

Safety	
Element ID	Research question
C0008	How safe is meniscal allograft transplant in comparison to conservative management?
C0002	Are the harms related to dosage or frequency of applying meniscal allograft transplant?
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 meniscal allograft transplant ?
C0007	Are meniscal allograft transplant and conservative management associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of meniscal allograft transplant and conservative management?

2.2 Sources

systematische Literatursuche und gezielte Handsuche

A systematic literature search (see Section 2.3), supplemented by targeted hand searching, was used to identify relevant literature to answer the research questions. The specific sources that were used to inform the research questions on **description of the technology, health problem and current use**, included:

Quellen: Hintergrundliteratur aus systematischer Suche, Leitlinien mittels Handsuche

- Background publications identified in database search (see Section 2.3) and additional hand searching of specific databases (e.g. PubMed, Scopus)
- Clinical practice guidelines identified by hand searching databases (e.g. www.guideline.gov)
- Hand search of the CRD database for Health Technology Assessments

2.3 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on the 22nd of December 2018 in the following databases:

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

systematische Suche: 1.009 Zitate

The systematic search was limited to articles published in English or German. Before de-duplication, 1,009 citations were identified from the database search. The specific search strategy employed can be found in the Appendix.

8 Treffer mittels Handsuche

In addition, 8 relevant studies were identified through hand searching the reference lists of included studies. Of these, only one relevant study was ultimately identified; however this case series was not included due to sample size limitations (n<40).

nach Deduplikation 721 Treffer, davon 6 Studien eingeschlossen

After de-duplication of the database searches and hand searches of reference lists, 721 hits were identified. In total, seven citations from six studies were included in the qualitative synthesis.

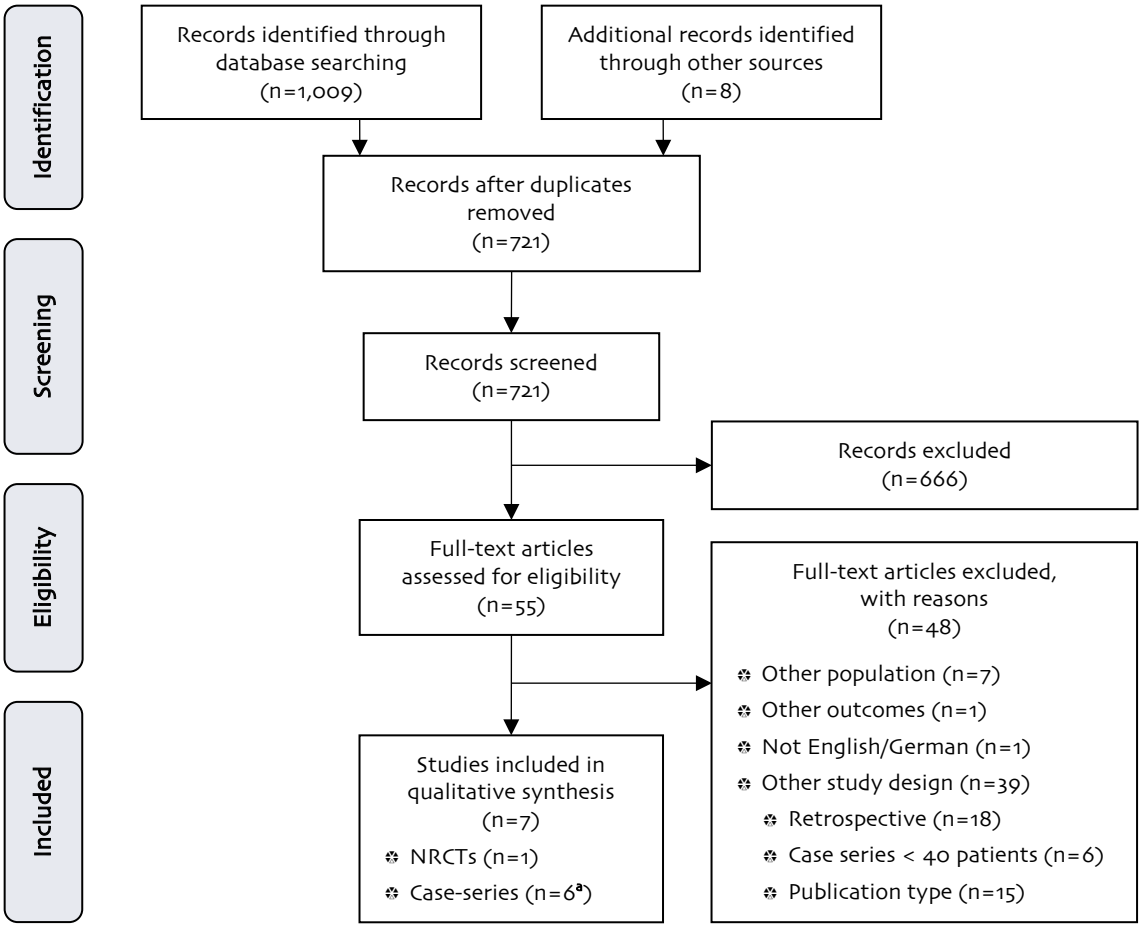
Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 3rd of January 2018.

Suche nach laufenden Studien

2.4 Flow chart of study selection

The references were screened by two independent researchers and in case of disagreement a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1.

Literaturauswahl



[a] *Two citations were included from the same study, with different follow-up results.*

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

2.5 Analysis

Datenextraktion und Kontrolle von 2 Wissenschaftlern, relatives Risiko berechnet, wenn nötig

Relevant data from the included studies were systematically extracted into data extraction tables by one reviewer (See Appendix Table A-1), based on study design and research question. The extracted data tables were validated for accuracy by a second reviewer. Relative risks were calculated from the primary data where necessary [using by: MedCalc©, Belgium, 2018[1]]. No further processing of the data was conducted. (e.g., indirect comparison).

Bewertung Studienqualität und Bias-Risiko durch 2 Wissenschaftler, mittels Checkliste

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-2 and Table A-3). Risk of bias of non-randomised studies was evaluated using the ROBINS-I tool (formerly the ACROBAT-NRSI tool) [12], as advised by the EUnetHTA Joint Action 2 reports on internal validity of randomised [13] and non-randomised studies [12]. Single arm case series were evaluated using the Institute of Health Economics checklist [14].

2.6 Synthesis

Evidenzsynthese mittels GRADE

The research questions were answered in plain text format, with reference to GRADE (Grading of Recommendations Assessment, Development and Evaluation) included in Table A-4, the data-extraction in Table A-1, and the risk of bias tables in Table A-2 and Table A-3 [15]. No quantitative analysis of outcomes was performed, due limited number of relevant comparative trials identified.

[1] MedCalc© (http://www.medcalc.org/calc/relative_risk.php)

3 Description and technical characteristics of technology

Features of the technology and comparators

B0001 – What are meniscal allograft transplantation (MAT) and conservative management?

Meniscal allograft transplantation (technology)

Meniskus als Puffer im Knie

A meniscus is a wedge- or crescent-shaped piece of cartilage that sits in the knee, between the femur and tibia. There are two menisci in the knee; the lateral meniscus spans the lateral side of the knee joint, and the medial meniscus spans the medial side. The primary functions of the meniscus are to share the distribution of load forces in the knee, provide shock absorption, and lubricate the knee joint [16, 17].

irreparabler Meniskusriss Indikation für Meniskektomie, manchmal persistierende Schmerzen nach Entfernung

Irreparable meniscal tears are common in sporting and motor vehicle injuries, or as a consequence of degenerative disease, and often require surgical treatment [18-20]. Meniscectomy procedures intended to remove some or all of a torn meniscus in an effort to improve pain and function [21]; however, this can result in increased contact stress between the femur and the tibia which can cause pain and instability. When a meniscectomy has failed, as defined by ongoing pain in the affected knee compartment, a meniscal allograft transplant may be considered [19].

bei Meniskustransplantation Spende von Verstorbenen

Meniscal allograft transplantation (MAT) is a procedure in which the meniscus from a cadaver is transplanted into a patient with a meniscal-deficient knee. The purpose of MAT is to restore a functional meniscus into the joint, with an aim to alleviate the symptoms associated with post-meniscectomy syndrome, and delay progression to osteoarthritis [18, 21].

Transplantation unter Anästhesie, Feststellung der Größe mittels bildgebender Verfahren, keine Immunsuppression nötig

The transplantation is performed under general or spinal anaesthesia, and is conducted using either arthroscopy or mini-arthrotomy. The donor menisci are matched for size (right/left, lateral and medial) based on imaging studies of the recipients knee [6]. The graft is fixed in place using sutures, bone plugs or bridges depending on surgeon preference and fixation site [19]. Since meniscal tissue is no “living” tissue, immunosuppression is not needed.

manchmal begleitende Eingriffe, wie Kreuzbandplastik

Other procedures to address underlying causes of joint degeneration or injury, such as anterior cruciate ligament (ACL) reconstruction are sometimes performed at the same time as MAT [19].

nach Transplantation Physiotherapie und Rehabilitation

Following MAT, patients undergo personalised physiotherapy regimens to aid in the recovery process. Rehabilitation often includes weight bearing exercise, quadriceps strengthening, and restoring full range of motion [6]; however, there is currently no agreement in the literature around the most effective treatment regimens [6].

Conservative management (comparator)

konservatives Management hat multimodalen Ansatz

Conservative management for patients with post-meniscectomy knee pain is a multi-modal treatment approach, that is commonly specialised to the specific needs of the patient [22].

Physiotherapie ist Hauptbestandteil

Physiotherapy is the core component of a conservative management approach, with an aim to increase the stability of the knee joint through strengthening the quadriceps, and increasing range of motion [23]. Over the longer term, exercises to improve strength, flexibility and proprioception may be indicated [21].

zusätzlich Medikamente und gegebenenfalls Injektionen

Oral pain medication and non-steroidal anti-inflammatory drugs are commonly used to manage mild pain and inflammation in the knee [24]. Similarly, cortisone or analgesic knee injections are often used in order to confirm a diagnosis of post-meniscectomy syndrome, and to provide symptomatic relief for stronger pain [22, 24].

eventuell auch Verhaltensanpassung

Behaviour modification may be advised in order to reduce stresses that can exacerbate knee pain, and to encourage weight loss [22].

No treatment

keine Therapy auch Alternative

The final alternative to MAT is to offer no treatment, and instead watch and wait for symptoms to progress (or not).

Alternative meniscus transplants

andere Alternativen, wie synthetische Menisken derzeit experimentell

Alternatives to MAT, such as synthetic meniscus transplants and scaffolds, have been developed in order to combat the limited supply of donor allografts [19]. These products are considered to be experimental and are therefore not considered in this review [25].

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

keine Medizinprodukte, daher kein CE

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

Gewebe- und Organspenden in EU über EUTCD geregelt

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 [26]. In this regard, individual suppliers of tissue samples that are licensed to distribute tissue samples under the EUTCD are able to distribute meniscal allografts within the EU.

gesetzliche Verankerung in Österreich über Bundesgesetz

Moreover, the principles of tissue and organ donation in Austria is positioned in the „Bundesgesetz über die Transplantation von menschlichen Organen“ (Organtransplantationsgesetz – OTPG) [27].

B0002 – What is the claimed benefit of meniscal allograft transplantation in relation to conservative management?

Meniskustransplantation zielt darauf ab Schmerzen zu reduzieren und langfristig eine Gelenksarthrose zu vermeiden

Meniscal allograft transplantation aims to restore the meniscal function in patients with previously removed menisci. In the context of post-meniscectomy syndrome, published literature on MAT suggests the primary aims of treatment are to relieve pain and effusions, restore functional capacity, lower the risk of osteoarthritis progression, and delay the requirement for total or partial knee arthroplasty and associated revision procedures [22, 28, 29]. In this regard, MAT is proposed to have superior effectiveness compared to conservative management [20].

Transplantation birgt zusätzliche Risiken, da Operation

As MAT is an additional surgical procedure, complications associated with MAT are considered to be additional safety risks not otherwise borne by patients treated with conservative management.

The submitting hospital did not propose a specific clinical claim in relation to an appropriate comparator, rather that there is no alternative technique for meniscal replacement in the context of post-meniscectomy syndrome.

in Einreicheantrag kein Hinweis auf potentiellen klinischen Nutzen

B0003 – What is the phase of development and implementation of meniscal allograft transplantation and conservative management?

Meniscal allograft transplantation was initially reported in 1984 and it has since been the subject of numerous publications [30, 31]. Although MAT is not a new orthopaedic procedure, it is not widely performed in most hospitals [32]. This is also reflected in the paucity of clinical practice guidelines recommending the use of MAT for treating post-meniscectomy syndrome.

Meniskustransplantation nicht neu, aber nicht verbreitet, daher Mangel an Leitlinien

Due to the lack of treatment options for post-meniscectomy syndrome, patients are currently treated by conservative management. This is largely because physiotherapy is a widely available treatment for knee injuries and rehabilitation, and does not carry the surgical risks associated with MAT [23]. However, there is not one accepted definition or treatment regime that constitutes conservative management for post-meniscectomy syndrome. Rather, treatment aims are typically designed to meet the requirements of a specific patient [22].

aufgrund mangelnder Behandlungsoptionen ist konservatives Management gängiger Therapieansatz

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

B0004 – Who administers meniscal allograft transplantation and conservative management, and in what context and level of care are they provided?

B0008 – What kind of special premises are needed to use meniscal allograft transplantation and conservative management?

Meniscal allograft transplantation should be performed by an orthopaedic surgeon that is fellowship trained in arthroscopic surgery of the knee. The procedure can be performed with the patient under a general anaesthetic or with a spinal block, depending on the patient's preference and associated risks [33]. The procedure should be done in a medical centre that is accustomed to doing arthroscopic meniscectomies [33].

Durchführung Eingriff durch orthopädische ChirurgInnen in spezialisiertem Zentrum

Meniscal transplant surgery can be performed with either an open or arthroscopic approach. If performed arthroscopically, MAT can be performed in either an outpatient or inpatient setting [28, 33]. For both approaches, sterile operating theatres are required.

Operation offen oder arthroskopisch, stationär oder auch ambulant

Conservative management can be provided by trained physiotherapists or occupational therapists. They can be administered in all facilities, whereas specific weight bearing exercises may require gym equipment.

konservatives Management durch Physiotherapeuten

B0009 – What supplies are needed to use meniscal allograft transplantation and conservative management?

The supplies required are dependent on the type of graft used (i.e. fresh-frozen, cryopreserved, deep frozen, fresh or freeze-dried), how the graft is sized, and the surgical approach (open or arthroscopic technique) [28, 34].

benötigte Materialen abhängig Art der Transplantation

Frozen grafts and cryopreserved grafts require refrigeration for storage. Fresh allografts require lactated ringer's solution at 4°C. Saline solution is required for thawing grafts [34].

Transplantat gefroren oder in Ringer-Lösung

Größenbestimmung meist durch Bildgebung

Sizing of allografts can be done using radiography, computed tomography, magnetic resonance imaging (MRI) or with direct measurements [28, 34].

generell chirurgisches Equipment

General surgical equipment includes anaesthesia, prophylactic antibiotics, a tourniquet and compression devices, arthroscopic equipment, sutures to attach the graft and guide pins [3, 34].

für Bone-Plug-Technik zusätzliches Equipment benötigt

The bone plug technique requires additional equipment including; bone plugs, oscillating saw, coring reamer, ronguer, specific needles and sutures, meniscal repair joystick instrument set system, knife, retriever/grasper and Swive-Lock Anchor [35].

für konservatives Management eventuell Kniebandage oder Injektionen

Conservative management may require knee braces (those are also needed for post-surgical treatment), injections, and potentially weight or resistance equipment for strength training. Injections may require local anaesthesia to administer [24].

Regulatory & reimbursement status

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

Intervention in Österreich derzeit nicht erstattet

Meniscal allograft transplantation is not currently included in the Austrian hospital benefit catalogue, and therefore is not reimbursed by the Austrian health care system. However, the intervention could be billed under another code, like for arthroscopic operations of the knee joint (Code NF020 – Arthroskopische Operationen des Kniegelenks) or refixations of the meniscus (NF040 – Meniskusrefixation – arthroskopisch).

4 Health Problem and Current Use

Overview of the disease or health condition

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

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

Fokus auf Postmeniskektomie-Syndrom

The health condition under investigation for this assessment is post-meniscectomy syndrome, characterised by intractable pain in the knee due to prior subtotal or total meniscectomy.

Entfernung Meniskus bei inoperablen Rissen, jedoch bleibende Schmerzen möglich

Meniscectomy has been performed for the management of meniscal tears for many years; however, following surgery some patients develop unicompartmental knee pain without significant articular cartilage wear, known as 'post-meniscectomy syndrome' [22]. The purpose of MAT is to substitute the missing meniscus, thereby restoring the load-bearing, shock absorption and lubrication mechanisms in the knee and reduce pain [16, 17].

A0003 – What are the known risk factors for post-meniscectomy syndrome?

Pathogenese unklar, mögliche Risikofaktoren unter anderem degenerative Veränderungen des Gelenks, laterale Meniskektomie

The pathogenesis of post-meniscectomy syndrome is not clear [22]. Removal of the meniscus, whilst effective in relieving symptoms for some patients, has long term consequences for the knee joint. Further, meniscectomy a risk factor for pain and functional impairment over the longer term (thus, the general aim is to preserve the meniscus, if possible) [36, 37]. Factors that might increase the risk of post-meniscectomy syndrome include: degenerative changes in the knee joint contributing to pain, lateral meniscectomy (as compared to medial meniscectomy), poor vascular supply to the repair zone, underlying malalignment of the knee, and factors contributing to greater joint loading such as high activity level and/or body mass index [22, 38].

A0004 – What is the natural course of post-meniscectomy syndrome?

Meniskektomie erhöht Risiko für Gelenksarthrose

Meniscectomy increases the risk of osteoarthritis [36, 37]; however, this elevated risk does not guarantee a patient who has had a subtotal or total meniscectomy will progress to osteoarthritis [39].

durch Gonarthrose Knorpelschädigung möglich

Osteoarthritis leads to cartilage damage. The extent of cartilage damage can be classified using the following grading systems (see Tables 4-1 to 4-3):

Table 4-1: Classification of cartilage defects by Outerbridge

Grade	Characteristics
0	Normal
1	Softening and swelling of cartilage
2	Fragmentation and fissuring, less than 1.5 cm-in diameter
3	Fragmentation and fissuring, greater than 1.5 cm in diameter
4	Erosion of cartilage down to exposed subchondral bone

Reference: [1]

Table 4-2: Classification of osteoarthritis of the knee joint by Ahlbäck

Grade	Characteristics
1	Joint space narrowing (les than 3mm)
2	Joing space obliteration
3	Minor bone attrition (0-5mm)
4	Moderate bone attrition (5-10mm)
5	Severe bone joint attrition (more than 10mm)

Reference: [2]

Table 4-3: Classification of chondral defects by International Cartilage Repair Society

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 (carilage defects >50% of cartilage depth
4	Severely abnormal (through the subchondral bone)

Reference: [40]

Knochennekrose auch mögliche Folge von Meniskektomie

Progression to osteonecrosis is another potential risk factor of post meniscectomy; however, the natural progression is not well understood [41]. There are a number of proposed mechanisms that can lead to osteonecrosis of femoral condyles, including:

- Overloading, causing impaired circulation in subchondral bone;
- Subchondral insufficiency fracture due to abnormal load transfer; and
- Intraosseous contact.

erhöhtes Risko für notwendigen Gelenksersatz

In addition to osteoarthritis, meniscectomy also increases the risk of total knee replacement [42].

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

A0005 – What is the burden of diseasefor patients with post-meniscectomy syndrome?

Schmerzen, Bewegungseinschränkungen

Patients with post-meniscectomy syndrome are suffering from pain and impaired mobility [43], leading to a lower quality of life.

vorzeitige Osteoarthritis, bis zu Gelenksersatz

In addition, the syndrome can lead to the development of degenerative osteoarthritis and a further progression can lead to the requirement of a joint replacement [42, 44, 45].

A0006 – What are the consequences of post-meniscectomy syndrome for society?

knapp 40.000 arthroskopische Knieoperationen in 2016

In 2016 there were nearly 80,000 surgeries of the knee joint in Austria. Of these, a total of 38,771 interventions were arthroscopic surgeries [46, 47]. However, no information on the number of meniscectomies, and the consequent risk of post-meniscectomy syndrome, has been identified.

The long-term consequences of post-meniscectomy syndrome can lead to high costs for required treatments, such as physiotherapy, medication, and surgeries (including total joint arthroplasty). Total knee arthroplasty is reimbursed for approximately 9,000 Euros [48-50]. In addition, there are indirect costs associated with post-meniscectomy syndrome, such as time and productivity losses, especially when considering that mainly young people in the age between 20 and 50 years are affected. However, an estimation of the interventional or total costs of post-meniscectomy syndrome for the society is not possible.

zum Teil hohe langfristige Kosten bei Postmeniskektomie-Syndrom

Current clinical management of the disease or health condition

A0024 – How is post-meniscectomy syndrome currently diagnosed according to published guidelines and in practice?

We could not identify published guidelines on the diagnosis of post-meniscectomy syndrome. Studies included in this report noted that the syndrome is confirmed by the presence of symptoms in the context of prior meniscectomy. Symptoms experienced by patients following meniscectomy included ipsilateral joint-line pain, activity-related swelling, crepitus, post activity effusions and the occasional giving way of the knee [51-53]. Patients are assessed for their suitability for MAT by a combination of MRI, x-rays, and arthroscopic images [53-55].

keine Leitlinien gefunden, laut Studien sind anhaltende Schmerzen nach Meniskusentfernung ausschlaggebend

A0025 – How is post-meniscectomy syndrome currently managed according to published guidelines and in practice?

No evidence-based guidelines for the treatment of post-meniscectomy syndrome were identified in this review. In practice, the main treatment options include no treatment, conservative management or surgery.

keine evidenzbasierten Leitlinien gefunden

Generally, the treatment of post-meniscectomy aims at pain reduction, regaining joint mobility, prevention of osteoarthritis, and eventually avoiding total joint replacement. No treatment, however, will probably not improve symptoms, but it can be considered as comparator (see section 1.1).

Behandlung verfolgt unter anderem Schmerzreduktion

Conservative management is described in section “B0001 – What are meniscal allograft transplantation (MAT) and conservative management?”.

konservativer Ansatz; bereits beschrieben

A last resort to treat post-meniscectomy pain is total knee arthroplasty (TKA). This procedure involves the removal of the damaged cartilage and bone from the knee joint and replacing it with a man-made joint of metal and plastic or ceramic. The surgery can cause scarring, blood clots, and, rarely, infections. Due to the high invasiveness of TKA, it is considered as a last resort treat post-meniscectomy pain, and is therefore not considered to be an appropriate comparator to MAT.

endgültige Option ist künstliches Gelenk, jedoch nicht als Vergleichsintervention berücksichtigt

Target population

A0007 – What is the target population in this assessment?

primäre Indikationen nicht eindeutig definiert

The primary indications for MAT have not been clearly established in the literature. Recent technical and systematic reviews recommend specific criteria, including [4, 28, 33]:

1. Patient age between 20 and 50 years
2. Previous meniscectomy
3. No severe degenerative changes to articular cartilage
4. Joint stability
5. Local pain and swelling in the meniscus-deficient compartment
6. Normal lower limb alignment

Zielpopulation in vorliegenden Bericht daher breit gefasst

Due to the clinical uncertainty around the proposed population, the target population in this assessment is broadly defined as patients with post-meniscectomy syndrome, and no significant articular cartilage wear. Significant articular cartilage wear is defined as Outerbridge Grade $<$ III [1], or Ahlbäck Grade $\leq$ II [2].

A0023 – How many people belong to the target population?

keine Daten zu Prävalenz oder Inzidenz identifiziert

No information on the Austrian, European or international data for the prevalence or incidence of post-meniscectomy syndrome was identified to inform this research question. Similarly, the frequency of meniscectomies conducted in Austria is currently unknown.

A0011 – How much is meniscus allograft transplantation utilised?

keine Angaben zu Meniskustransplantation

There is currently no data that can be used to estimate the overall size of the population that is eligible for MAT.

geschätzte Erbringung in Österreich: 200 p.a.

Based on the information provided in the VAEV, the estimated annual utilisation of MAT in the submitting hospital is around 10 procedures. In contrast, the annual utilisation in Austria is estimated to be around 200 procedures.

keine Angaben zu Häufigkeit konservatives Management

It is not possible to estimate the number of patients with post-meniscectomy syndrome that are currently treated with conservative management.

5 Clinical effectiveness

5.1 Outcomes

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

entscheidende Endpunkte für Wirksamkeit

- **Decrease in pain**
- **Increase in function**
- **Prolonged or prevented total joint replacement**

The clinical outcomes chosen as *critical* to derive a recommendation are based on the primary treatment goals of MAT (see "A0025 – How is post-meniscectomy syndrome currently managed according to published guidelines and in practice?").

Auswahl basierend auf Behandlungszielen

Pain is the primary symptom that is used to diagnose post-meniscectomy syndrome. It is most often measured using patient-reported or observer-reported questionnaire scales, and as such is difficult to measure objectively. Pain can be measured using generic scales, such as a visual analogue scale, or disease-specific questionnaires, such as the Knee injury and Osteoarthritis Outcome Score (KOOS) pain subscale for knee osteoarthritis.

Schmerzen; Messung z. B. anhand von Fragebogen

Function is a measure of how the disease impacts daily life and activities. It can be measured using a range of different scoring tools, including:

Funktion; Messung mittels verschiedener Instrumente

- KOOS is a composite measure of a patient's opinion about their knee, incorporating 5 subscales: pain (KOOS-Pain), other symptoms, function in daily life (KOOS-ADLs), function in sports and recreation (KOOS-Sports), and knee-related quality of life (KOOS-QoL). The KOOS and subscale scores range from 0 (extreme symptoms/disability) to 100 (no symptoms/disability) [56].
- The Lysholm scale is a composite measure of knee function, administered by clinicians, ranging between 0 (severe symptoms/disability) and 100 (no symptoms/disability) [56].
- International Knee Documentation Committee (IKDC) is a subjective, patient-reported knee evaluation form designed to detect changes in symptoms, function and sports activities due to knee impairment. The IKDC is a composite measure of overall function ranging from 0 (severe symptoms/disability) to 100 (no symptoms/disability) [56].

Prolonging or preventing total joint replacement is a key long-term treatment goal of MAT. This outcome is measured by reported rates of TKA following MAT or conservative management (or no treatment). In order to evaluate this outcome comprehensively, long-term follow-up data is required.

Herauszögerung oder Vermeidung Knieprothese

In addition to the *critical* outcomes, two additional outcomes were considered to be *important* but not *critical* to the decision:

zusätzlich Lebensqualität, Rückkehr zu täglicher Aktivität

- Increase in quality of life
- Return to daily activities

Quality of life and return to daily activities are important outcomes of MAT, which follow as a consequence of achieving the primary treatment goals. These two outcomes were considered to be important, though not crucial, because pain and function affect quality of life and the return of patients to daily activities.

Schmerzen und Funktion bedingen Lebensqualität und Rückkehr zu täglicher Aktivität

5.2 Included studies

(nicht) randomisierte kontrollierte Studien eingeschlossen

To evaluate the effectiveness of MAT for treating post-meniscectomy syndrome, we considered RCTs and non-randomised studies comparing MAT to conservative management or no therapy/treatment.

eine Kohortenstudie identifiziert

Only one comparative study met the pre-defined inclusion criteria; a prospective cohort study with a nested RCT, which compared MAT with conservative management [23]. This study was categorised as a cohort study despite including a nested RCT, because the results of the randomised and non-randomised groups were combined. Therefore, this study is considered to be a cohort study for the purposes of this review.

Studie aus Großbritannien, 36 PatientInnen

The cohort study was conducted in the United Kingdom and enrolled 36 patients with post-meniscectomy syndrome, where the treating surgeon thought the patient would benefit from MAT [23].

21 PatientInnen randomisiert, 15 durften Behandlung wählen

From the total sample, 21 patients were randomised to receive either MAT or physical knee therapy, and the remaining 15 patients were allowed to select their treatment allocation. This design was used in order to maximise recruitment numbers. All patients received physiotherapy rehabilitation following MAT.

Durchschnittsalter 29 vs. 27 Jahre, Zeit nach Meniskektomie 8,2 vs. 7,6 Jahre, Großteil männlich

The average age of participants was 29 in the MAT group and 27 in the conservative management group, and the average time since meniscectomy to treatment was similar between groups (8.2 years vs 7.6 years). The majority of the sample were male (n=26, 72%). There was a greater proportion of lateral compared to medical menisci treated overall (n=28 vs 8), and a slightly higher proportion of lateral menisci were treated in the MAT group (87.5% vs 70.0%) [23].

drei PatientInnen in Interventionsgruppe zusätzlich Osteotomie

The study did not specify the clinical grade of cartilage status, but reportedly excluded patients that had exposed subchondral bone due to arthritis, and those who had undergone previous cartilage modifying procedures. Three MAT patients had concomitant osteotomy [23]. The number of previous surgeries was not reported.

Tabellen in Anhang

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

keine Studien zu Meniskustransplantation vs. keine Therapie

Since we could not identify any controlled studies comparing MAT with no therapy/no treatment, the results are exclusively for MAT versus conservative treatment.

5.3 Results

Mortality

D0001 – What is the expected beneficial effect of meniscal allograft transplant on mortality?

D0003 – What is the effect of meniscal allograft transplant on the mortality due to causes other than post-meniscectomy syndrome?

Mortalität im nächsten Kapitel zu Sicherheit behandelt

Since post-meniscectomy syndrome is not life-threatening, and MAT was considered not to have an effect on mortality, these research questions are not relevant. However, procedure-related mortality was considered as safety-outcome (see "C0008 – How safe is meniscal allograft transplant in comparison to conservative management?")

Morbidity

D0005 – How does meniscal allograft transplant affect the symptoms and findings (severity, frequency) of post-meniscectomy syndrome?

Beantwortung Frage anhand Endpunkt „Schmerzen"

Answering this research question was based on the *critical* outcome "pain". Patient-reported pain was measured using the KOOS-Pain subscale questionnaire [23]. Pain scores were measured at baseline and after 12 months. The mean change in pain score at 12 months was compared between the MAT and physiotherapy groups.

Verbesserung Schmerzen für Intervention signifikant besser

After 12 months, the mean difference in the change in KOOS-Pain score from baseline was 15.1 (95% CI 2.4 to 27.8, p=0.021) (Figure 6-1). These results demonstrate a significantly greater improvement in knee-related pain in favour of MAT [23].

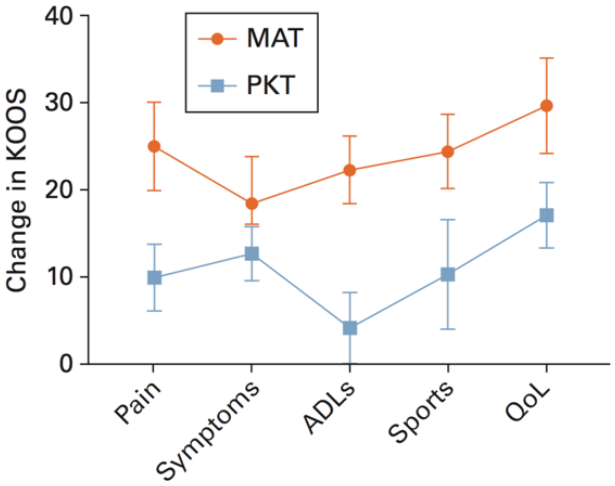


Figure 6-1: Mean change in Knee injury and Osteoarthritis Outcome Score (KOOS). Subscales from baseline to 12 months in the pooled meniscal allograft transplantation (MAT) and personalized knee therapy (PKT) group. QoL = Quality of life; ADL = activities of daily living (Reference: Smith 2018 [23]).

weiterer Endpunkt: KOOS-Symptome keine signifikanten Unterschiede zwischen Studiengruppen

Furthermore, the identified study also reported on symptoms (see Figure 6-1) by using the KOOS-Symptoms subscale; a composite score comprised of swelling, noise (e.g. clicking), knee locking, straightening and bending [56]. However, since we did not consider this outcome in our PICO question (pain and function scores were considered to be the most relevant outcomes to express symptoms), this outcome was not extracted. Nevertheless, the improvement in symptoms was not significantly higher for MAT-patients compared to physiotherapy (mean difference 5.7, 95% CI -6.4 to 17.9, p=0.341) [23].

D0006 – How does meniscal allograft transplant affect progression (or recurrence) of post-meniscectomy syndrome?

Frage kann nicht beantwortet werden, da keine Evidenz

This research question was supposed to be answered by the *critical* outcome "necessity of total joint replacement". However, no comparative data were identified on this outcome. Thus, this research question cannot be answered.

Function

D0011 – What is the effect of meniscal allograft transplant on patients' body functions?

Frage mit nachfolgender Frage zusammengelegt

This research question is answered within the following section ("D0016").

D0016 – How does the use of meniscal allograft transplant affect activities of daily living?

Scores zu Funktionalität

Function scores were the primary outcomes used to determine the impact of MAT in comparison to conservative management on activities of daily living.

Messung in Studie mittels verschiedener Scores

Function was measured using the KOOS-ADL, KOOS-Sports and KOOS-Composite subscale questionnaires, as well as Lysholm and IKDC questionnaires [23]. Function scores were measured at baseline and after 12 months. The mean change in function scores at 12 months were compared between the MAT and physiotherapy groups.

keine signifikanten Unterschiede bei Lysholm, IKDC und KOOS-Sports

The mean difference in the change in scores was not statistically significant for Lysholm (MD=7.3, 95% CI -4.5 to 19.1, p=0.22), IKDC (MD=8.4, 95% CI -3.6 to 20.5, p=0.16) or KOOS-Sports (MD=14.0, 95% CI -2.7 to 30.8, p=0.098, see also Figure 6-1) [23].

Transplantation signifikant besser bei: KOOS-Composite und KOOS-ADL

Significant increases in function scores, favouring MAT, were observed for KOOS-Composite (MD 11.9, 95% CI 1.1 to 22.7, *p=0.034*), and KOOS-ADL (MD 18.2, 95% CI 6.0 to 30.5, *p=0.005*, see also Figure 6-1) [23].

Health-related quality of life

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

keine Evidenz

No comparative data on generic health-related quality of life was identified to answer this question.

D0013 – What is the effect of meniscal allograft transplant on disease-specific quality of life?

Lebensqualität mittel KOOS zu Lebensqualität in Studie

Disease-specific quality of life was measured using the KOOS-QoL subscale questionnaire [23]. Quality of life scores were measured at baseline and after 12 months. The mean change in KOOS-QoL scores at 12 months was compared between the MAT and physiotherapy groups.

zwar klinisch relevante Verbesserung, aber keine signifikanten Unterschiede zwischen Studiengruppen

After 12 months, the mean difference in the change in KOOS-QoL score from baseline was 12.6 (95% CI -0.4 to 25.6, p=0.058, see also Figure 6-1) favouring MAT [23]. These results demonstrate a minimum clinically important increase in knee-related quality of life in favour of MAT [57], but which did not reach statistical significance.

Patient satisfaction

D0017 – Was the use of meniscal allograft transplant worthwhile?

keine Evidenz

No comparative data was identified to answer this question.

6 Safety

6.1 Outcomes

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

entscheidende Endpunkte für Sicherheit

- **Complications**
- **Transplant failure/time to failure**

Procedure-related complications are adverse events that are specifically related to the intervention [24]. Complications have been defined broadly as to be inclusive of all types of adverse events that may be related to MAT or conservative management. Possible procedure-related complications of MAT include, but are not limited to, infection, meniscal tears, haematoma, and arthrofibrosis.

Komplikationen, die mit Intervention (oder konservativem Management) assoziiert sind

Transplant failure can be measured in a number of ways, including persistent pain after MAT, removal of the graft, or progression to the requirement for TKA [51, 52, 54, 58]. Graft failures often require invasive additional surgeries and, depending on their timing, may also demonstrate clinically inappropriate care.

Transplantatsversagen; verschieden messbar

In addition to the *critical* outcomes, two additional outcomes were considered to be important but not crucial to the decision:

zusätzlich Zeit bis Transplantatsversagen Reoperationen, eingriffsbezogene Mortalität

- Re-operation/additional surgery
- Procedure-related mortality

Re-operations are an indication of additional procedures that were directly caused by implementation of the intervention or comparator. Re-operations can result in additional time, resources, and risks. They were included as important outcomes, but not critical, as all major complications that required re-operation are likely to be captured under the complications and transplant failure outcomes.

Reoperationen als Indikator für zusätzliche Eingriffe

Procedure-related mortality is a very rare but potential outcome of MAT. This outcome has been included in order to determine whether or not there is any procedure-related mortality risk associated with MAT.

eingriffsbezogene Mortalität als möglicher Risikofaktor

6.2 Included Studies

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

Tabellen in Anhang

A total of six studies with a total of 344 patients were identified to inform the recommendation on the safety of MAT. Five case series [51-55, 58] and one cohort study with a nested RCT, comparing MAT with conservative treatment [23] were included. All were prospective in design. Follow-up time ranged between 12 to 120 months. The case series reported all results at a mean follow-up time (range 22 to 56 months) [51-55, 58], whereas the cohort study reported all results at 12-month follow-up [23].

5 Fallserien und eine nicht-randomisierte kontrollierte Studie (non-RCT)

in Fallserien 40-88 PatientInnen, Durchschnittsalter 25-40 Jahre

Patient numbers ranged from 40 to 88 in the case series [51-55, 58]. In the cohort study with nested RCT, 21 patients were included in the RCT and 15 in the non-randomised group [23]. Mean patient age ranged from 25 to 40 years across all studies.

verschiedene Operationstechniken in Studien

With respect to the intervention, two studies used MAT with bone plug fixation [52, 53], two studies used MAT with soft tissue fixation [23, 54, 55], one study used MAT with suture-only or bony fixation [51]. The remaining study used MAT with bone block and/or soft tissue fixation for lateral menisci, and soft tissue fixation alone for medial menisci [58].

in jeder Studie PatientInnen mit begleitenden Interventionen

Three of the included studies reported that patients had undergone prior surgeries [51-53]. Prior surgery status was not reported in the other three studies. All studies reported that at least some of the patients had concomitant interventions with the number ranging from 18% to 50% [23, 51-55, 58]. The types of concomitant interventions included osteotomies, ACL reconstructions, microfracture, chondral shaving, hardware removal, autologous chondrocyte implantation, ligament reconstructions, osteoarticular allografts and osteochondritis dissecan fixations.

Klassifikationen der Erkrankung Grad 0-3

In the case series studies, patients were reported as low-grade cartilage damage, indicated by Outerbridge Grade 0-II [52, 53], Ahlbäck Grade I, International Cartilage Repair Society (ICRS) Grade 0-3b involving $<1cm^2$ (defined as 'good' in the study) [54, 55]. One case series did not describe cartilage status [58], and as such the applicability of the population in this study is uncertain.

keine Studien zu Meniskustransplantation vs. keine Therapie

Since we could not identify any controlled studies comparing MAT with no therapy/no treatment, the comparative results are exclusively for MAT versus conservative treatment.

6.3 Results

Patient safety

C0008 – How safe is meniscal allograft transplant in comparison to conservative management?

Beantwortung Frage anhand von vier Endpunkten"

To answer this research question, the outcomes "complications", "transplant failure", "time to failure", and "transplant failure" were considered.

MAT vs. conservative management

relatives Risiko für Komplikationen: 6,92

The relative risk of complications for MAT was 6.92 (95% CI 0.91 to 52.45, $p>0.05$) compared to conservative management; however, this difference was not statistically significant. Further, the complications in the MAT group were not adequately defined [23].

alle Komplikationen bei Transplantation benötigten Reoperation

All five complications in the MAT group required re-operation with arthroscopy, whereas the only complication in the conservative management group was a thigh bruise that did not require any intervention [23].

Transplantatsversagen und Zeit bis Versagen nicht berichtet

Transplant failure and time to failure were not reported.

Single arm studies

The overall complication rate for MAT across all of the case series was 20.2% (range 0.0% to 30%). All but one complication (56 of 57) related to MAT required re-operation, typically with an arthroscopic procedure [51, 52, 54, 55, 58]. Specific complications reported in the single-arm trials are described in Table A-1.

Komplikationsrate 20,2%, fast alle benötigten Reoperation

The overall failure rate of meniscal allografts was 4.4% (range 1.7% to 7.7%) at a mean follow-up time of 46 months (range 13 to 120) [51, 52, 54, 55, 58]. Time to failure was only reported by one study, which reported three failures (7.7%) with a mean time to failure of 15 months (range 9 to 21 months) [52].

4,4 % der Transplantate versagten, dies dauerte im Mittel 15 Monate

No instances of procedure-related mortality were reported in any of the included studies (0.0%, 0/295) [23, 51-55, 58].

keine eingriffsbezogene Mortalität

C0002 – Are the harms related to dosage or frequency of applying meniscal allograft transplant?

No reliable data was identified to answer this research question. It is unclear if patients are likely to be considered for a replacement of MAT on a previously treated transplanted compartment.

keine verlässliche Informationen

C0004 – How does the frequency or severity of harms change over time or in different settings?

No reliable data was identified to answer this research question. The controlled cohort study reported results for all outcomes at 12-month follow-up [23]. The case series reported complication and failure rates at an overall mean follow-up time, which varied between studies (range 30 to 60 months) [51-55,58] (see also question "C0008 – How safe is meniscal allograft transplant in comparison to conservative management?"). Relative survival rates of MAT in patients with varying levels of cartilage degeneration are reported below (see question "C0005" below).

keine verlässliche Evidenz

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of meniscal allograft transplant?

MAT cartilage Grade: 'Good' vs 'Bare'

One study investigated graft survival rates of meniscal allografts in patients with 'good' (n=60) versus 'bare' cartilage status (n=39). 'Good' cartilage was defined as ICRS Grade 3b chondral damage of $<1cm^2$, while 'bare' was defined as ICRS Grade 3b chondral damage of $>1cm^2$ or worse [54].

eine Fallserie untersuchte Einfluss von Knorpel-Status

Patients with 'good' cartilage status reported significantly greater 2-year survival compared to patients with 'bare' cartilage (97.9% vs 78.0%, $p=0.002$) [54]. Similarly, the 'good' cartilage group reported significantly lower overall complication rates (30% vs 46%, $p=0.05$), and significantly lower major complication rates (13% vs 31%, $p=0.035$) [54].

guter Knorpel-Status, besseres Transplantat-Überleben und weniger Komplikationen

MAT fixation type: Suture vs Bone Plug

One study reported the relative complication rate of MAT using suture fixation compared to bone plug fixation. Suture fixation reported a 33.3% (n=11/33) complication rate, including seven re-operations for graft tears. Of these, three grafts had to be removed completely (i.e. transplant failure) [51].

eine Fallserie untersuchte Einfluss von Operationstechnik

Bone-Plug-Technik mit etwas weniger Komplikationen assoziiert

In comparison, the bone-plug technique reported a 16.4% (n=9/55) complication rate, including four tears that results in re-operations. In two of these operations the graft had to be removed completely (i.e. transplant failure) [51].

Unterschiede nicht signifikant

Neither the reported difference in complications nor graft failures were statistically significant [51].

C0007 – Are meniscal allograft transplant and conservative management associated with user-dependent harms?

keine Evidenz

No evidence was identified to answer this question.

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of meniscal allograft transplant and conservative management?

keine Evidenz

No evidence was found to answer this research question. International, prospective registry data will better inform the long-term safety of MAT; however, due to the absence of clinical data on the comparative effectiveness of MAT, this type of resource-intensive monitoring strategy is not warranted at present.

7 Quality of evidence

Bias-Risiko der Kohortenstudie hoch

Risk of bias in the cohort study was appraised using the ROBINS-I tool [59], and is presented in Table A-2 (see Appendix). Importantly, this study was categorised as a cohort study despite including a nested RCT, because the results of the randomised and non-randomised groups were combined. The comparative study had a serious overall risk of bias due to possible confounding, selection bias, missing data, and the use of un-blinded patient-reported outcome measures.

Bias-Risiko der Fallserien moderat bis hoch

Risk of bias in the single arm studies was appraised using the Institute of Health Economics (IHE) appraisal tool for case series studies [14], and is presented in Table A-3 (see Appendix). The single arm studies were at moderate to serious risk of bias. The main reasons for increasing the risk of bias were due to single-centre design, unclear method for capturing complications, poor reporting of the follow-up period, and failure to disclose both competing interest and sources of support for the study.

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema [60] for each endpoint individually. 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 [60].

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.

Zusammenfassung GRADE nächste Seite

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below (Table 7-1) and in the evidence profile in Appendix Table A-6.

Evidenzstärke sehr gering

Overall, the strength of evidence for the effectiveness and safety of MAT in comparison to conservative management is “very low”. The strength of evidence for the safety of MAT from the identified case series is also “very low”.

keine Evidenz zu Meniskustransplantation vs. keine Therapie

Moreover, we could not identify any comparative studies on MAT versus no therapy/no treatment.

Table 7-1: Summary of findings table of meniscal allograft transplantation (compared to conservative management) for the treatment of post-meniscectomy syndrome

Outcome	Anticipated absolute effects (95% CI)			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with MAT	Risk with conservative management	Difference				
EFFICACY							
Pain: Change in pain score Follow up: 12 months; assessed with: KOOS – Pain Subscale; Scale from: 0 to 100	NR	NR	MD **15.1 points higher in MAT group** (2.4 higher to 27.8 higher)	Not estimable	31 (1)	⨁◯◯◯ VERY LOW[2,3]	Higher scores indicate improved pain
Function: Change in function score Follow up: 12 months; assessed with: Lysholm; Scale from: 0 to 100	NR	NR	MD **7.3 points higher in MAT group** (4.5 lower to 19.1 higher)	Not estimable	31 (1)	⨁◯◯◯ VERY LOW[2,3]	Higher scores indicate improved function, no significant differences
Function: Change in function score Follow up: 12 months; assessed with: IKDC; Scale from: 0 to 100	NR	NR	MD **8.44 points higher in MAT group** (3.8 lower to 20.5 higher)	Not estimable	31 (1)	⨁◯◯◯ VERY LOW[2,3]	Higher scores indicate improved function, no significant differences
Function: Change in function score Follow up: 12; assessed with: KOOS-Composite; Scale from: 0 to 100	NR	NR	MD **11.9 points higher** in MAT group (1.1 higher to 22.7 higher)	Not estimable	31 (1)	⨁◯◯◯ VERY LOW[2,3]	Higher scores indicate improved function
Function: Change in function score Follow up: 12; assessed with: KOOS-ADL; Scale from: 0 to 100	NR	NR	MD **18.2 points higher in MAT group** (6 higher to 30.5 higher)	Not estimable	31 (1)	⨁◯◯◯ VERY LOW[2,3]	Higher scores indicate improved function
Function: Change in function score Follow up: 12; assessed with: KOOS-Sports; Scale from: 0 to 100	NR	NR	MD **14 points higher in MAT group** (2.7 lower to 30.8 higher)	Not estimable	31 (1)	⨁◯◯◯ VERY LOW[2,3]	Higher scores indicate improved function, no significant differences
Necessity of total joint replacement	-	-	-	-	-	-	Outcome not reported

[2] There was a serious risk of bias due to possible confounding, missing data, the use of unblinded patient-reported outcome measures and inadequate reporting of complications

[3] Sample size is below optimal information size. Conventional sample size calculation required 50 patients in each study arm.

Outcome	Anticipated absolute effects (95% CI)			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with MAT	Risk with conservative management	Difference				
SAFETY							
Complications (comparative) Follow up: 12 months	384 per 1,000 (51 to 1,000)	56 per 1,000	32.9% more (0.5 fewer to 285.8 more)	**RR 6.92** (0.91 to 52.45)	31 (1)	⨁◯◯◯ VERY LOW[4,5,6]	All complications in the MAT group required re-operation, no significant differences
Complications (single arm) Follow up: range 13 months to 120 months	Overall complications: 57/282 (20.2%, range 0.0 to 38.5%) Median complication rate: 21.7%			Not estimable	282 (5)	⨁◯◯◯ VERY LOW[6,7,8]	All complications in the MAT group required re-operation (e.g. arthroscopy) except for one
Transplant failure (single arm) Follow up: range 13 months to 120 months; assessed with: removal or replacement of the graft, or progression to TKA	Overall transplant failures: 11/248 (4.4, range 1.7% to 7.7%) Median transplant failure rate: 4.5%			Not estimable	248 (4)	⨁◯◯◯ VERY LOW[4,5,6,9,10]	Failures were defined as removal of the graft and/or progression to TKA

Abbreviations: *ADL = activities of daily living; IKDC = International Knee Documentation Committee; KOOS = Knee injury and Osteoarthritis Outcome Score; NR = not reported (in study); TKA = total knee arthroplasty.*

[4] Single-centre trials

[5] Unclear if all follow-up data were available

[6] No estimates of the random variability in the reported outcome data

[7] The method for capturing complications was not adequately reported. It is unclear whether all relevant complications were reported

[8] Heterogeneity in reported rates across studies

[9] Thresholds for failure were poorly defined

[10] Heterogeneity in reported rates across studies

8 Discussion

Patients that experience significant meniscal tears, typically due to sporting injuries at a younger age, often undergo partial or total meniscectomy for symptom control where there is no chance to preserve the meniscus [18-20]. However, pain may persist following meniscectomy, which can limit activities of daily living, cause discomfort, and potentially lead to the progression of osteoarthritis and total knee arthroplasty (TKA).

bei irreparabler Meniskusverletzung meist Meniskektomie, anhaltende Schmerzen möglich

Meniscal allograft transplantation (MAT) is a potential therapeutic option for these patients, which aims to replace the previously removed meniscus and restore the capacity of the knee for load-bearing, shock absorption and lubrication. This technique has been researched since the mid 1980's, and presents as one of few treatment options available to patients with post-meniscectomy syndrome.

Meniskustransplantation als mögliche Behandlungsoption

The aim of this systematic review was to evaluate the safety and effectiveness of MAT in comparison to conservative management and no therapy.

Bewertung Wirksamkeit und Sicherheit Transplantation

Interpretation of findings

Study quality, validity and overall level of evidence

Only one comparative study (MAT vs. conservative management) was identified that could inform the recommendation based on clinical effectiveness [23]. This study had a high risk of bias, as discussed in Section 7. Of note, the study included patients which the treating surgeon specifically thought would benefit from MAT; in doing so, the results may have systematically included patients likely to derive a greater benefit from MAT than conservative management. This study was underpowered to detect a significant difference; therefore the results should be interpreted with caution due to the increased risk of type 1 error (i.e. accepting a significant effect where none exists).

lediglich eine Vergleichsstudie: zu Transplantation im Vergleich zu konservativem Management

The comparative study reported differences between all effectiveness outcomes that favoured MAT in terms of the direction of effect, but only reported significantly greater differences for KOOS-Pain, KOOS-Composite and KOOS-ADL. These results demonstrate that MAT had a significantly greater improvement in pain and functions of daily living compared to conservative management at 12 months. In contrast, Lysholm, IKDC and KOOS-Sports were not significantly different, but did favour MAT in terms of direction of effect. The small sample size of the trial limited the precision of the estimates, and it is possible that a larger study would bear clinically and statistically significant results; however, in the absence of additional information it is unknown whether these differences are meaningful or not. Moreover, patients in both the intervention and control group showed improvements in all effectiveness-related outcomes.

Vergleichsstudie zeigte teileweise signifikant bessere Ergebnisse bei Meniskustransplantation, jedoch Ergebnisse mit erheblichen Limitationen

Although single arm studies were not formally included to evaluate effectiveness, we extracted outcomes for narrative comparison with the results of the cohort study. Interestingly, data on the efficacy outcomes demonstrated conflicting results regarding improvements in pain scores, function scores, and quality of life scores. Further, these results were often confounded by concomitant procedures, and limited by low precision due to small sample sizes.

Vorher-Nachher-Untersuchungen der Fallserien zeigten unterschiedliche Ergebnisse bezüglich Wirksamkeit

Komplikationen in allen Studien eher dürftig berichtet

Regarding the safety of MAT, complications were reported poorly in all of the included studies. Based on the quality and reporting of the comparative study, the additional risks associated with MAT in comparison to conservative management are highly unclear. Furthermore, due to the risk of bias, and variable nature of follow-ups reported in the single arm trials, the results for graft failure and progression to TKA are subject to substantial uncertainty.

Ergebnisse vorliegender Bericht durch 2 existierende Berichte unterstützt

The results of this present review are supplemented by two recent, independent systematic reviews of MAT [61, 62]. One review reported high, but variable failure rates (mean 18.7%, range from 0.0% to 45.3%), and reoperation rates for MAT (mean 31.3%, range from 0.0% to 45.3%) [61]. However, this review included retrospective studies, and defined failure as poor post-operative knee function, whereas we considered failure to be related to graft removal or the need for TKA [61]. The second review investigated MAT with or without concomitant surgeries, and found no significant difference in relation to patient-reported outcomes. The review could not draw reliable conclusions on complications, reoperations, survivorship or failure rates on due to insufficient data [62].

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

Endpunkte zu Wirksamkeit zwar konsistent gemessen, aber zum Teil äußerst subjektiv

The effectiveness outcomes included in this review directly measured the impact of MAT on disease-related outcomes of pain, function and quality of life. The main effectiveness endpoints, KOOS, IKDC, Lysholm, were valid, and measured and reported in a consistent way. However, two of these outcomes are measured with patient-completed questionnaires, which involve a level of subjectiveness. Unfortunately, it is not possible to blind patients to their treatment allocation when comparing MAT to conservative management; but it is possible to blind investigators that administer other questionnaires such as Lysholm, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Tegner activity scores [57]. The applicability of the included studies, including population, interventions, comparators and outcomes, is outlined in the Appendices (Table A-5).

Evidence gaps and ongoing studies

große Lücken in Evidenz

Despite the relatively long history of research conducted on MAT [30, 31], only one comparative study has compared MAT with the closest eligible intervention – conservative management. In the absence of more comparative data, it is difficult to properly understand the benefits associated with MAT. Single arm trials do not provide sufficient evidence to demonstrate a clinical benefit of MAT. Indeed, recent systematic reviews are now advocating that comparative trials should be conducted [63].

keine adäquaten laufenden Studien

In addition, there are no adequate registered ongoing trials that are comparing MAT with conservative management or even no therapy. Prospective, randomised controlled trials comparing MAT to the standard of care, with at least 50 patients in each treatment arm, are needed to adequately inform the relative effectiveness of MAT [23].

Limitations in the report

ausschließlich Fallserien mit mehr als 40 PatientInnen

The results of this review should be interpreted in light of the limitations. First, we only included case series with more than 40 patients to evaluate the safety of MAT. This may have systematically excluded relevant studies with smaller samples, and as such may have excluded case studies that report rare adverse events.

ausschließlich prosektive Studien

Second, we only included prospective studies, which excluded several large retrospective studies; however, retrospective studies are prone to internal validity concerns due to the limited information on or adjustment for confounding factors, selective recruitment of patients, and retrospective measurement of relevant outcomes.

Conclusion

gegenwärtige Evidenz erlaubt keine gesicherten Aussagen zu Wirksamkeit und Sicherheit

In the absence of comparative data with long-term follow-up, it is difficult to properly understand the relative risks and benefits of MAT compared to conservative management (or even no therapy). Furthermore, the identified single-arm trials were subject to small sample sizes, confounding by concomitant procedures, varied techniques used to secure allografts, and prior procedures. In consideration of these points, the comparative safety and effectiveness of MAT for the treatment of post-meniscectomy syndrome are highly uncertain.

9 Recommendation

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

Empfehlungsschema

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 not sufficient to prove that the assessed technology, MAT, is more effective and equally safe compared to the main comparator, conservative management. Furthermore, there was no evidence identified comparing MAT with no therapy.

keine ausreichend robuste Evidenz

New study results from comparative studies, with a minimum of 50 patients in each treatment arm, and with longer-term follow-up may change the recommendation; however, at this time there are currently only two ongoing trials of MAT, both of which are single arm trials. Therefore, the recommendation to fund MAT is unlikely to change on the basis of upcoming evidence.

Studien mit mehr PatientInnen + längerer Nachbeobachtung nötig, derzeit keine entsprechenden laufenden Studien

On the basis of the limited evidence demonstrating a benefit of MAT relative to the main comparator, as well as the lack of ongoing trials, inclusion in the catalogue is not recommended.

Aufnahme nicht empfohlen

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Meniscal allograft transplantation (MAT) for patients with post-meniscectomy syndrome: Results from observational studies

Author, year	Smith 2018 [23]	Abat 2013 [51]	Dirisamer 2012 [58]	Kempshall 2015 [54] (Parkinson 2016 [55])	Cole 2006 [52]	LaPrade 2010 [53]
Country	United Kingdom	Spain	Germany	United Kingdom	United States	United States
Sponsor	Arthritis Research UK	None	None	None	None	None
Intervention	MAT with soft tissue fixation	MAT with suture-only or bony fixation	MAT with bone block and/or soft tissue fixation for lateral, and soft tissue fixation for medial	MAT with soft tissue fixation	MAT with bone plug fixation	MAT with bone plug fixation
Comparator	Physiotherapy (including quadriceps control + strength and core strengthening programme for minimum 3 months)	None	None	None	None	None
Study design	Prospective cohort study with nested RCT[11]	Prospective case series[12]	Prospective case series	Prospective case series	Prospective case series	Prospective case series
Number of pts, n	Randomised: 10 vs 11 Non-randomised: 6 vs 9	88 (88 menisci)	80 (81 menisci)	60 (60 menisci)[13]	40 (45 menisci)	40 (40 menisci)
Inclusion criteria	Age 16-50, post-meniscectomy syndrome, surgeon believes patient may benefit from MAT	Post-meniscectomy syndrome	Post-meniscectomy syndrome	Age < 50 years, post-meniscectomy syndrome	Post-meniscectomy syndrome, well-preserved articular cartilage (Grade 0-II), normal knee alignment, stable joint (realignable + stabilisable joints by concomitant procedure were also included)	Post-meniscectomy syndrome

[11] A parallel group of patients that chose their treatment allocation was included in order to improve recruitment and external validity to "real world" patients.

[12] Study compared MAT with suture fixation and bony fixation. For this review, both study groups were combined into a single (MAT) arm.

[13] Only data from patients with good articular cartilage were extracted for this review. Data from 39 patients with severe cartilage damage were not extracted.

Author, year	Smith 2018 [23]	Abat 2013 [51]	Dirisamer 2012 [58]	Kempshall 2015 [54] (Parkinson 2016 [55])	Cole 2006 [52]	LaPrade 2010 [53]
Exclusion criteria	Previous cartilage modifying procedures (e.g. autologous chondrocyte implantation), significant exposed subchondral bone due to arthritis, concomitant ligament stabilisation, contraindication to anaesthetic, inability to adhere to trial procedures	Ahlbäck greater than Grade II[14], malalignment (defined as above 5° varus alignment, and above 7° valgus alignment)	NR	Inflammatory arthritis, advanced joint arthrosis in compartments distinct from the recipient compartment	Severe arthritic change (defined as more than isolated Outerbridge Grade III changes),[15] femoral condyle or tibial flattening, subchondral sclerosis	Patients with more than small localised areas of Outerbridge Grade IV chondromalacia, Grade IV "kissing lesions" of affected tibiofemoral surfaces
Postoperative treatment/ rehabilitation	Physiotherapy rehabilitation included hinged knee brace, crutches and toe touch weight bearing for 6 weeks, cycling after 6 weeks, strength training after 12 weeks.	Rehabilitation included partial weight bearing with a knee immobilizer after 3 weeks and full weight bearing after 6 weeks. Physiotherapy protocols were not described.	NR	Personalised physiotherapy rehabilitation included limited weight bearing for 6 weeks, weight bearing and strength training from 6 weeks, and sport-specific rehabilitation from 6 months	Rehabilitation included immediate weight bearing with crutches and hinged knee brace up to 6 weeks, jogging allowed at 12 weeks	Rehabilitation included knee brace, daily 325 mg aspirin, quadriceps and straight leg exercises for up to 6 weeks, weight bearing exercise after 6 weeks, full low-impact activity from 6 to 9 months
Number of prior surgeries per patient, n (range)	NR	Mean 1.69	NR	NR	Mean 2.7 (1 to 6)	All patients had undergone at least 1 prior ipsilateral knee surgery
Patients with concomitant interventions, n (%)	3 (18.8) vs 7 (0.0)[16]	37 (42.0)[17]	40 (50.5)[18]	21 (35.0)[19]	19 (47.5)[20]	21 (50.0)[21]

[14] Ahlbäck classification is a measure of osteoarthritis progression in the knee joint, with Grade I representing joint space narrowing of less than 3mm, and Grade V representing severe bone attrition of more than 10mm.

[15] Outerbridge classification of 0 represents normal cartilage, Grade II represents a partial thickness defect with fissures on the surface that do not reach subchondral bone or exceed 1.5 cm in diameter.

[16] Concomitant interventions included 2 high tibial osteotomies and 1 distal femoral osteotomy in the MAT group, and 7 knee braces in the physiotherapy group.

[17] Concomitant interventions included 18 ACL reconstruction, 15 microfracture, 9 chondral shaving, 3 hardware removal, 2 cartilage repair.

[18] The reported sum of concomitant and isolated interventions was 82 procedures. Thus, double-counting was suspected. Concomitant interventions included 15 ACL reconstructions and 23 high tibial osteotomies, 1 distal femoral osteotomy and one identifiable intervention.

[19] Concomitant interventions included 5 distal femoral osteotomy, 6 high tibial osteotomy, 6 revision ACL reconstruction, 1 meniscal repair (other compartment), 2 micro fracture, 2 Trufit Plug.

[20] Concomitant interventions included 3 osteochondral allografts, 3 osteochondral autografts, 2 microfractures, 2 osteochondritis dissecans fixations, 1 autologous chondrocyte implantation, 1 chondral debridement, 6 concurrent ligament reconstructions, 1 osteotomy.

[21] Concomitant procedures included 10 ACL reconstruction, 3 distal femoral osteotomy, 5 microfracture, 4 hardware removal, 3 osteoarticular allograft. Note: Some patients had more than one concomitant procedure.

Author, year	Smith 2018 [23]	Abat 2013 [51]	Dirisamer 2012 [58]	Kempshall 2015 [54] (Parkinson 2016 [55])	Cole 2006 [52]	LaPrade 2010 [53]
Age of patients, years (range)	Mean 29 (NR) vs 27 (NR)	Mean 37 (15 to 51)	Mean 40 (14 to 57)	Median 27 (16 to 48)	Mean 31 (16 to 48)	Mean 25 (20 to 40)
Time since menis-cectomy, years (range)	8.2 (NR) vs 7.6 (NR)	Mean 13.89 (NR)	NR	Mean 6.9 (1.0 to 25.4)	NR	Mean 4.5 (1 to 26)
Medial:lateral, n (%)	2 (12.5) : 14 (87.5) vs 6 (30.0) : 14 (70.0)	40 (45.5) : 48 (54.5)	55 (67.9) : 26 (32.1)	14 (23.3) : 46 (76.7)	25 (62.5) : 19 (37.5)	19 (47.5) : 21 (52.5)
Clinical classification	NR	Ahlbäck Grade I-II	NR	Up to ICRS Grade 3b[22]	Outerbridge Grade 0-II	Outerbridge Grade 0-IV
Type of transplant(s)	Fresh-frozen, non-irradiated allografts	Fresh-frozen (-80°C), non-irradiated, non-antigen-matched allografts	Fresh-frozen allografts	Fresh-frozen, non-irradiated allografts	Cryopreserved or fresh-frozen, non-irradiated allografts	Non-irradiated, cryopreserved (-20°C short term, -80°C long term) allografts
Characteristics of surgeon(s)	Senior surgeons familiar with technique, number of surgeons NR	Single surgeon (senior)	Two surgeons	Single surgeon	Single surgeon	Single surgeon (senior)
Sex, n male (%)	13 (81.2) vs. 13 (65)	56 (64.0)	NR	40 (66.7)	22 (61.1)	27 (67.5)
Follow-up, months (range)	12 vs. 12	Mean 60 (30 to 120)	Mean 45.4	Mean 35 (13 to 109)	Mean 33.5 (24 to 57)	Mean 30 (22 to 48)
Loss to follow-up, n (%)	3 (18.8) vs 2 (10.0)	0 (0.0)	19 (24.8) at 12 months	0 (0.0)[23]	1 (2.5)	6 (15.0)
Efficacy Outcomes						
Mean pain scores (VAS: lower scores indicate lower pain) (KOOS: higher scores indicate lower pain)	**KOOS – Pain** Mean difference in change after 12 months: 15.1 (95% CI 2.4 to 27.8, ***p=0.021***)	**VAS** Baseline: 6.59 Follow up (mean 60 months): 1.13 Mean change: -5.46, p=NR	NR	**KOOS – Pain** Baseline: 61.3 Follow-up (24 months): 83.6 Change: 22.3, ***p<0.001***	**KOOS – Pain** Baseline: 60.2 Follow-up (mean 33.5 months): 77.2 Change: 17, ***p<0.05*** **VAS** Baseline: 5.8 Follow-up (mean 33.5 months): 3.2 Mean change: -2.6, ***p<0.05***	NR
Function scores (higher scores indicate better function)	**Lysholm** Mean difference in change after 12 months: 7.3 (95% CI -4.5 to 19.1, p=0.22)	**Lysholm** Baseline: 64.46 Last follow-up (mean 60 months): 90.23 Mean change: 26.76, p>0.05	**Lysholm** Baseline: 43 Last follow-up (mean 48 months): 69[24] Mean change: 26, p=NR	**Lysholm** Baseline: 58.6 Follow-up (24 months): 80.2 Mean change: 21.6, ***p<0.001***	**Lysholm** Baseline: 52.4 Follow-up (mean 33.5 months): 71.6 Mean Change: 19.2, ***p<0.05***	**Cincinnatti knee rating** Baseline: 53.7 Follow-up (mean 30 months): 75.3 Mean change: 21.6, ***p<0.001***

[22] International Cartilage Repair Society (ICSR) cartilage Grade 3b involving less than 1cm^2 was defined as "good" cartilage status by the study authors.

[23] Applies for a follow-up of 12 months.

[24] Measured in 31 patients.

Author, year	Smith 2018 [23]	Abat 2013 [51]	Dirisamer 2012 [58]	Kempshall 2015 [54] (Parkinson 2016 [55])	Cole 2006 [52]	LaPrade 2010 [53]
Function scores (higher scores indicate better function) *(continuation)*	**IKDC** Mean difference in change after 12 months: 8.44 (95% CI -3.6 to 20.5, p=0.16) **KOOS – Composite** Mean difference in change after 12 months: 11.9 (95% CI 1.1 to 22.7, ***p=0.034***) **KOOS – ADL** Mean difference in change after 12 months: 18.2 (95% CI 6.0 to 30.5, ***p=0.005***) **KOOS – Sports** Mean difference in change after 12 months: 14.0 (95% CI -2.7 to 30.8, p=0.098)	**Tegner** Baseline: 3 Last follow-up (mean 60 months): 6 Mean change: 3, p>0.05	**Tegner** Baseline: 4 Last follow-up (mean 36 months): 7[25] Mean change: 3, p=NR	**Tegner** Baseline: 2 Follow-up (24 months): 4 Mean change: 2, ***p<0.05*** **IKDC** Baseline: 43.1 Follow-up (24 months): 68.8 Mean change: 25.7, ***p<0.001*** **KOOS – ADL** Baseline: 71.4 Follow-up (24 months): 90.2 Mean change: 18.8, ***p<0.001*** **KOOS – Sports** Baseline: 30.8 Follow-up (24 months): 60.0 Mean change: 29.2, ***p<0.001***	**Tegner** Baseline: 5 Follow-up (mean 33.5 months): 6.5 Mean change: 1.5, ***p<0.05*** **IKDC** Baseline: 46.2 Follow-up (mean 33.5 months): 64.1 Mean change: 17.9, ***p<0.05*** **KOOS – ADL** Baseline: 80.1 Follow-up (mean 33.5 months): 87.8 Mean change: 7.8, ***p<0.05*** **KOOS – Sports** Baseline: 30.1 Follow-up (mean 33.5 months): 51.6 Mean change: 21.5, ***p<0.05***	**IKDC** Baseline (mean): 54.3 Follow-up (mean 30 months): 72 Mean change: 17.7, ***p<0.001***
Quality of life scores (higher scores indicate better health)	**KOOS – QoL** Mean difference in change after 12 months: 12.6 (95% CI -0.4 to 25.6, p=0.058)	NR	NR	**KOOS – QoL** Baseline: 28.9 Follow-up (24 months): 52.7 Mean change: 23.8, ***p<0.001***	**KOOS – QoL** Baseline: 27.5 Follow-up (mean 33.5 months): 50.4 Mean change: 23.0, p=0.16	NR
Return to daily activities	NR	NR	NR	NR	NR	NR
Necessity of total joint replacement	NR	NR	At mean 36 months: 2 (2.5)	NR	At mean 33.5 months: 3 (7.5)[26]	NR
Patient satisfaction (higher scores indicate greater satisfaction)	NR	Mean VAS score at last follow-up (mean 60 months): 3.7 ± 0.3 (out of 4)	NR	NR	Mean VAS score at last follow-up (mean 33.5 months): 7.63 (out of 10) 75.0% (27/36) were completely or mostly satisfied with procedure at last follow-up (mean 33.5 months)	NR

[25] Measured in an unclear number of patients.

[26] Two patients needed a total knee arthroplasty, one patient needed a unicompartmental knee replacement.

Author, year	Smith 2018 [23]	Abat 2013 [51]	Dirisamer 2012 [58]	Kempshall 2015 [54] (Parkinson 2016 [55])	Cole 2006 [52]	LaPrade 2010 [53]
Safety Outcomes						
Complications, n (%)	5 (38.5) vs 1 (5.6) MAT: complications not adequately defined Physio: 1 thigh bruising due to knee brace	20 (22.7) 5 arthrofibrosis 4 infection 11 meniscus tear	12 (19.7)[27] 6 MAT re-fixations 1 partial meniscectomy 1 MAT removal 1 new MAT 2 joint replacements 1 post-surgical infection	18 (30.0): 8 meniscus tear, 1 haematoma, 1 common peroneal nerve palsy, 4 painful suture removal, 4 second look scope	0 (0.0)	7 (20.6): 1 infection, 1 low-Grade synovitis, 5 meniscal tears, (Average 24 months to re-injury)
Transplant failure, n (%)	NR	5 (5.7)[28]	2 (3.3)[29]	1 (1.7)[30] within 2 years (2-year survival: 97.9%)	3 (7.7)[31]	NR
Time to failure, months (range)	NR	NR	NR	NR	Mean 15 (9 to 21)	NR
Re-operation, n (%)	4 (30.8)[32] vs N/A	20 (22.7)[33]	12 (19.7)[34]	18 (30.0)[35]	3 (7.7)[36]	7 (20.6)[37]
Procedure-related mortality, n (%)	0 (0.0)	0 (0.0)	NR	0 (0.0)	0 (0.0)	0 (0.0)

***Abbreviations: ADL** = activities of daily living; CT = (non-randomised) controlled trial; ICRS = International Cartilage Repair Society; IKDC = International Knee Documentation Committee; KOOS = Knee injury and Osteoarthritis Outcome Score; MAT = meniscal allograft transplantation; N/A = not applicable; NR = not reported; QoL = quality of life; RCT = randomised controlled trial; VAS = visual analogue scale.*

[27] Complications were exclusively stated in terms of re-operations.

[28] Failure was defined as removal of the graft.

[29] Failure was defined as the removal or replacement of the graft. Joint replacements were not counted.

[30] Failure was defined as removal of the graft or progression to arthroplasty.

[31] Failure was defined as progression to arthroplasty. Four additional patients had "clinical failure" due to worsening IKDC scores, but did not have the graft removed or joint replaced.

[32] Four patients had subsequent arthroscopy.

[33] All complications required a secondary operation, including 5 arthroscopic arthrolysis, 4 arthroscopic lavage, and 6 MAT re-fixation, and 5 MAT removals.

[34] All complications required a secondary operation, including 6 MAT re-fixations, 1 partial meniscectomy, 1 MAT removal, 1 new MAT, 2 joint replacements, 1 post-surgical infection.

[35] All complications required a secondary operation, including 4 second-look arthroscopies, 6 MAT re-fixation, 1 MAT trim, and 1 MAT removal.

[36] Three patients required total knee replacement.

[37] Five patients required meniscectomy to treat a meniscal tear, 1 patient required arthroscopic synovectomy to treat low-grade synovitis, 1 arthroscopic irrigation and debridement of infection.

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. Disagreements were settled via consensus. The ROBNS-I tool was used to evaluate the risk of bias in the non-randomised comparative study [59]. A more detailed description of the criteria used to assess the internal validity of the non-randomised comparative trial can be found from the Cochrane Collaboration [59], and in the Guidelines of EUnetHTA [64]. Single arm studies were appraised according to the Institute of Health Economics (IHE) appraisal tool for case series studies [14].

Table A-2: Risk of bias – study level (non – randomised studies comparing meniscus allograft transplantation versus physiotherapy), see [59]

Study reference/ID	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of intervention	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Smith 2018 [23] (Smith 2016 [65])[38]	Serious[39]	Moderate[40]	Low	Moderate[41]	Serious[42]	Serious[43]	Serious[44]	Serious	-

[38] Additional details about the study design were provided in the RCT protocol [65], therefore, both publications were used to assess the risk of bias.

[39] Distribution of key confounding factors (e.g. subsequent procedures) were not comprehensively evaluated or adjusted for in the analysis.

[40] A small number of patients (n=4) were excluded because the treating surgeon did not think they would benefit from the intervention, no justification was provided.

[41] Inadequate information was provided about the use, or not, of subsequent procedures and interventions, or adherence to post-operative physiotherapy in the MAT group.

[42] There was a large proportion of missing data, which is likely to have affected the results.

[43] Research associates that assessed post-operative outcomes and conducted the analyses were blinded to the treatment allocation; however, patients could not be blinded to the intervention. As the outcomes are subjective, they are likely to be influenced by knowledge of the treatment allocation.

[44] The primary outcomes of interest for this review were reported in accordance with the protocol; Additional outcomes, including cartilage thickness and loss, were defined in the protocol but not reported in the clinical trial publication. Complications were poorly defined in the protocol, and poorly reported in the trial publication.

Table A-3: Risk of bias – study level (case series), see [14]

Study reference/ID	Abat 2013 [51]	Dirisamer 2012 [58]	Kempshall 2015 [54] (Parkinson 2016 [55])	Cole 2006 [52]	LaPrade 2010 [53]
Study objective					
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	Yes	No	Yes	Yes	Yes
Study population					
2. Are the characteristics of the participants included in the study described?	Yes	No[45]	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	No	No	No	No	No
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	Yes	No[46]	Yes	Yes	Yes
5. Were participants recruited consecutively?	Yes	Yes	Yes	Yes	Yes
6. Did participants enter the study at similar point in the disease?	Yes	Unclear[47]	Yes	Yes	No
Intervention and co-intervention					
7. Was the intervention clearly described in the study?	Yes	Yes	Yes	Yes	Yes
8. Were additional interventions (co-interventions) clearly reported in the study?	Yes	Yes	Yes	Yes	Yes
Outcome measures					
9. Are the outcome measures clearly defined in the introduction or methods section?	Yes	No[48]	Yes	Yes	Yes
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	No[49]	No	No[50]	Yes	Yes
11. Were outcomes measured before and after intervention?	Yes	Yes	Yes	Yes	Yes
Statistical Analysis					
12. Were the statistical tests used to assess the relevant outcomes appropriate?	No	No[51]	Yes	Yes	Yes
Results and Conclusions					
13. Was the length of follow-up reported?	Yes	Yes	Yes	Yes	Yes
14. Was the loss to follow-up reported?	Yes	Yes	No[52]	Yes	Yes
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	Yes	No	Yes	No	No
16. Are adverse events reported?	Yes	Yes	Yes	Yes	Yes

[45] There were several characteristics missing (e.g. sex, information on postoperative treatment and number of prior surgeries).

[46] Exclusion criteria were not stated.

[47] Clinical classification not stated.

[48] Study did not provide a clear section on methods that described outcomes measures.

[49] The method for capturing complications was not adequately reported. It is unclear whether all relevant complications were reported.

[50] The method for capturing complications was not adequately reported. It is unclear whether all relevant complications were reported.

[51] Study did not conduct statistical tests.

[52] It is not clear if all data were available for the 2-year follow-up.

Study reference/ID	Abat 2013 [51]	Dirisamer 2012 [58]	Kempshall 2015 [54] (Parkinson 2016 [55])	Cole 2006 [52]	LaPrade 2010 [53]
17. Are the conclusions of the study supported by results?	Yes	No	No	No	Yes
Competing interest and source of support					
18. Are both competing interest and source of support for the study reported?	No	No	Yes	No	No
Overall risk of bias	**Moderate**	**Serious**	**Moderate**	**Moderate**	**Moderate**

Table A-4: Evidence profile: efficacy and safety of meniscal allograft transplantation compared to conservative management in patients with post-meniscectomy syndrome

Quality assessment							Summary of findings				
							Number of patients		Effect		
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MAT	Conservative management	Relative (95% CI)	Absolute (95% CI)	Quality
Efficacy											
Pain: change in pain score (follow up: 12 months; assessed with: KOOS – Pain Subscale; Scale from: 0 to 100 (better))											
1	observational study [53]	serious [54]	N/A (only one trial)	not serious	serious [55]	none	13	18	-	MD 15.1 points higher (2.4 higher to 27.8 higher)	⊕◯◯◯ VERY LOW
Function: Change in function score (follow up: 12 months; assessed with: Lysholm; Scale from: 0 to 100 (better))											
1	observational study [53]	serious [54]	N/A (only one trial)	not serious	serious [55]	none	13	18	-	MD 7.3 points higher (4.5 lower to 19.1 higher)	⊕◯◯◯ VERY LOW
Function: Change in function score (follow up: 12 months; assessed with: IKDC; Scale from: 0 to 100 (better))											
1	observational study [53]	serious [54]	N/A (only one trial)	not serious	serious [55]	none	13	18	-	MD 8.44 points higher (3.6 lower to 20.5 higher)	⊕◯◯◯ VERY LOW
Function: Change in function score (follow up: 12; assessed with: KOOS-Composite; Scale from: 0 to 100 (better))											
1	observational study [53]	serious [54]	N/A (only one trial)	not serious	serious [55]	none	13	18	-	MD 11.9 points higher (1.1 higher to 22.7 higher)	⊕◯◯◯ VERY LOW
Function: Change in function score (follow up: 12; assessed with: KOOS-ADL; Scale from: 0 to 100 (better))											
1	observational study [53]	serious [54]	N/A (only one trial)	not serious	serious [55]	none	13	18	-	MD 18.2 points higher (6 higher to 30.5 higher)	⊕◯◯◯ VERY LOW
Function: Change in function score (follow up: 12; assessed with: KOOS-Sports; Scale from: 0 to 100 (better))											
1	observational study [53]	serious [54]	not serious	not serious	serious [55]	none	13	18	-	MD 14 points higher (2.7 lower to 30.8 higher)	⊕◯◯◯ VERY LOW
Necessity of total joint replacement: not measured											

[53] Prospective cohort study with nested RCT

[54] There was a serious risk of bias due to possible confounding, missing data, and the use of un-blinded patient-reported outcome measures

[55] Sample size of the prospective cohort study with nested RCT is below optimal information size. Conventional sample size calculation required 50 patients in each study arm

Quality assessment							Summary of findings				
							Number of patients		Effect		
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MAT	Conservative management	Relative (95% CI)	Absolute (95% CI)	Quality
Safety											
Complications (follow up: 12 months)											
1	observational study [53]	serious [54,56]	N/A (only one trial)	not serious	serious [55,57]	none	5/13 (38.5%)	1/18 (5.6%)	RR 6.92 (0.91 lower to 52.45 higher)[58]	329 more per 1,000 (from 5 fewer to 1,000 more)	⨁◯◯◯ VERY LOW
Complications (follow up: range 13 months to 120 months)											
5	observational studies [59]	serious [56,60,61]	serious [62]	not serious	serious [57]	none	Overall complications: 57/282 (20.2%, range 0.0 to 38.5%) Median complication rate: 21.7%				⨁◯◯◯ VERY LOW
Transplant failure (follow up: range 13 months to 120 months; assessed with: removal or replacement of the graft, or progression to TKA)											
4	observational studies [63]	Serious [61,62,64]	not serious	not serious	serious [57,65]	none	Overall transplant failures: 11/248 (4.4, range 1.7% to 7.7%) Median transplant failure rate: 4.5%				⨁◯◯◯ VERY LOW

Abbreviations: *ADL = activities of daily living; IKDC = International Knee Documentation Committee; KOOS = Knee injury and Osteoarthritis Outcome Score; N/A = not applicable*

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

[56] The method for capturing complications was not adequately reported. It is unclear whether all relevant complications were reported

[57] No estimates of the random variability in the reported outcome data

[58] Calculated manually by using 'MedCalc' (http://www.medcalc.org/calc/relative_risk.php)

[59] 5 case series

[60] Single-centre trials (applies for single-arm studies/case series)

[61] Unclear if all follow-up data were available

[62] Heterogeneity in reported rates across studies

[63] 4 case series

[64] Thresholds for failure were poorly defined

[65] Low event rates and small sample sizes

Applicability table

Table A-5: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The broad patient characteristics in relation to age, sex, cartilage status and indication (i.e. post-meniscectomy syndrome) were relatively homogenous across studies. However, there was considerable variation in time from meniscectomy to surgery for MAT (meniscal allograft transplantation), and the proportion of medial or lateral menisci transplanted. Overall, the populations in the included studies broadly reflect the target population in clinical practice, i.e. mostly young patients (mean age 33, range 14-57), with post-meniscectomy syndrome and no significant chondral defects (i.e. Outerbridge Grade 0-II, Ahlbäck Grade I).
Intervention	The intervention was conducted via arthroscopy in all but one study, whereby the authors used a combination of arthroscopy and mini-arthrotomy. Allografts were predominantly non-irradiated fresh-frozen; a minority of allografts across the included studies were cryopreserved. The technique used to fix the allografts differed between studies (bone-plug or soft-tissue). All patients received post-operative rehabilitation following surgery. There was significant heterogeneity in the number and type of concomitant interventions conducted in the observational trials. It is unclear how reflective these concomitant interventions are of an Austrian post-meniscectomy population.
Comparators	International guidelines on the recommended use of MAT are not currently available. The primary purpose of meniscal allograft transplant in the context of post-meniscectomy syndrome is symptom control, and to delay the need for total knee arthroplasty. In this context, the most suitable alternatives to MAT are conventional management or no treatment. The comparator used in the observational trial was personalised physiotherapy, including quadriceps control and core strength training for a minimum of three months. Symptomatic management, including knee injections, non-steroidal anti inflammatory drugs and other pain medication were not described. Conservative management protocols to treat post-meniscectomy syndrome are often based on specific patient requirements. Therefore, the comparator is likely to reflect the likely physiotherapy strategy for Austrian patients.
Outcomes	The comparative study reported most of the critical/important clinical outcomes, with the exception of graft failure and necessity of total joint replacement. It is possible that there were no reported cases of either outcome due to the short follow-up period (12 months), however this was not stated. Some safety outcomes, such as procedure-related complications, were not recorded in a comprehensive or consistent way. Follow-up times were reported variably. Efficay outcomes from the comparative study were reported at 12 months, therefore cannot inform the long-term efficacy of MAT in the proposed population. The single-arm trials reported safety outcomes at an average of 44 months (range 13 to 120).
Setting	The included comparative study was conducted in a single centre in the United Kingdom (UK). The allografts used in the study were supplied by the National Health Service Blood and Transplant (UK), or JRF Ortho (United States). The single arm studies included for safety outcomes were conducted in Spain, Germany, the United Kingdom, and the United States. All studies were conducted in teaching hospitals, by orthopaedic surgeons. The settings in which MAT was conducted in the included trials is largely reflective of the intended use of the procedure in clinical practice.

***Abbreviations**: MAT = meniscal allograft transplantation; UK = United Kingdom.*

List of ongoing randomised controlled trials

Table A-6: List of ongoing trials of meniscus allograft transplantation

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT01059409	Patients with post-meniscectomy Estimated enrollment = 120 participants	MAT	None (case series with 120 patients)	"Function" Subscale in the Koos Scale	September 2017	Assistance Publique – Hôpitaux de Paris
NTR6630	Patients with post-meniscectomised, symptomatic knee Estimated enrollment = 119 participants	MAT	None (case series with 119 patients)	Overview of patients' previous operations, patients' satisfaction	October 2017	Haaglanden Medical Center, The Hague

Literature search strategies

Search strategy for The Cochrane Library

Search Date: 22/12/2017	
ID	Search
#1	meniscectom* (Word variations have been searched)
#2	meniscectom* (Word variations have been searched)
#3	MeSH descriptor: [Tibial Meniscus Injuries] explode all trees
#4	MeSH descriptor: [Meniscus] explode all trees and with qualifier(s): [Injuries – IN, Surgery – SU]
#5	MeSH descriptor: [Menisci, Tibial] explode all trees and with qualifier(s): [Surgery – SU]
#6	post-meniscectom* near syndrome* (Word variations have been searched)
#7	"postmeniscectomy" (Word variations have been searched)
#8	"post-meniscectomy" (Word variations have been searched)
#9	menisc* near (deficien* or insufficien*) (Word variations have been searched)
#10	symptomatic near menisc* (Word variations have been searched)
#11	"joint line pain*" (Word variations have been searched)
#12	allogenic menisc* transplant* (Word variations have been searched)
#13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#14	MeSH descriptor: [Allografts] explode all trees
#15	MeSH descriptor: [Composite Tissue Allografts] explode all trees
#16	MeSH descriptor: [Transplantation, Homologous] explode all trees
#17	allograft* or allogeneic or homograft* (Word variations have been searched)
#18	#14 or #15 or #16 or #17
#19	MeSH descriptor: [Menisci, Tibial] explode all trees
#20	MeSH descriptor: [Meniscus] explode all trees
#21	menisc* (Word variations have been searched)
#22	MeSH descriptor: [Knee] explode all trees
#23	knee* (Word variations have been searched)
#24	#19 or #20 or #21 or #22 or #23
#25	#18 and #24v
#26	MeSH descriptor: [Meniscus] explode all trees and with qualifier(s): [Transplantation – TR]
#27	MeSH descriptor: [Menisci, Tibial] explode all trees and with qualifier(s): [Transplantation – TR]
#28	MAT:ti,ab,kw (Word variations have been searched)
#29	#25 or #26 or #27 or #28
#30	#13 and #29
#31	(menisc* or knee*) near (allograft* or allogeneic or homograft*) (Word variations have been searched)
#32	Menisc* Allograft* Transplant* (Word variations have been searched)
#33	#30 or #31 or #32
Total: 85 Hits	

Search strategy for Ovid Medline

Database: Ovid MEDLINE(R) <1946 to December Week 2 2017>, Ovid MEDLINE(R) Epub Ahead of Print <December 21, 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 21, 2017>, Ovid MEDLINE(R) Daily Update <December 21, 2017>	
Search Strategy:	
1	menis#e#tom*.mp. (3114)
2	(menisc* adj5 remov*).mp. (353)
3	exp Tibial Meniscus Injuries/ (4465)
4	exp *Meniscus/in, su [Injuries, Surgery] (2317)
5	exp *Menisci, Tibial/in, su [Injuries, Surgery] (2295)
6	post*menis#e#tom* syndrome*.mp. (4)
7	post?menis#e#tom*.mp. (70)
8	(menisc* adj3 (deficien* or insufficien*)).mp. (183)
9	(symptomatic adj3 menisc*).mp. (241)
10	joint line pain*.mp. (47)
11	allogenic menisc* transplant*.mp. (4)
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (7515)
13	exp Allografts/ (6004)
14	exp Composite Tissue Allografts/ (124)
15	exp Transplantation, Homologous/ (87630)
16	(allograft* or allogeneic or homograft*).mp. (126772)
17	13 or 14 or 15 or 16 (170020)
18	exp Menisci, Tibial/ (7400)
19	exp Meniscus/ (7483)
20	menisc*.mp. (17733)
21	exp Knee/ (13955)
22	knee*.mp. (162462)
23	18 or 19 or 20 or 21 or 22 (167769)
24	17 and 23 (3430)
25	((menisc* or knee*) adj5 (allograft* or allogeneic or homograft*)).mp. (938)
26	Menisc* Allograft* Transplant*.mp. (299)
27	MAT.ti,ab. (8475)
28	exp *Meniscus/tr [Transplantation] (397)
29	exp *Menisci, Tibial/tr [Transplantation] (394)
30	24 or 25 or 26 or 27 or 28 or 29 (11868)
31	12 and 30 (459)
32	remove duplicates from 31 (387)
Search date: 22/12/2017	

Search strategy for Embase

No.	Query Results	Results	Date
#27	#10 AND #26	482	22 Dec 2017
#26	#21 OR #22 OR #23 OR #24 OR #25	13,500	22 Dec 2017
#25	'meniscal transplantation'/exp	349	22 Dec 2017
#24	mat:ti,ab	9,228	22 Dec 2017
#23	'menisc* allograft* transplant*'	304	22 Dec 2017
#22	(menisc* OR knee*) NEAR/5 (allograft* OR allogeneic OR homograft*)	1,102	22 Dec 2017
#21	#15 AND #20	4,268	22 Dec 2017
#20	#16 OR #17 OR #18 OR #19	206,536	22 Dec 2017
#19	knee*	203,416	22 Dec 2017
#18	'knee'/exp	59,379	22 Dec 2017
#17	menisc*	20,780	22 Dec 2017
#16	'knee meniscus'/exp	7,555	22 Dec 2017
#15	#11 OR #12 OR #13 OR #14	207,882	22 Dec 2017
#14	allograft* OR allogeneic OR homograft*	184,673	22 Dec 2017
#13	'allotransplantation'/exp	34,755	22 Dec 2017
#12	'composite graft'/exp	2,243	22 Dec 2017
#11	allograft'/exp	36,957	22 Dec 2017
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	4,996	22 Dec 2017
#9	allogenic menisc* transplant*':ti,ab	4	22 Dec 2017
#8	'joint line pain*':ti,ab	55	22 Dec 2017
#7	(symptomatic NEAR/3 menisc*):ti,ab	226	22 Dec 2017
#6	(menisc* NEAR/3 (deficien* OR insufficien*)):ti,ab	196	22 Dec 2017
#5	post*menis*e*tom*:ti,ab	78	22 Dec 2017
#4	'post*menis*e*tom* syndrome*':ti,ab	8	22 Dec 2017
#3	(menisc* NEAR/5 remov*):ti,ab	419	22 Dec 2017
#2	menis*e*tom*:ti,ab	3,461	22 Dec 2017
#1	'meniscectomy'/exp	2,922	22 Dec 2017

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

Search Date: 22/12/2017	
#1	MeSH DESCRIPTOR Allografts EXPLODE ALL TREES
#2	MeSH DESCRIPTOR Composite Tissue Allografts EXPLODE ALL TREES
#3	MeSH DESCRIPTOR Transplantation, Homologous EXPLODE ALL TREES
#4	(allograft* OR allogeneic OR homograft*)
#5	#1 OR #2 OR #3 OR #4
#6	MeSH DESCRIPTOR Menisci, Tibial EXPLODE ALL TREES
#7	MeSH DESCRIPTOR Meniscus EXPLODE ALL TREES
#8	(menisc*)
#9	MeSH DESCRIPTOR Knee EXPLODE ALL TREES
#10	(Knee*)
#11	#6 OR #7 OR #8 OR #9 OR #10
#12	#5 AND #11
#13	((menisc* OR knee*) NEAR (allograft* OR allogeneic OR homograft*))
#14	(Menisc* Allograft* Transplant*)
#15	(MAT)
#16	MeSH DESCRIPTOR Meniscus EXPLODE ALL TREES WITH QUALIFIER TR
#17	MeSH DESCRIPTOR Menisci, Tibial EXPLODE ALL TREES WITH QUALIFIER TR
#18	(post*menis*e*tom*)
#19	(menisc* NEAR (deficien* or insufficien*))
#20	(symptomatic NEAR menisc*)
#21	(joint line pain*)
#22	(allogenic menisc* transplant*)
Total:55 Hits	

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