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Meniscal allograft transplantation in a symptomatic meniscal deficient knee: a systematic review

Nick A. Smith · Nicola MacKay · Matthew Costa · Tim Spalding

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Abstract
Purpose The primary objective of this study was to perform an updated systematic review and meta-analysis of meniscal allograft transplantation using patient reported outcome measures at final follow-up as the outcome tool. The secondary objective was to provide an up to date review of the indications, associated procedures, operative technique, rehabilitation, failures, complications, radiological outcomes, and graft healing.
Methods Medline, Embase and CENTRAL databases, trials registries, and Web-of Science were searched for studies using pre-defined eligibility criteria. Included studies were reviewed with Lysholm, International Knee Documentation Committee (IKDC) and Tegner scores, failures and complications pooled. Studies were also qualitatively assessed.
Results There were 1,332 patients (1,374 knees) in 35 studies eligible for analysis. The mean follow-up was 5.1 years. Across all studies, Lysholm scores improved from 55.7 to 81.3, IKDC scores from 47.0 to 70.0, and Tegner activity scores from 3.1 to 4.7 between pre-operative and final follow-up assessments, respectively. The mean failure rate across all studies was 10.6 % at 4.8 years, and complication rate was 13.9 % at 4.7 years. There is a high risk of bias across the studies due to study design and missing outcomes.
Conclusion Based on current evidence, meniscal allograft transplantation appears to be an effective intervention for patients with a symptomatic meniscal deficient knee. This should ideally be confirmed with a randomised controlled trial. There is not currently enough evidence to determine whether it is chondroprotective.

Keywords Meniscal allograft transplantation · Systematic review · Meniscectomy · Patient reported outcome measures

N. A. Smith (✉)
Clinical Sciences Research Laboratories, University of Warwick, Clifford Bridge Road, Coventry CV2 2DX, UK
e-mail: nickasmith@doctors.net.uk

N. MacKay
Western Infirmary Glasgow, Dumbarton Road, Glasgow G11 6NT, UK

M. Costa
Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry CV4 7AL, UK

T. Spalding
University Hospitals Coventry and Warwickshire, 5th floor UHCW, Clifford Bridge Road, Coventry CV2 2DX, UK

Introduction

The menisci have important functions in the knee including load sharing and joint stability [30, 44, 53]. Meniscal tears are the most common knee injury, with an incidence of 61 per 100,000 per year [3]. With the increased recognition of the importance of the menisci, treatment has been aimed at preserving menisci where possible [31]. However, the blood supply diminishes away from the periphery of the meniscus, which decreases the chances of a successful repair [36]. The mean failure rate of meniscal repairs was found to be 23.1 % in a recent meta-analysis [35]. Patients with a tear that is not repairable, or have had a failed repair undergo a meniscectomy.

The consequences of meniscectomy have been widely reported. A systematic review by Papalia et al. [38] found that the mean prevalence of osteoarthritis (OA) was 53.5 % (range 16–92.9 %) at a mean of 7.4 years following

meniscectomy. In the same study, 39.6 % of post-meniscectomy patients had OA diagnosed radiologically, compared with 6.4 % in non-operated contralateral knees (controls). It has been shown that the amount of meniscus removed is the most important predictor for the development of OA [31, 38].

Meniscal allograft transplantation (MAT) was first performed in 1984 [34]. It has since been advocated for the treatment of post-meniscectomy symptoms, which can consist of pain, swelling, and loss of function [12, 27]. In 2011 (search performed in January 2010), a systematic review and meta-analysis showed an improvement in symptoms and function, but highlighted a lack of good-quality studies [12]. Since then, there have been a number of further studies and longer follow-up of some older studies has been reported. The primary objective of this study was to perform an updated systematic review of MAT to reflect the clinical outcomes of recently published studies. The secondary objective was to identify trend changes by systematically reviewing the indications, associated procedures, operative technique, rehabilitation, failures, complications, radiological outcomes, and graft healing.

Materials and methods

Quality of methodology

This study has been reported in accordance with the PRISMA statement for reporting systematic reviews [28]. Details of the systematic review protocol can be found at http://www.crd.york.ac.uk/PROSPERO (CRD42014009134).

Eligibility criteria

Study type

- Any case series or clinical comparative study (including randomised controlled trials) written in the English language. Biomechanical studies, case reports, and systematic reviews that do not contain new patient data were excluded.

Participants

- Any human of any age.

Intervention

- Meniscal allograft transplantation using any allograft preserving method and any grafting type.
- Any rehabilitation regime post-operatively.

Comparator

- If a comparator group exists, it should be a reasonable alternative treatment to MAT or a difference in MAT methodology, for example different allograft fixation technique.

Outcome measures

- A study must include a PROM at a minimum of 1 year post-operatively for every patient. Commonly used PROMs include Lysholm, International Knee Documentation Committee (IKDC), and Tegner activity index, but any other PROM was accepted.

Search strategy

A search was undertaken for both published and unpublished studies. The design of the search strategy was sensitivity maximising in order to reduce the risk of missing eligible studies. The published search strategy was developed using a combination of keywords and 'subject headings', which were exploded to maximise the inclusion of potentially relevant studies. The databases of Medline (Ovid), Embase (Ovid) and the Cochrane library (CENTRAL) were searched (Tables 1, 2, 3, respectively). The references of eligible studies and previous systematic reviews were searched for other potentially relevant studies. Unpublished studies were searched according to recommendations from a recent article published in the British Medical Journal [9]. The World Health Organisation International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) and Clinical Trials Registry (http://clinicaltrials.gov) were searched for ongoing or complete trials. The 'Web-of Science' (http://thomsonreuters.com/web-of-science/) was searched for conference proceedings.

Selection and appraisal method

Figures 1 and 2 show flow diagrams of the selection processes for published and unpublished studies, respectively.

Table 1 Search strategy for Ovid Medline (1946 to March week 3 2014), performed on the April 2, 2014

1	Exp Menisci, Tibial/	6,007
2	Menisc*.mp.	10,957
3	(Allograft* or transplant*).mp.	519,356
4	1 or 2	10,957
5	3 and 4	796
6	(Case series or compar* or randomi* or clinical or trial*).mp.	6,121,278
7	5 and 6	469
8	Limit 7 to (english language and humans)	338

Table 2 Search strategy for Ovid Embase (1947–2014 week 13), performed on April 2, 2014

1	Exp knee meniscus/	6,088
2	Menisc*.mp.	16,114
3	(Allograft* or transplant*).mp.	686,442
4	1 or 2	16,114
5	3 and 4	1,083
6	Exp meniscal transplantation/	171
7	5 or 6	1,083
8	(Case series or compar* or randomi* or clinical or trial*).mp.	10,146,373
9	7 and 8	677
10	Limit 9 to (human and english language)	486

Table 3 Search strategy for CENTRAL, performed on the April 2, 2014

1	Menisc*:ti,ab,kw (word variations have been searched)	498
2	MeSH descriptor: [Menisci, Tibial] explode all trees	185
3	Allograft* or transplant*	22,073
4	(#1 or #2) and #3	38

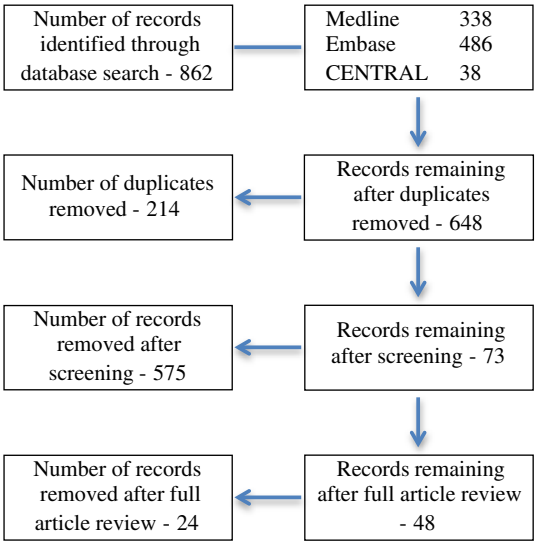

Fig. 1 Flow diagram for the appraisal of published studies

Results of the database searches were transferred into EndNote, and duplicates were automatically discarded. Our pre-defined criteria were used to assess the eligibility of the remaining studies from their title and abstract. The full papers of the remaining studies were then reviewed.

Data from eligible studies were extracted, and studies that contained some or all of the same patients were grouped. In order to reduce the risk of duplicate publication bias [23], the study with the longest mean follow-up was included in the analysis, with the other studies cited in the references but excluded from further analysis.

Failures and complications were collected as reported by each study. If failures were not specifically defined, a failure was considered to be either the complete removal of the allograft, revision MAT, or conversion to joint replacement. If complications were not defined, a complication was considered to be any reported adverse event that the patient experiences.

Results

There were 1,332 patients (1,374 knees) in 35 studies included in this systematic review (Table 4). There were no prospective controlled trials (randomised or otherwise), eligible for inclusion. The follow-up range across all studies was from 1 to 20 years, with a mean of 5.1 years. The youngest and eldest patients were 13 [37] and 69 [47] years old, respectively, with a mean age across all studies of 33.7 years. Of the 1,332 patients, 762 were male and 343 were female; the gender was not reported for 227 patients. There were 587 medial and 657 lateral allografts across all studies.

Patient reported outcome measures

The Lysholm score is graded from 0 (worst) to 100 (best) and was designed to assess outcomes following knee ligament surgery [50]. It was the most commonly used PROM,

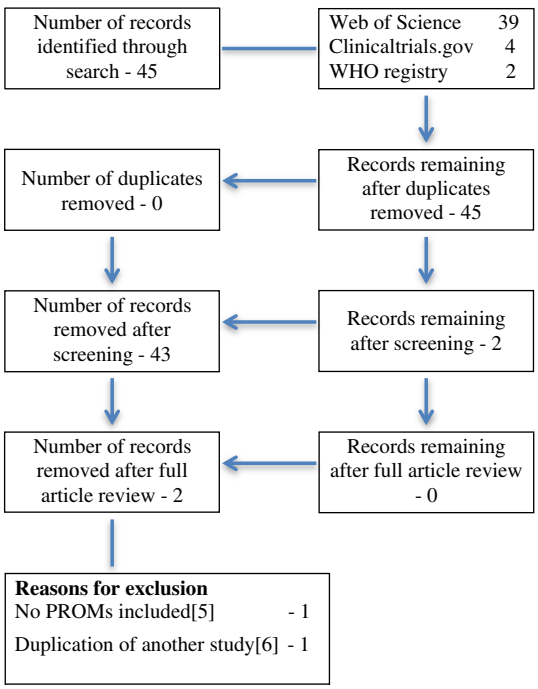

Fig. 2 Flow diagram for the appraisal of unpublished studies

Table 4 Summary of included studies

Author(s)	Year	Study type	Participants	PROM
Chalmers et al. [8]	2013	Retrospective case series	13	Lysholm, IKDC,
Stone et al. [48]	2013	Case series	68	IKDC, Tegner, WOMAC
Hardy et al. [18]	2013	Retrospective case series	22	Lysholm, IKDC, KOOS
Abat et al. [1]	2012	Parallel prospective case series	88	Lysholm
Binnet et al. [5]	2012	Case series	4	Lysholm, Tegner
Carter [7]	2012	Prospective case series	40	Lysholm, IKDC
Kim et al. [25]	2012	Retrospective case series	106	Lysholm
Koh et al. [26]	2012	Retrospective case series	99	Lysholm
Marcacci et al. [29]	2012	Prospective case series	32	Lysholm, IKDC, Tegner
Saltzman et al. [43]	2012	Retrospective case series	22	Lysholm, IKDC
Zhang et al. [57]	2012	Prospective case series	18	Lysholm
Jang et al. [24]	2011	Parallel prospective case series	36	Lysholm
Alenthorn et al. [2]	2010	Retrospective case series	15	Lysholm, IKDC
Ha et al. [16]	2010	Retrospective case series	36	Lysholm
LaPrade et al. [27]	2010	Prospective case series	34	IKDC
Vunderlinckx et al. [54]	2010	Retrospective case series	34	Lysholm, Tegner
Gommell et al. [14]	2009	Case series	7	Lysholm, IKDC
van der Wal et al. [51]	2009	Case series	57	Lysholm, HSS
Verdonk et al. [52]	2009	Prospective case series	100	HSS pain and function
Rue et al. [40]	2008	Prospective case series	30	Lysholm, IKDC, Tegner
Bhosdale et al. [4]	2007	Prospective case series	8	Lysholm
Farr et al. [13]	2007	Prospective case series	29	Lysholm
Hommen et al. [21]	2007	Case series	20	Lysholm, Tegner
Cole et al. [10]	2006	Prospective case series	36	Lysholm, IKDC, Tegner
Rueff et al. [41]	2006	Retrospective case control	16	Lysholm, IKDC
Sekiya et al. [46]	2006	Retrospective case series	25	Lysholm and IKDC follow-up scores
Stone et al. [49]	2006	Prospective case series	45	Self reported pain, activity and functioning
Sekiya et al. [45]	2003	Retrospective case series	28	Lysholm follow-up scores
Yoldas et al. [56]	2003	Retrospective case series	31	Lysholm
Ryu et al. [42]	2002	Retrospective case series	25	Lysholm, Tegner
Wirth et al. [55]	2002	Prospective case series with retrospective control groups	21	Tegner
Rath et al. [39]	2001	Prospective case series	18	SF36
Stollsteimer et al. [47]	2000	Prospective case series	22	Lysholm, Tegner
Cameron et al. [6]	1997	Case series	63	Tegner, Fulkerson
Noyes et al. [37]	1995	Case series	82	ADLs and pain

being used in 25 studies. The mean pre-operative score was 55.7, and at final follow-up, the mean score was 81.3 (Fig. 3). A poor score is considered to be under 65, fair 65–83, good 84–90, and excellent over 90. Using these measures, the average pre-operative score was easily within the 'poor' range. At final follow-up, the score was 'fair', although close to the 'good' range.

The IKDC subjective knee form evaluates symptoms and function in activities of daily living [20]. It was initially designed to assess ligament disruption in the knee, but has been shown to be useful for a broad range of knee pathologies [17]. The range is from 0 (worst) and 100 (best). It was used in 12 studies, with pre-operative and final follow-up scores of 47.8 and 70, respectively (Fig. 4). These scores are consistent with the improvement seen in Lysholm scores, as pre-operative scores are very low for a young patient population, and final follow-up scores are significantly better, but not near the best possible score.

The Tegner activity level scale is a single score from 0 (worst) to 10 (best) that denotes the highest activity level that the patient can perform [50]. It was used in 11 studies with pre-operative and final follow-up scores of 3.1 and 4.7, respectively (Fig. 5).

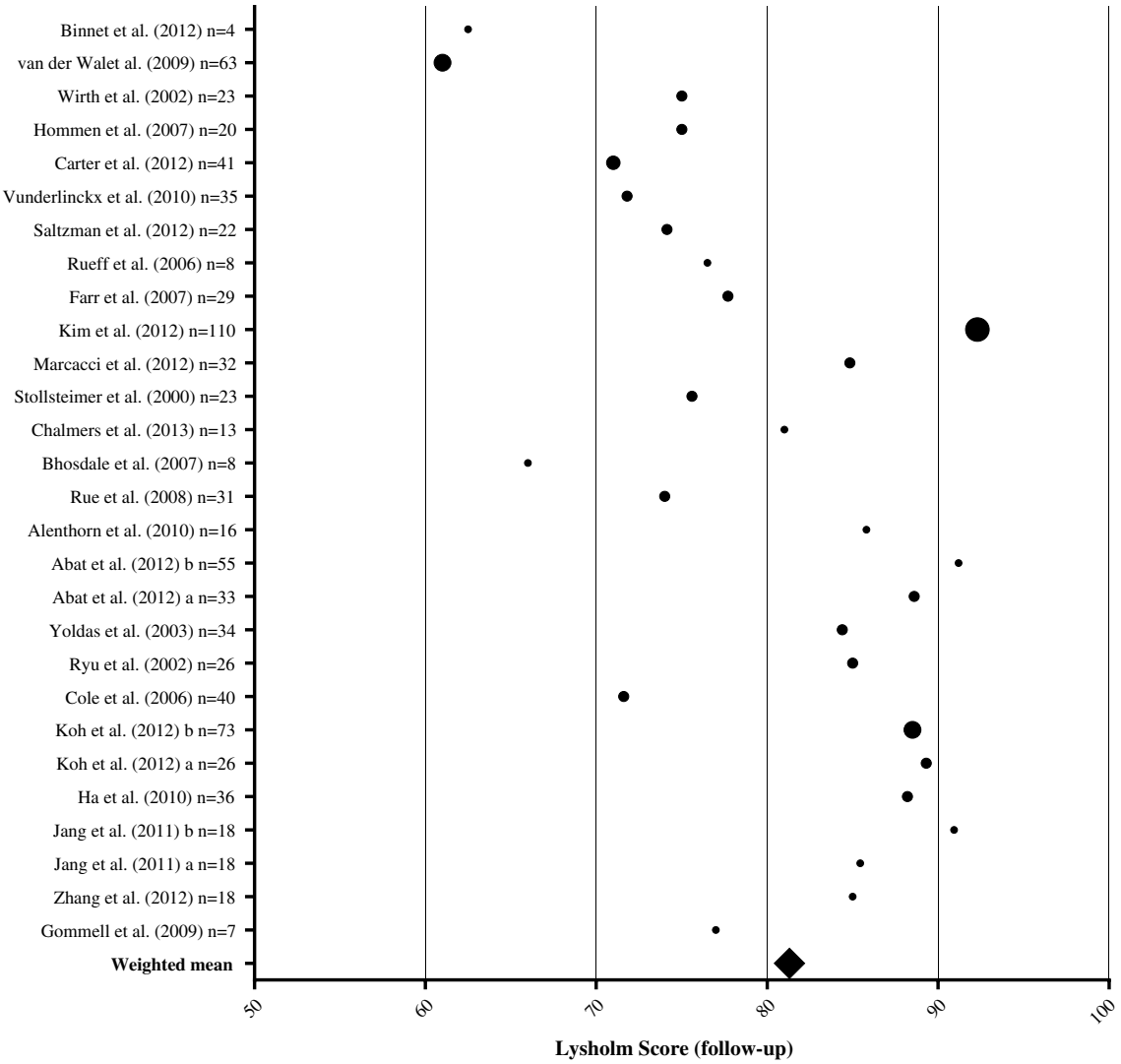

Fig. 3 Follow-up Lysholm scores

Some studies used other PROMs such as the Fulkerson questionnaire [6], SF 36 [39], Hospital for Special Surgery (HSS) [52], Knee Osteoarthritis Outcome Score (KOOS) [18], Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [48], as well as pain and activities of daily living scores [37]; these showed improvements broadly in line with the more commonly used PROMs (results not shown).

Indications

The most frequently reported indications for MAT were a symptomatic (pain, swelling or stiffness) knee and a previous total or near total meniscectomy. Most studies did not define the extent of meniscectomy, although Farr et al. [13] said that it should be within 3 mm of the posterior horn. Most studies included an upper age limit or described eligible patients as 'young'. Only two studies included patients over 55 years old [25, 49]. Severe cartilage damage or osteoarthritis was exclusion criteria for a significant number of studies [10, 16, 21, 24, 25, 29, 39, 41, 46, 57], although were inclusion criteria for a limited number of other studies [4, 6, 14]. Normal alignment and/or a stable knee was a common requirement; this could usually be corrected intraoperatively [10, 16, 24, 25, 29, 39, 40, 46].

Graft type

The graft type was known in 1,186 allografts. There were 796 fresh frozen, 269 cryopreserved, 100 fresh, and 21 lyophilised allografts used across all studies. Although cryopreserved and fresh frozen grafts were used in roughly equal numbers until 2010 [12], all studies published since then have used fresh frozen grafts, with the exception of a

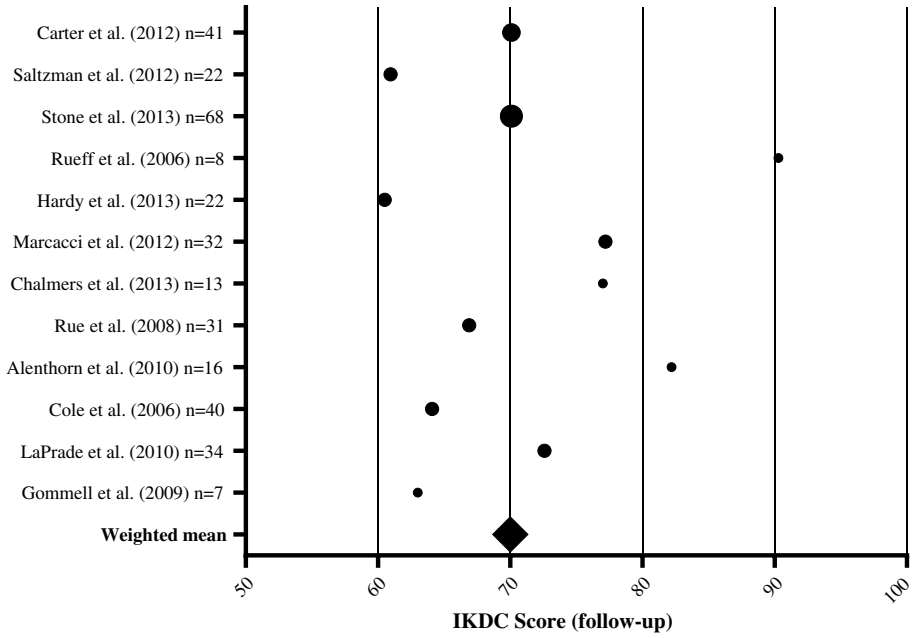

Fig. 4 Follow-up IKDC scores

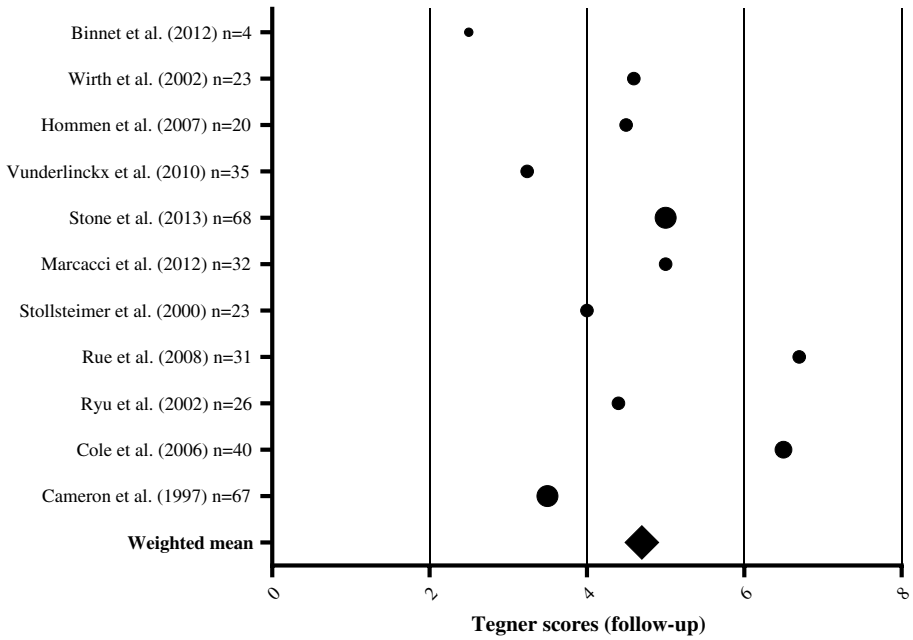

Fig. 5 Follow-up Tegner scores

long-term follow-up case series of 4 grafts [1, 5, 8, 18, 24–26, 29, 57]. This represents a significant change in practice from the previously reported systematic review by Elattar et al. [12]. Grafts in earlier studies were irradiated [6, 37], but this practice has now stopped.

Operative technique

The surgical technique was described in 1,263 allografts. Earlier studies used an open technique, with collateral ligament detachment or joint distraction [6, 42, 51, 55]. Once an arthroscopic-assisted technique had been pioneered, it quickly became the technique of choice. Bone bridge or plug fixation for the meniscal roots was the most common method, being used in 904 allografts (across 26 studies), whereas an all suture technique was used in 359 allografts (across 13 studies). One study found more cases of major extrusion on MRI with their soft tissue fixation than their bone plug fixation, although PROMs were not significantly different between the groups [1].

Associated procedures

Other knee procedures performed at the time of MAT were common. The inclusion criteria for a number of studies were a stable knee with normal alignment, which was often corrected intraoperatively with an osteotomy ± ACL reconstruction. Other commonly reported procedures included articular cartilage repair procedures including autologous chondrocyte implantation (ACI) and microfracture. Only 243 allografts were clearly performed as isolated procedures, although this is likely to be higher as reporting of isolated MAT in some studies was either not clear or not described.

Rehabilitation

Although there were variations in post-operative rehabilitation, most studies reported a post-operative period of either partial or non-weight bearing and a restriction on flexion from 0° to between 60° and 90°. Most studies had allowed full weight bearing by 6 weeks, with a gradual progression to running by 3–6 months. Return to full pivoting/cutting sports was controversial with some studies recommending lifelong limits [16, 39, 45, 46, 56]. However, it was more common to allow return to full sports, usually after 6–12 months [2, 5, 8, 14, 24, 29, 40, 47, 48, 52]. Stone et al. [48] reported no correlation with post-operative sporting level and failure in patients with a high pre-injury activity level.

Failures and complications

The most common definition of failure was conversion to a joint replacement or excision of the allograft. There were 6 studies (198 allografts) that did not show evidence of reporting possible failures [5, 26, 41, 45, 46, 56]. Therefore, there were a total of 128 failures in 1,174 allografts implanted at a mean of 4.8 years across included studies (10.9 % failure rate). The study with the highest number of failures had 29 out of 96 allografts at 2 year follow-up [37].

Complications were varied and included infection, synovitis, meniscal tears, and partial meniscal detachments. Complications ascribed to concomitant procedures such as osteotomy or anterior cruciate ligament (ACL) reconstruction were also common. Six studies (238 allografts) did not report complications [7, 26, 41, 45, 46, 56]. Therefore, there were 154 complications in 1,134 allografts at a mean of 4.7 years across included studies (13.6 % complication rate).

Radiological findings

Only a limited number of studies reported radiographic progression of osteoarthritis findings at follow-up. One study reported no change in Kellgren and Lawrence OA grade in 28 out of 36 knees on plain radiographs at a mean follow-up time of 2.6 years [16]. One study reported no joint space narrowing [15], while other studies reported small reductions in joint space at final follow-up [18, 21, 39]. Two studies compared the joint spaces of the same compartment in the contralateral knee and found no statistically significant changes at baseline and final follow-up in either compartment [39, 45].

Meniscal extrusion was a common MRI finding, with most studies reporting either a mean extrusion of more than 3 mm or the majority of allografts classified as ‘extruded’ or ‘major’ extrusion [1, 16, 18, 24–26, 29].

Graft healing

Ha et al. [16] performed second look arthroscopy at an average of 26.3 months for various reasons. They found that 11 had completely healed to the capsule, while 7 had partially detached; there were no cases of complete detachment. Rath et al. found that all 10 allografts undergoing post-operative arthroscopy had completely healed to the capsule, and Wirth et al. found that 17 of 19 allografts had completely healed at post-operative arthroscopy [39, 55].

Hardy et al. [18] performed MRIs on 14 of 21 patients at 6 months post-operatively, finding 57.1 % total healing, 14.3 % partial healing, and 28.6 % no healing according to the Henning criteria. Noyes et al. [37] devised a new score for graft healing using MRI and arthroscopy, reporting a 40 % complete or partial healing rate.

Risk of bias

- Missing studies

There were no completed registered trials on any searched registry. Only studies written in the English language were reviewed; therefore, some otherwise eligible studies may not have been included.

- Study type

All studies included in this systematic review were case series. Some studies described control groups, but the selection for each intervention was for specific reasons, such as a change of technique part way through the study [1]. Therefore, there is a high risk of selection bias in all included studies. A large number of studies were retrospective, which increases the risk of measurement error (Table 4).

- Missing outcomes

A number of studies did not report failures or complications. These were not included in the analysis of average

complication and failure rate. A number of studies specifically excluded patients that had a 'failed' treatment from the analysis of PROMs [10, 13, 43]. It is likely that patients with failed treatments would have worse PROMs scores. Moreover, complications or failures were commonly not defined. It is therefore unknown whether some studies did not consider some patients to have had a complication or failure when others did.

Discussion

The most important finding is that there are significant improvements in all mean PROMs at final follow-up. The baseline PROMs scores are very low considering the young patient group, which indicates the severity of symptoms in patients undergoing MAT. It is also important to note that although there are significant gains in PROMs at final follow-up, mean scores are still well below top scores in this young patient group. This may reflect either non-modifiable damage to the knee or the failure of treatment to completely reverse symptoms.

Despite this systematic review containing many new studies, the results are roughly comparable with older systematic review results [11, 12, 19]. In addition to the weighted means of the outcome measures, most studies showed significant improvements in PROMs, with an acceptable complication and failure rate. This is the strongest evidence to date for the efficacy of MAT in patients with a symptomatic meniscal deficient knee. Future studies must have an improved methodology and reporting quality and ideally have a prospective control group. The relatively low volume of MAT compared with more common operations makes randomised trials more difficult.

One trend change in newer studies has been the more common usage of fresh frozen allografts over other preservative methods. Cryopreservation involves controlled freezing to around −196 °C with the meniscus bathed in cryoprotectant and then thawed under strict protocols. There is no strong evidence that cryopreservation maintains the integrity of the meniscal allograft better than fresh freezing [32]. Cryopreservation also requires strict thawing protocols, which are difficult to achieve in the clinical environment. These factors may have contributed to the increased use of fresh frozen allografts.

Another controversy is the method of meniscal root fixation. This systematic review shows that bone plug or bone bridge fixation remains the most popular method, although an all suture technique through bone tunnels is used in significant numbers. Abat et al. [1] reported more cases of major meniscal extrusion on MRI in patients that had suture fixation of grafts when compared to bone plug fixation. However, inferences from this should be drawn with caution as the two groups were not directly comparable and should thus be considered as parallel case series. Bone fixation is often done in the hope that it provides a stronger fixation, while an all suture technique is less technically demanding. A biomechanical study has shown a similar pull-out strength with either technique [22], whereas another showed that a suture only technique allows a slightly higher contact pressure on the tibial cartilage [33].

In general, the quality of evidence was low, with the vast majority of studies being case series. Due to the low quality of studies, there is a high risk of biased results. Patients that were described as having a failed treatment were often excluded from analysis, which could lead to an overestimation of the benefit of treatment. The wide variation in failures and complications also suggests that some reporting was more detailed than others. Therefore, failures and complications may also be underreported.

Indications for MAT varied among studies, but all studies required patients to have a symptomatic meniscal deficient compartment of the knee. Therefore, the success or failure of the treatment may be judged against symptom relief, as judged by PROMs. However, many studies refer to the potential for MAT to reduce the risk of OA in these patients. This systematic review did not find strong evidence to support or refute this hypothesis.

Conclusion

This systematic review shows a consistent and significant improvement in all used PROMs for MAT at final follow-up. The low pre-operative scores and young patient group indicate that there is a significant disease burden that appears to be improved by MAT. A future randomised controlled trial would be able to provide definitive evidence of its effectiveness.

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This study does not contain new patient data.

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