Meniscal allograft transplantation. Part 1: systematic review of graft biology, graft shrinkage, graft extrusion, graft sizing, and graft fixation

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Meniscal allograft transplantation. Part 1: systematic review of graft biology, graft shrinkage, graft extrusion, graft sizing, and graft fixation

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Abstract
Purpose To provide a systematic review of the literature regarding five topics in meniscal allograft transplantation: graft biology, shrinkage, extrusion, sizing, and fixation.
Methods A systematic literature search was conducted using the PubMed (MEDLINE), ScienceDirect, and EBSCO-CINAHL databases. Articles were classified only in one topic, but information contained could be reported into other topics. Information was classified according to type of study (animal, in vitro human, and in vivo human) and level of evidence (for in vivo human studies).
Results Sixty-two studies were finally included: 30 biology, 3 graft shrinkage, 11 graft extrusion, 17 graft size, and 6 graft fixation (some studies were categorized in more than one topic). These studies corresponded to 22 animal studies, 22 in vitro human studies, and 23 in vivo human studies (7 level II, 10 level III, and 6 level IV).
Conclusions The principal conclusions were as follows: (a) Donor cells decrease after MAT and grafts are repopulated with host cells form synovium; (b) graft preservation alters collagen network (deep freezing) and causes cell apoptosis with loss of viable cells (cryopreservation); (c) graft shrinkage occurs mainly in lyophilized and gamma-irradiated grafts (less with cryopreservation); (d) graft extrusion is common but has no clinical/functional implications; (e) overall, MRI is not superior to plain radiograph for graft sizing; (f) graft width size matching is more important than length size matching; (g) height appears to be the most important factor influencing meniscal size; (h) bone fixation better restores contact mechanics than suture fixation, but there are no differences for pullout strength or functional results; and (i) suture fixation has more risk of graft extrusion compared to bone fixation.
Level of evidence Systematic review of level II–IV studies, Level IV.

Keywords Meniscal allograft transplantation · Graft biology · Graft shrinkage · Graft extrusion · Graft sizing · Graft fixation

Introduction

Meniscal injuries have a tremendous physical and economic impact on the population. It has been estimated that more than 1.7 million patients undergo meniscal surgery every year in the world [52]. Partial or total meniscectomy is a very common surgical procedure in orthopedic surgery when the meniscal tear is not repairable. However, the loss of meniscal tissue has been associated with early onset of knee osteoarthritis due to a decrease in tibiofemoral contact area and an increase in joint contact pressures, especially among the active population [7, 17, 53]. Articular cartilage degeneration often presents with pain and functional limitations, impacting clearly on the patients' quality of life. Meniscal allograft transplantation (MAT) has become a powerful tool in experienced hands with proven

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clinical and functional efficacy in relatively young and active meniscectomized symptomatic patients.

Most of the review studies available have focused on the outcomes but very few on reviewing the graft biology, shrinkage, extrusion, sizing, and fixation. Matava [37] published in 2007 a review article where several of these topics were covered, but only 15 studies were finally included. There has been a huge increase in the number of studies related to MAT in the lasts years. In addition, conclusions on each of these topics have to be elaborated based also on the methodological quality and level of evidence of studies. Therefore, an updated systematic review on graft biology, shrinkage, extrusion, sizing and fixation with studies reviewed based on its quality is timely. This article may help the surgeon on the decision-making regarding several aspects related to MAT that may influence the final clinical outcome and may also serve to generate ideas for future research regarding areas with still controversy.

This is part one of a two-part review article addressing controversial questions in MAT. The purpose of this study was to provide a comprehensive and updated systematic review of the literature regarding five controversial issues: graft biology, shrinkage, extrusion, sizing, and fixation.

Materials and methods

The methods for this study followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement for systematic reviews [44].

Eligibility criteria

All studies investigating graft biology and basic science aspects of menisci, and biomechanical, clinical, or functional outcomes related to MAT were approached for eligibility. Studies were included if they were animal or human studies, in vitro or in vivo studies, level of evidence between I and IV for clinical human studies, written in English language, and contained information on the topics targeted for this study. The five topics were selected in consensus among all co-authors and were based on own experience and existing literature. Other systematic review and meta-analyses were excluded from the systematic search but taken into account to assist in discussion and conclusions on each topic.

Information sources and search

Electronic search

A systematic electronic literature search was conducted using the PubMed (MEDLINE), ScienceDirect, and EBSCO-CINAHL databases up to December 2013 by one of the authors. The search strategy and key words employed in this study were (meniscus OR meniscal OR menisci OR fibrocartilage) AND (transplant OR transplants OR transplantation OR transplantations OR allograft OR allogenic OR allogeneic) for both free and MeSH terms, whenever available.

Other search methods

The reference lists of all included articles and systematic review/meta-analyses encountered were reviewed to search for potential studies not previously identified.

Data collection and analysis

Study selection

All abstracts were read and articles of potential interest were reviewed in detail (full text) by one author to decide on inclusion or exclusion from this systematic review. In cases of disagreement, two authors reviewed and discussed the studies and a final decision was made in consensus regarding its inclusion or exclusion.

Data collection process

Information regarding the five topics in MAT was extracted in a systematic fashion from included studies by one author. Data extraction was then verified by the rest of the authors. Articles were classified in each topic according to the principal purpose of the investigation. Articles were classified only in one topic, but information contained could be reported into other topics if their secondary purposes had enough quality and extension. For each topic, information was classified according to type of study (animal study, in vitro human studies, and in vivo human studies) and level of evidence (for in vivo human studies). Conclusions were established for each topic. The topics included:

1. Biologic characteristics of meniscal allografts: graft selection, preservation, and biomechanical behavior.
2. Graft shrinkage: Is it a common phenomenon? Is it related to meniscal processing or surgical technique? Does it affect the outcomes?
3. Graft extrusion: Is it dependent on the surgical technique? Is it a frequent or devastating complication of MAT?
4. Graft sizing: Does size matter? What is the most effective method for measuring?
5. Graft horns fixation—bone plug versus soft tissue: Does it really matter?

Assessment of the risk of bias

The methodological quality of the included studies was evaluated through a summary table of several important aspects potentially related to bias in the investigation of MAT. This assessment was performed by answering yes, no, unknown, or not clearly reported to the following information from each study: purpose clearly stated, prospective nature clearly defined, concealed allocation (yes = group assignment was made by an independent person who had no information about study participants), similarities at baseline between groups (yes = study groups were statistically similar in age, sex, and anthropometric characteristics), blinding of participants (yes = study population blinding was clearly described and acceptable), blinding of data collectors (yes = data collectors were blinded regarding group assignments), blinding of outcome assessor (yes = outcome assessor who evaluated the participants were blinded regarding group assignments), similar distribution of athletes and/or athletes at competitive level between groups, similar distribution of associated procedures between groups, similar distribution of previous major knee injuries and/or osteoarthritic changes between groups, no graft irradiation reported or comparable distribution between groups, similar surgical technique between groups, similar graft preservation techniques between groups, acceptable compliance (yes = compliance was regularly checked or otherwise strictly supervised by someone other than study participants, and it was more than 70 % in every study group), acceptable dropout rate (yes = dropout rate was <30 %), duration of intervention comparable between groups, and intention-to-treat analysis (yes = all subjects assigned to a group at the beginning of the study were included in the analysis). A final quality score was given for each study, where yes was one point and any other response (no, unknown, not clearly reported) were zero points. The assessment of the risk of bias in included studies was based on the articles by Aaltonen et al. [1], and Slim et al. [55].

Results

Study selection

The literature search elicited a total of 1,548 references (PubMed = 753; ScienceDirect = 570; EBSCO-CINAHL = 225), from which 1,407 were excluded because of duplicates, non-English articles, case reports, review articles, technical notes, unrelated studies, studies not reporting on the topics considered for the present study (Fig. 1). A total of 141 studies were reviewed in full text, and 61 were included. In addition, one article was added after reviewing the reference lists of included studies. Therefore, 62 articles met the final inclusion criteria for the current systematic review.

Characteristics of the studies

The number of studies included in each topic was as follows: 30 biology, 3 graft shrinkage, 11 graft extrusion,

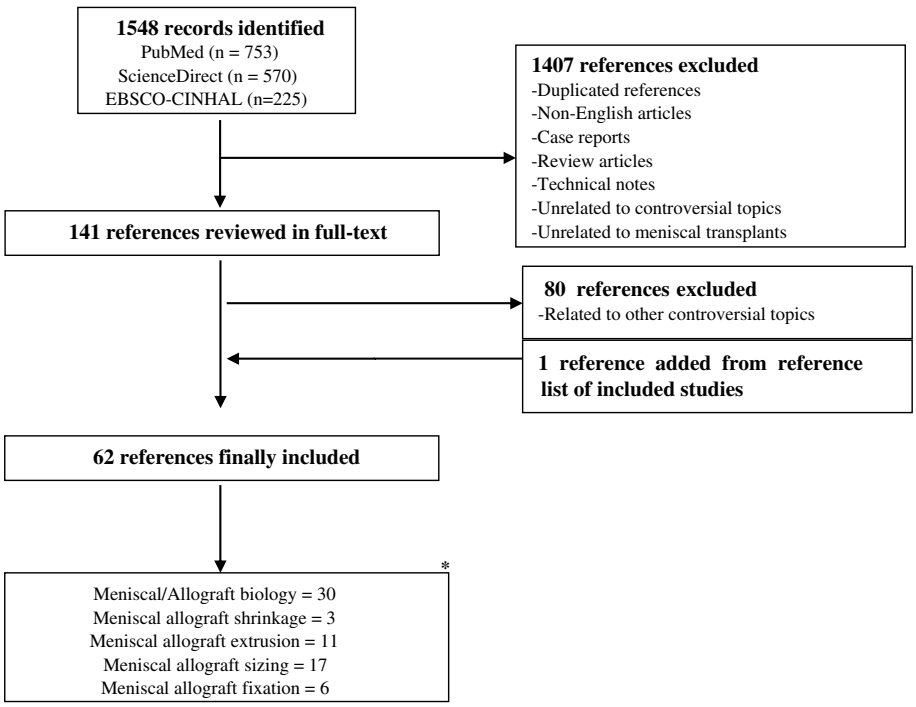

Fig. 1 Flow diagram for the literature search and selection of studies for the systematic review. *Some studies could be classified in more than one topic

17 graft size, and 6 graft fixation (some studies were categorized in more than one topic). These studies corresponded to 22 animal studies, 22 in vitro human studies, and 23 in vivo human studies. Further characteristics of included studies are specified in each section. Table 1 summarizes the assessment of the risk of bias for the included studies.

The information extracted from all included studies in each of the five topics was:

Biologics of meniscal allograft

Most of the studies that have been published about this topic are product of animal experimentation or basic science works, and hence, only in vivo studies were classified by level of evidence. A total of 30 studies were found, of which 22 corresponded to animal studies, six in vitro human studies, and two in vivo human studies.

Animal studies The animals most commonly used in the literature are rabbit, dog, sheep, goat, rat, mice, and pig. The majority of studies using an animal model are related to graft preservation and sterilization. The investigation of allograft incorporation and healing has been conducted in dogs [9, 41, 42] and rabbits [36]. Canham and Stanish [9] observed that meniscal autograft re-implantation and tissue culture-stored allogenic menisci transplantation both had successful attachment with no loose bodies at 2 months. However, allogenic menisci preserved in glutaraldehyde (termed bioprosthesis) had less attachment to the joint capsule at 2 months and elicited more knee effusion at 1 and 2 weeks [9]. The studies by Mikic et al. [41, 42] in dogs demonstrated that fresh-frozen allografts had adequate healing potential, which was also confirmed in rabbits utilizing allograft treated with growth factor retrovirus-derived gene transfers [36].

Table 1 Assessment of the risk of bias in included studies involving humans

T	Study	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	Score
1	Ochi et al. [46, 47]	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	1	1	6
1	Rodeo et al. [51]	1	0	0	0	0	0	0	0	0	0	1	0	1	1	0	0	1	5
2	Carter and Economopoulos [10]	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	5
2	Lee et al. [30, 31]	1	1	0	1	0	0	0	0	1	1	1	1	1	1	1	1	1	12
2	Milachowski et al. [43]	0	0	0	0	0	0	0	0	1	1	0	1	0	0	0	1	0	4
3	Abat et al. [2]	1	1	0	1	0	0	1	0	0	1	1	1	1	1	1	1	0	11
3	Ha et al. [20]	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	0	4
3	Jang et al. [27]	1	0	0	1	0	0	0	0	1	1	0	0	1	1	1	1	0	8
3	Koh et al. [29]	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	0	4
3	Lee et al. [33]	1	0	0	1	0	0	0	0	0	0	0	1	1	1	0	1	1	7
3	Lee et al. [32]	1	0	0	1	0	0	0	0	1	1	0	1	1	1	1	1	0	9
3	Lee et al. [34]	1	0	0	0	0	1	0	0	0	0	1	1	1	1	1	1	1	9
3	Verdonk et al. [59]	1	0	1	1	0	0	0	0	1	1	1	1	1	1	1	1	1	12
3	Yoon et al. [69–71]	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	4
3	De Coninck et al. [12]	1	0	0	0	0	0	0	0	0	0	1	0	1	1	1	1	1	7
4	Jang et al. [27]	1	0	0	1	0	0	0	0	1	1	0	0	1	1	1	1	0	8
4	Lee et al. [30, 31]	1	0	0	1	0	0	0	0	1	1	0	1	1	1	1	1	0	9
5	Abat et al. [2]	1	1	0	1	0	0	1	0	0	1	1	1	1	1	1	1	0	11
5	Abat et al. [3]	1	1	0	1	0	1	0	1	1	1	1	0	1	1	1	0	1	12
5	De Coninck et al. [12]	1	0	0	0	0	0	0	0	0	0	1	0	1	1	1	1	1	7

T, topic (1: biologic characteristics of meniscal allografts; 2: graft shrinkage; 3: graft extrusion; 4: graft sizing; 5: graft fixation); 0, no, unknown, not clearly reported; 1, yes; A, purpose clearly stated; B, prospective; C, concealed allocation; D, similarities at baseline between groups; E, blinding of participants; F, blinding of data collectors; G, blinding of outcome assessor; H, similar distribution of athletes and/or athletes at competitive level between groups; I, similar distribution of associated procedures between groups; J, similar distribution of previous major knee injuries and/or osteoarthritic changes between groups; K, no graft irradiation reported or comparable distribution between groups; L, similar surgical technique between groups; M, similar graft preservation techniques between groups; N, acceptable compliance; O, acceptable dropout rate; P, duration of intervention comparable between groups; and Q, intention-to-treat analysis (see text for more details)

Items D, H, I, J, K, L, M, and P requires group comparisons. Items for case series without different subgroups were responded considering the whole sample (i.e., if similar graft preservation techniques (item M) was employed for all patients, this was considered a "Yes"). Studies were classified in each topic (question) depending on the principal purpose of the study. This table only includes studies using MAT in humans

Animal studies have also provided information regarding biomechanical characteristics of meniscal allografts, especially for dogs [65], sheep [23, 40, 43], and pigs [22]. It was observed that the use of glutaraldehyde-cross-linked allografts used to protect the graft against deterioration caused lower tensile strength, lower tensile modulus, higher compressive stiffness, lower compressive strains, and increased graft permeability [22, 65]. Despite an increase in permeability [22], it was observed that the water content was not different between fresh- and glutaraldehyde-treated grafts [65]. Interestingly, when reducing the concentration of glutaraldehyde, the material properties of treated menisci were comparable to those of control grafts [22]. More recently, it was demonstrated in sheep that the stabilization of meniscal allografts with triglycidyl amine improved compressive properties compared to glutaraldehyde-treated allografts while maintaining a good resistance to collagenase degradation [23]. McNickle et al. [40] demonstrated that the low-temperature chemical sterilization process using pressure-vacuum cycling (sterilization process) had similar compressive strength compared to aseptically prepared meniscal allografts (immersion in antibiotic solution), but lower compared to untreated allografts. The comparison of two graft preservation techniques, lyophilized and deep frozen, elicited no differences in tensile strength but both decreased in size, as small as a regenerated meniscus in some cases. In general, the deep-frozen menisci showed better results after second-look arthroscopy [43]. Regarding sterilization methods, Yahia et al. [67] observed that gamma-irradiated frozen allograft produced a decrease in viscoelasticity (compliance to long-term creep) compared to non-irradiated frozen and fresh allografts in rats.

Most studies have focused on the preparation, preservation, and sterilization process of allografts. Milachowski et al. [43] compared lyophilized, gamma-irradiated meniscal allografts to deep-frozen grafts in sheep. Both methods demonstrated adequate healing and synovium hypertrophy, but lyophilized grafts had greater revascularization and remodeling in terms of fibroblast proliferation and newly formed collagen fiber structure compared to deep-frozen allografts [43]. Similar findings regarding altered graft remodeling in deep-frozen grafts were observed by Arnoczky et al. [5] in dogs, as they found that this method had a loss of normal collagen architecture in the superficial layers of the meniscus. Regarding the intensity of freezing, Reckers et al. [50] found that the number of viable cells was similar in the first 2 weeks after transplantation under any freezing temperature in the range between −7 and −73 °C, but the lowest temperatures had a lower number of viable cells after 2 weeks. Comparing fresh and cryopreserved allografts, Jackson et al. [24] observed that both grafts had normal peripheral vascularity, but higher increases in water content and decreased proteoglycan concentration compared to control menisci. Immunosuppression with cyclosporin A in rats with fresh allografts elicited better survival of the graft compared to fresh allografts, cryopreserved allografts, and control isografts [61]. Regarding sterilization, the method described above by McNickle et al. [40] (low-temperature chemical sterilization process using pressure-vacuum cycling) demonstrated lower cell viability compared to control allografts (contralateral unoperated native grafts), but similar compared to aseptically prepared meniscal allografts (immersion in antibiotic solution). Irradiation-mediated sterilization of deep-frozen allografts has demonstrated adequate tissue healing and regeneration (formation of meniscus-like tissue) and decrease in articular cartilage degeneration in the short term in rabbits [28].

Histology studies not specifically investigating preservation or sterilization methods have arrived at several conclusions. In sheep, neither lyophilized, gamma-irradiated nor deep-frozen allografts demonstrated histologic signs of inflammation or rejection [43]. Similar findings were observed in mice, as meniscal allografts elicited no significant lymphocyte stimulation reaction (infiltration), and no antibodies were detected in sera during the first 24 weeks after the transplant [45, 46]. The authors found that the number of fibrochondrocytes decreased in the allografts [45, 46]. In goats, Jackson et al. [25, 26] observed that donor cells present in the meniscal allografts at the time of implantation did not survive after 4 weeks and that allografts were repopulated with host cells. It was suggested that this repopulation process originated from the synovium [5]. In dogs, both deep-freezing [5] and fresh-frozen [41, 42] allografts demonstrated a significant loss of donor cells. However, it was observed in rabbits that deep-frozen allografts had active collagen remodeling, revascularization, and cellular repopulation in the first 12–26 weeks after transplantation [62]. The repopulation of allografts was explained by an increase in the expression of type I and III procollagen mRNAs at 12 weeks, although this expression was normalized at 26 weeks [62]. An interesting study in rabbits compared with the revascularization process in three types of allografts: covered with vascularized synovial flaps, covered with free synovial flaps, and covered with fibrin clots [68]. The first type demonstrated the fastest revascularization process, although the last two types had faster revascularization compared to control allografts [68]. Comparing autografts and allografts in rabbits, Xue et al. [66] found no significant differences in revascularization, expression of VEGF, and repopulation of cells and fibers.

In vitro human studies The available information regarding biologic aspects of meniscal allograft in the human model is much less compared to the animal model. From

a biomechanical standpoint, it was found that age of the donor did not influence the static tensile stiffness and dynamic tensile modulus of meniscal allografts [8]. Lewis et al. [35] observed that multiple cycles of freeze and thaw evoked a significant decrease in Young's modulus (resistance to compression) compared to a single cycle in human menisci. Regarding cellular repopulation, Debeer et al. [13] demonstrated that 1 year after MAT, the DNA of the meniscal allograft was 95 % identical to that of the human recipient, showing that the allograft is nearly completely repopulated by host cells. Regarding non-cellular composition changes, Bursac et al. [8] found that collagen and proteoglycan content in the medial and lateral menisci of human subjects was not influenced by donor age. Also, Gelber et al. [18] found that freezing caused a disruption of the collagen net in human menisci. Lewis et al. [35] further demonstrated the effects of multiple freeze–thaw cycles compared to single freeze–thaw cycle: Multiple cycles caused a nonsignificant increase in water content and proteoglycan per weight (but no histologic changes) compared to a single cycle. Regarding cryopreservation, Gelber et al. [19] demonstrated that this method did not alter meniscal ultrastructure (mainly collagen fiber diameter and degree of disarray) compared to fresh menisci, but the cellular viability of cryopreserved menisci was highly unpredictable. Villalba et al. [60] published 3 years later that cryopreservation caused an apoptosis-mediated donor-cell loss. The researchers also found that the number of cells was significantly lower in the cryopreserved compared to fresh grafts [60].

In vivo human studies Rodeo et al. [51] compared the histological and immunohistochemistry characteristics (aimed to assess the immune response elicited against the graft) of MAT to age-matched control group (un-implanted allografts) at a mean of 16 months post-transplantation. The authors took meniscal and synovial membrane biopsy specimens during a follow-up arthroscopy, and they found an incomplete re-popularization of viable cells with positive markers for synovial and fibroblast-type cells. These cells were active in remodeling the extracellular matrix. The authors also found evidence of a subtle immune response against the transplant, although this reaction did not adversely affect the clinical outcomes.

In a case series of five young (mean age 26 years) patients, it was demonstrated in a second-look arthroscopy plus meniscal allograft biopsy approximately 1 year after surgery that the graft was well incorporated, had no shrinkage, and had no gap with surrounding articular cartilage [47]. The host cells infiltrated and repopulated the meniscus allograft and were morphologically similar to fibrochondrocytes, but no hyalinization occurred.

Graft shrinkage

Graft shrinkage is a potential complication of MAT, although less observed with current preservation techniques. There were three studies identified for this topic, all of them classified as in vivo human studies, with level of evidence ranging from 2 to 4 [10, 30, 43].

In vivo human studies Milachowski et al. [43] reported data on graft shrinkage at a mean of 14 months depending on the type of meniscal preservation method: lyophilized, gamma irradiated, or deep frozen. Of the five patients with deep-frozen grafts who underwent postoperative arthroscopy, three had menisci normal in size, one had 1/3 reduction, and another patient 2/3 reduction in size. Of the ten patients who underwent postoperative arthroscopy in the lyophilized, gamma-irradiated graft, meniscal shrinkage was observed in nine (3 with a reduction of 1/3, 4 with 2/3 reduction, and 2 a 3/3 reduction). Thus, graft shrinkage was higher in lyophilized, gamma-irradiated grafts compared to deep-frozen preservation technique.

In a prospective cohort study involving 31 patients, Lee et al. [30] investigated the gross structure of fresh-frozen meniscus allografts through magnetic resonance imaging (MRI) at a maximum follow-up of 1 year after transplantation. The authors observed a decrease in meniscal width at the mid-body area and an increase in thickness at 12 months. The horn areas were less involved in gross structure changes. Shrinkage occurred during the first 3 months, but stabilized thereafter. Sixty-five percent of patients developed minimal shrinkage, 20 % mild shrinkage, 16 % moderate shrinkage, and none had severe meniscal shrinkage. The preoperative alignment, cartilage status, age, gender, extrusion, and time from previous meniscectomy did not influence the degree of meniscal shrinkage. The morphologic changes did not correlate with clinical outcomes.

Carter and Economopoulos [10] reported a prospective MRI study on meniscal shrinkage in a series of 25 patients undergoing cryopreserved MAT. The authors found that the average amount of shrinkage was 7 % (range 0 to 22 %), with 32 % being at least 10 % meniscal shrinkage. This phenomenon was present as early as 6 months postoperative.

Graft extrusion

The investigation of allograft extrusion elicited more references than meniscal shrinkage. Eleven studies were finally included, all of them grouped as in vivo human studies: 3 level II evidence [2, 29, 31], 4 level III evidence [12, 27, 33, 59], and 4 level IV evidence [20, 32, 34, 69].

In vivo human studies Three studies have compared graft extrusion depending on the fixation technique [2], medial or lateral meniscus [29], or depending on the sizing method [31]. Abat et al. [2] compared the degree of meniscal extrusion between fixation of the allograft with the use of sutures or bone plugs in a prospective cohort study at a mean follow-up of 3 years. The rate of meniscal extrusion was significantly higher in the suture fixation compared to bone plug fixation (36 and 28 %, respectively). There were no significant differences for medial or lateral meniscus extrusion within each group. The degree of graft extrusion had no influence on the functional (Lysholm) outcomes.

Koh et al. [29] compared the graft extrusion between lateral and medial menisci at a mean follow-up of 32 months and investigated its correlation with clinical (Lysholm) outcomes. The authors found that mean graft extrusion was significantly higher in the lateral compared to the medial meniscus (4.7 and 2.9 mm, respectively). The mean percentage of extrusion was also significantly higher in the lateral compared to the medial meniscus (52 and 31 %, respectively). There was no correlation between the degree of extrusion and the Lysholm scores.

Lee et al. [31] evaluated graft extrusion depending on the sizing method. The researchers found that menisci (all lateral) had the following position: mean lateral distance of mid-body in coronal plane 1.7 mm, anterior horn at a mean of 2 mm, and posterior horn at a mean of −3.8 mm from the articular edge in the sagittal plane. Twenty-six percent of individuals had meniscal extrusion in the mid-body area (>3 mm displacement). Most of meniscal extrusions occurred in the anterior horn or mid-body. Considering all zones, the total number of meniscal extrusions was 62 (extrusions could be found in more than one zone) [31].

Jang et al. [27] compared the percentage of meniscal extrusion between two different graft sizing methods. From a total sample of 36 patients, only two had no graft extrusion at all. The mean meniscal extrusion ranged from 4 to 3.6 mm depending on the sizing method. There were a total of 27 major extrusions (>3 mm). The relative percentage of extrusion (percentage of the width of the extruded meniscus compared with the entire meniscal width) ranged from 46 to 35 % depending on the sizing method. The graft extrusion was not significantly different between medial and lateral menisci. The authors found no correlation between graft extrusion and Lysholm score, joint space narrowing, and osteoarthritis.

Lee et al. [33] published a cohort study where 43 patients with MAT were classified in two groups depending on the degree of extrusion (less or equal/more than 3 mm) at 1 year evaluated through MRI. The authors found that there were no differences in clinical or radiological findings (joint space narrowing) between patients with (equal/more than 3 mm) and without (<3 mm) meniscal extrusion [33].

Verdonk et al. [59] compared the degree of meniscal extrusion between two measurement methods (using MRI or ultrasound) in patients with MAT and normal individuals. The authors used no bone blocks for meniscal fixation. They observed that transplanted menisci extruded laterally more than normal menisci and that the anterior horn of both normal and transplanted menisci extruded more laterally than the posterior horn. It was concluded in this investigation that the use of both MRI and ultrasound was adequate as meniscal extrusion evaluation tool.

Finally, De Coninck et al. [12] reported an interesting study comparing the degree of allograft extrusion between open versus arthroscopic MAT. In the open procedure, the fixation was performed through sutures to meniscal horn remnants and sutures in the periphery, whereas in the arthroscopic procedure, the fixation was achieved through transosseous sutures (using bone tunnels) for meniscal horns and sutures in the periphery. Extrusion was evaluated at 1 year postoperative using MRI with a cutoff point of 3 mm. The authors found that meniscal extrusion was significantly higher in open compared to the arthroscopic MAT [12].

Ha et al. [20] investigated the rate of meniscal extrusion and its relationship to clinical outcomes at a mean follow-up of 31 months. The researchers found that meniscal extrusion occurred in most cases. The extrusion was minor in 19 %, major in 75 %, and absent in 5 %. The extent of extrusion was 3.87 mm, and the relative percentage was 42 %, with no differences between the medial and lateral meniscus. Extrusion was not correlated with any associated outcome: Lysholm, radiographs for osteoarthritis, cartilage status in MRI, or second-look arthroscopy.

Lee et al. [34] published a study aimed to investigate the change in meniscal allograft extrusion during the first year postoperative. They observed that meniscal extrusion occurs in the first 6 weeks postoperatively and remains stable until 1 year postoperatively. In patients in whom no extrusion is observed in the first 6 weeks, it does not appear afterward [34]. The same group reported a case series of 49 patients in whom they investigated the effect of bony trough obliquity in graft extrusion of the lateral meniscus in the bone bridge technique [32]. They found that the risk of graft extrusion increased with greater axial plane bony trough angle, which could be reduced by ensuring a bone trough starting point not too lateral [32].

Finally, Yoon et al. evaluated a new method for keyhole drilling of lateral MAT through a transpatellar approach [69]. The authors reported a mean extrusion of 1.6 mm at 1 year postoperative in a series of 11 patients in whom the keyhole was performed through the mentioned approach.

Graft sizing

Most of the evidence about graft sizing originates from basic science studies and cadaver models that are not classifiable within levels of evidence. There were 17 studies found for graft sizing, all for humans: 13 studies were in vitro human studies and 4 in vivo human studies.

In vitro human studies The most commonly used sizing method is plain radiograph. Pollard et al. [48] described a method for meniscal allograft sizing using plain radiographs in a cadaveric study. The authors employed 21 fresh-frozen knee specimens where the menisci were painted with a radiopaque tantalum powder-cyanoacrylic mixture. This study demonstrated that meniscal size can be adequately determined with plain anterior-posterior and lateral radiographs. The meniscus width equaled the distance from the peak of the tibial eminence to the periphery of the tibial metaphysis on anterior-posterior plain radiograph, whereas the meniscal length was different for the medial and lateral menisci. Meniscal length was evaluated with lateral radiograph and corresponded to 80 and 70 % of the sagittal length of the tibial plateau for the medial and lateral menisci, respectively [48].

Yoon et al. [70] compared the lateral meniscus length sizing accuracy of their method and the one published by Pollard et al. [48], with respect to the actual anatomical dimensions. In their method, the anterior and posterior transition points of the lateral tibial plateau are identified in the lateral radiograph performed by slightly tilting the projection beam 10° caudally. The transition points are the turning points from the slope to the lateral plateau. The distance between these two points is the meniscal length. The authors found that lateral meniscus length was more accurately predicted with their method compared to the one by Pollard et al., with a deviation from actual anatomical dimensions of 1.4 mm compared to 4.1 mm in the latter [70]. The accuracy (measurements falling within 10 % of actual anatomical measurements) was 98 % in their method and 40 % in the Pollard's method. The authors suggested a new equation to calculate the meniscal size: anatomical length = 0.52 × plateau length (according to Pollard's method) + 5.2, with a diagnostic accuracy of 92 % [70].

Yoon et al. [71] evaluated the relationship between lateral meniscal allograft width and length anatomical measurements. The measurement method employed in their study was published by Shaffer et al. [54]. Yoon et al. [71] found that the length could not be accurately predicted with the width of the meniscus. They further observed that the height, weight, gender, and BMI were not good estimates of lateral meniscus dimensions. Their recommendation was that the length and width of the lateral meniscus allograft had to be measured independently.

McDermott et al. [39] studied the correlation between tibial plateau and meniscal dimensions in 44 cadaveric knees. They observed that meniscal dimensions could be accurately predicted with tibial plateau measurements using plain radiograph. The length and width of tibial plateau was more accurate than the use of width alone, but this difference was not statistically significant. The mean (SD) error was 5 % (6.4 %) [39].

Wilmes et al. [63, 64] investigated the meniscal horns position using plain radiograph for the medial and lateral menisci in cadavers. The authors employed a marking method with radiopaque steel balls placed at the meniscal horns, and then, radiographs with different parameters were obtained. The authors found that the anterior horn of the medial meniscus was at 57.3 % of the tibial width and the posterior horn at 56.5 % of tibial width, and 12 and 81.6 % of tibial depth, respectively [63]. For the lateral meniscus, these distances for the anterior and posterior horns were 45.1 and 49.8 % for tibial width, respectively, and 41.9 and 72.1 % for tibial depth, respectively [64]. This method was precise and reproducible for both menisci.

The use of MRI for graft sizing has also been reported. Stone et al. [57] evaluated the usefulness of MRI at determining the meniscal size in fresh cadaver knees. Each meniscus was evaluated through the imaging study and then compared to the water volume displacement method after excision. They found that MRI is precise and reproducible but not accurate and would only be useful to assess changes over time [57]. Donahue et al. [15] conducted a cadaveric study with human specimens to develop regression equations using contralateral knee dimensions evaluated with MRI to predict graft size in the injured knee. These equations were then incorporated in a new algorithm for choosing the best graft in terms of size and shape. This algorithm was useful for technicians working in tissue bank to provide adequate allograft for patients [15]. Elsner et al. [16] presented an anatomical/anthropometric MRI-based study to determine the values and variability of knee dimensions and propose a model to predict meniscal allograft sizing. The authors found typical knee proportions for a given tibial width that could be used to predict allograft size.

In addition, some studies comparing different imaging techniques were found. Shaffer et al. [54] compared plain radiograph and MRI for accuracy of meniscal sizing in 12 cadaveric knees. MRI was only slightly more accurate than plain radiograph. In fact, the mean difference between MRI and actual meniscus size was 2.25 mm (2.35 mm between plain radiograph and anatomical measurement). Only 35 % of measurements with both imaging methods were within 2 mm of the actual meniscus dimension, but the intra-observer agreement was significantly higher in the MRI compared to plain radiograph [54]. Prodromos et al. [49] evaluated the usefulness of MRI in determining

allograft sizing. The authors compared MRI measurements of contralateral normal meniscus to plain radiographs of the recipient tibial plateau for meniscal allograft sizing. They observed that menisci were symmetric in size and that MRI of the contralateral normal meniscus was more accurate at predict meniscal size than plain radiograph [49]. McConkey et al. [38] published a study where the 3D CT scan was compared to plain radiograph for accuracy and reliability of meniscal allograft sizing. The authors used both imaging methods and then compared each one to dimensions measured anatomically in disarticulated knee specimens. They found that CT scan was more accurate at determining the tibial plateau dimensions compared to plain radiograph, with variability between 2 and 5 mm. They therefore recommended the use of CT scan over plain radiograph for meniscal allograft sizing [38]. Recently, Berhouet et al. [6] evaluated the accuracy of meniscus sizing between the Pollard's method, the direct anatomical measurement, and the photographic method using cadavers. The authors found that the photographic method used during graft harvesting is not reliable, with a mean measurement error of 24 % compared to the anatomical method. This error was 7.9 % for the Pollard's method. Overall, it was concluded that the direct measurement of the specimen during allograft harvesting was the best method for meniscal sizing [6].

In vivo human studies In the study by Lee et al. [31], previously reviewed, the authors found that adequate graft width matching was more important than graft length matching. They found that graft width mismatch was associated with significantly more meniscal extrusion than length mismatch.

Stone et al. [56] published a cross-sectional correlational study between meniscal size and gender, height, and weight. An independent radiologist performed the MRI-based meniscal size measurements, and these values were correlated to the mentioned demographic characteristics. The authors found that gender, height, and weight were proportional to meniscal tissue dimensions. Taller individuals, those with greater BMI, and males demonstrated bigger meniscal dimensions [56]. In a similar study, Van Thiel et al. [58] further observed that height was a more powerful predictor of meniscal size than weight. The average difference between the MRI-measured meniscal size and the actual meniscal size was 5.2–6.5 % for length and 5.2–6 % for width.

As previously reviewed in graft extrusion section, Jang et al. [27] evaluated the relationship between the meniscal sizing and the rate of extrusion. The authors found that, by reducing a 5 % of the dimensions obtained with the Pollard's method, the rate of extrusion was significantly reduced with no adverse effects on clinical and radiographic outcomes.

Graft horns fixation: bone plug versus soft tissue

There were six studies found in the literature comparing graft fixation methods: three in vitro human studies and three in vivo human studies.

In vitro human studies Alhalki et al. [4] evaluated the effects of three fixation methods of the medial meniscus on tibial contact mechanics. The authors assessed maximum pressure, mean pressure, contact area, and location of the center of maximum pressure under different compressive loads in the intact knee, the meniscectomized knee, and the re-implanted meniscal autograft, using different fixation methods. The authors demonstrated that the use of bone plugs restored contact mechanics closer to normal than other fixation methods, but the maximum pressure was greater than the intact knee [4]. In contrast, the use of sutures-only fixation did not restore the normal contact mechanics, and the authors recommended anatomical fixation of medial meniscal horns through bone plugs. Hunt et al. [21] published a biomechanical study aimed to compare the bone plug versus suture fixation through bone tunnel of the posterior horn of the medial meniscal allograft using knee specimens. After the surgical procedure on the specimens, all knees were loaded to failure and the authors observed no differences in the mean pullout strength of medial meniscal allograft posterior horn fixation between both methods [21].

Chen et al. [11] evaluated the effects of horn fixation of the lateral meniscus on joint contact pressure in a cadaver study. They loaded the specimens at 350 N of compression and evaluated the contact pressure and contact area in six situations: intact knee, total meniscectomy, transplantation with bone bridge fixation, no horns secured, anterior horn secured, posterior horn secured, and both horns secured using bone plugs. Essentially, the authors observed that the bone bridge fixation or the fixation of both horns independently elicited similar results to those for the intact knee. Interestingly, the absence of horn fixation gave results comparable to total meniscectomy [11].

In vivo human studies Abat et al. [2, 3] published two clinical studies regarding fixation techniques in MAT. One study was previously reviewed and involved the comparison of meniscal extrusion depending on whether suture-only or bony fixation of the allograft was performed [2]. The authors found that using suture-only fixation, the rate of meniscal extrusion was significantly higher compared to bony fixation. The same group also compared these two fixation methods with respect to mid-term functional and radiographic outcomes [3]. Essentially, they found that both methods had similar results.

It was previously reviewed in the article by De Coninck et al. [12] that the use of open MAT using soft-tissue

fixation to meniscal remnants elicited greater extrusion at 1 year postoperatively compared to arthroscopic bone tunnel fixation through transosseous sutures.

Discussion

The principal findings of this systematic review have been summarized in the conclusions section. The methodological quality of the included studies is, in general, suboptimal. In addition, the level of evidence of the studies reviewed for in vivo human investigations is low, as most of them were level III–IV and not level II.

Animal studies have been useful to show that the presence of living cells in the allograft is not needed or justified because donor cells are completely repopulated by host cells [25, 26]. This has also been observed in the human model [13]. In any case, the presence of donor cells in the allograft did not elicit any significant immune reaction after MAT in animals [45, 46]. With this regard, there is no need for immunosuppression treatment in transplanted patients. One of the concerns with allograft use has been traditionally the risk of disease transmission. This has evoked the use of various sterilization methods. However, there is a reasonable concern on how the sterilization method may affect tissue integrity. Animal studies have demonstrated that the sterilization process did not alter tissue integrity and would provide a safer scenario for prevention of infection transmission [40]. In contrast, it has been demonstrated that the graft preservation method may affect the meniscal composition in terms of number of cells and the alteration of normal collagen architecture [43, 60]. Research on basic science related to MAT should be focused on the identification of methods for improving graft incorporation into recipient knees, maintaining safe conditions and gaining a better understanding of the histological changes with the different preservation techniques.

While graft shrinkage is clearly an undesired complication of MAT, the relevance or clinical implications of graft shrinkage and other issues like meniscal extrusion are not well known. It is clearly necessary to further investigate the biomechanical implications of graft extrusion and the modification of tibiofemoral contact area and peak pressures depending on the degree of extrusion. In a similar way, the effects of graft size mismatch (either under or oversized) on knee biomechanics need to be further investigated. Dienst et al. [14] conducted a controlled laboratory study with human cadaveric knee joints to evaluate the effects of graft size on contact mechanics of the femoral condyle and tibial plateau. The principal conclusion was that an oversized and undersized allograft increased forces across the articular cartilage (mainly on the tibial plateau) and allograft itself, respectively. Another interesting result was the observation of contact mechanics in the transplanted group resembled those of the intact knees if less than 10 % graft mismatch was achieved. Allograft mismatch may cause failure of the graft and development of cartilage degeneration. Therefore, a precise and careful graft sizing preoperatively must be done in order to avoid potential short- and mid-term complications. However, there is not a completely reliable graft sizing method. There is no consistency on which method is the best, and it is generally accepted that some degree of graft size mismatch can be acceptable. The investigation on the long-term outcomes of MAT depending on the graft size mismatch is warranted to know its real clinical implications.

There are not many studies comparing different allograft fixation methods. However, the ones included in this systematic review for this topic have demonstrated the highest methodological quality (Table 1). In general, it is accepted that meniscal horns must be fixed in order to restore more closely normal knee biomechanics. However, there is no clear consensus on the biomechanical and functional differences between the use of bone or sutures for graft fixation. Many surgeons use a bone bridge for lateral meniscus transplant and bone plugs for medial meniscal transplant. It is likely that the results with any fixation method are comparable whenever the meniscal horns are adequately placed, the graft heals adequately to the periphery, and the patient undergoes an optimal rehabilitation protocol.

This systematic review has some limitations. First, it only used three databases for the literature search and only English-written articles were included. Therefore, there is a risk of missing some interesting references. Second, there is a risk of publication bias by not including "negative" studies that were not published. Third, the high heterogeneity of the measurement methods, methodological quality, and reporting of results make any comparison highly difficult. Despite these limitations, this systematic review offers an up-to-date comprehensive literature review regarding some of the most debatable topics in MAT, and provides evidence-based conclusions for each of the included topics, and identifies areas for future research.

Conclusions

The principal conclusions of this systematic review (provided according to the level of evidence whenever available) for each topic included are as follows:

1. Graft biology:
   - Animal studies:
     - Meniscal allografts have demonstrated adequate graft healing and incorporation.

- Allografts do not create a significant inflammatory or rejection reaction.
- Treatment of allograft with glutaraldehyde or gamma irradiation produces impairment in biomechanical properties of meniscal allografts.
- Immunosuppression of the allograft elicits adequate survival of the graft without a compromise of tissue healing and remodeling.
- Deep freezing of the allograft alters the normal collagen architecture.
- Donor cells present in the allografts are repopulated with host cells.
- Synovium appears to play an important role in graft cellular repopulation and revascularization.

- Human studies:

  - The age of the donor does not influence biomechanical properties or non-cellular composition of the allografts.
  - Donor cells present in meniscal allograft decrease with time and allografts are repopulated with host cells, similar to fibrochondrocytes.
  - The synovium may play an important role in graft cellular repopulation.
  - Deep freezing causes disruption of the collagen network, and an increase in water content and proteoglycan per weight.
  - Cryopreservation produces no significant changes in meniscal ultrastructure but a loss of viable cells through cellular apoptosis.

2. Graft shrinkage:

   - Meniscal allograft shrinkage is a relatively common phenomenon, with an average 7 % in cryopreserved allografts (level IV evidence).
   - Lyophilized and gamma-irradiated allografts demonstrated a higher rate of meniscal shrinkage compared to deep-frozen allografts (level II evidence).
   - Meniscal allograft shrinkage tends to appear in the firsts months after MAT and stabilizes thereafter (level III evidence).

3. Graft extrusion:

   - Graft extrusion is a very common phenomenon.
   - Graft extrusion is more frequent in lateral compared to medial MAT (level II evidence).
   - Meniscal extrusion does not correlate with clinical and functional outcomes (level II evidence).
   - Meniscal extrusion occurs most frequently in the anterior horn or mid-body (level II evidence).
   - The practical implications of meniscal extrusion are not well understood.

4. Graft sizing:

   - Both plain radiographs and MRI can be used for graft sizing.
   - There is no definitive evidence that MRI is better than plain radiograph for graft sizing. Further studies are needed comparing both imaging techniques.
   - Graft width size matching is more important than graft length size matching (level II evidence).
   - Meniscal size is influenced by gender, height, and weight. Height appears to be a more important predictor of meniscal size than weight (level III evidence).

5. Graft horns fixation:

   - In cadaveric studies, the fixation of meniscal horns restores joint contact pressures better than transplants performed without fixation of the meniscal horns.
   - Based on cadaveric studies, bone fixation of the medial meniscus horn attachments better restores knee contact mechanics compared to suture fixation.
   - There are no differences in pullout strength of the medial meniscus between sutures or bone fixation methods.
   - There are no differences in functional results between the use of sutures and bone fixation methods (level II evidence).
   - The use of suture fixation has more risk of graft extrusion compared to bone fixation (level II evidence).

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