Graft Selection Between Tendon Autograft and Allograft in Anterior Cruciate Ligament Reconstruction Based on the Histological Perspective: A Meta-Analysis

Seleção de enxerto entre autoenxerto e aloenxerto de tendão na reconstrução do ligamento cruzado anterior com base na perspectiva histológica: uma metanálise

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Abstract

Objective: The purpose of this meta-analysis is to compare ligament healing on autograft and allograft in anterior cruciate ligament (ACL) reconstruction.

Methods: The selection of appropriate studies was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We made a statistical analysis using a review manager. Electronic reports were searched using the PubMed, Medline, and Cochrane Library databases. The inclusion criteria were animal studies and cellular histology of both grafts as an outcome.

Results: The initial search revealed 412 potential articles. After duplicates were removed, 246 articles remained. Then, 14 articles were obtained and screened for relevance and eligibility. The relevant articles were searched manually, checking for eligibility and details in order not to miss included reports. Subsequently, 5 studies were included, with a total of 232 samples, reporting the biopsied results with quantitative histology of ligament healing between allograft and autograft. The biopsy samples in those studies were examined under light or electron microscope, to analyze the cellular distribution area and ligamentization stages in each group. Meta-analyses found significant difference between autograft and allograft (Heterogeneity, I2 = 89%;

Keywords
- Adolescent
- Allograft
- Anterior cruciate ligament reconstruction
- Autograft

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Mean Difference, 95% confidence interval [CI] = −34.92, −54.90, −14.93; $p = 0.0006$). There is also a significant difference on both graft in cellular count at over 24 weeks (Heterogeneity, I2 = 26%; Mean Difference, 95% CI = −14.59, −16.24, −12.94; $p < 0.00001$).

Conclusion: In the current meta-analysis, autograft shows a significant difference when compared to allograft, with more cellular accumulation and faster remodeling response on the ligamentization process being noticed in the former. However, a larger clinical trial will be needed to emphasize this literature's result.

Resumo

Objetivo: O objetivo desta metanálise é comparar a cicatrização de ligamentos no autoenxerto e aloenxerto na reconstrução do ligamento cruzado anterior (LCA).

Métodos: A seleção dos estudos adequados foi realizada de acordo com as diretrizes de Relatórios Preferenciais para Revisões Sistemáticas e Metanálises (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses* – PRISMA). Uma análise estatística foi feita usando um gerente de revisão. Os relatórios eletrônicos foram pesquisados usando os bancos de dados PubMed, Medline e Cochrane Library. Os critérios de inclusão foram estudos em animais e a histologia celular de ambos os enxertos como desfecho.

Resultado: A pesquisa inicial revelou 412 artigos potenciais. Após a retirada das duplicatas, restaram 246 artigos. Então, 14 artigos foram obtidos e selecionados pela relevância e elegibilidade. Os artigos relevantes foram pesquisados manualmente, verificando sua elegibilidade e detalhando os estudos para não perder os relatórios incluídos. Posteriormente, foram incluídos 5 estudos, com um total de 232 amostras, relatando os resultados de biópsia com histologia quantitativa de cicatrização de ligamento entre aloenxerto e autoenxerto. As amostras de biópsia nesses estudos foram examinadas sob microscópio leve ou eletrônico, para análise da área de distribuição celular e estágios de ligamentização em cada grupo. As metanálise encontraram diferença significativa entre autoenxerto e aloenxerto (Heterogeneidade, I2 = 89%; Diferença média, 95% intervalo de confiança [IC] = −34,92, −54,90, −14,93; $p = 0{,}0006$). Também há uma diferença significativa nos dois enxertos na contagem celular de mais de 24 semanas (Heterogeneidade, I2 = 26%; Diferença média, 95% IC = −14,59 , −16,24, −12,94; $p < 0{,}00001$).

Conclusão: Na presente metanálise, o autoenxerto mostra resultados significativos quando comparado ao aloenxerto, com mais acúmulo celular e resposta de remodelagem mais rápida no processo de ligamentização sendo observado no primeiro. No entanto, será necessário um estudo clínico maior para enfatizar o resultado desta literatura.

Palavras-chave
- Adolescente
- Aloenxerto
- Autoenxertos
- Reconstrução do ligamento cruzado anterior

Introduction

Injuries to the anterior cruciate ligament (ACL) of the knee are among the most commonly found injuries in young populations. Though it has not been well defined, some literatures estimated the incidence ranged from 30 to 78 per 100.000 people per year.[1] Furthermore, ACL rupture may also cause significant morbidity, where it impairs knee stability and results in difficulty participating in sport activity, as well as increasing the risk of meniscal injury and associated with structure damage. Due to the high incidence of ACL injuries, surgical reconstruction of ACL plays an important role in restoring knee function, especially in the field of Orthopedic Sports Medicine.[2]

Unlike other tissues, such as the medial collateral ligament (MCL), ACL will not heal spontaneously once it is ruptured. The reason is still unclear, but it may be caused by a lack of vascular supply or due to intrinsic failure of the ACL cells to produce new collagen. The main structure of ACL is 90% comprised of collagen type 1, and the remainder 10% is collagen type III, both of which are excreted intracellularly and modified extracellularly; then, they are self-assembled into the microfibrils. The collagen in ACL will be degraded continuously within 300 to 500 days. Beyond the collagen molecules, only 1% of the dry weight ligament is comprised of other molecules, including proteoglycan (chondroitin-4-

sulfate and dermatan sulfate). Fibroblasts are also located in the collagen line, functioning as cell communication to coordinate cellular and metabolic processes, as well as producing and maintaining the extracellular matrix.[3–6]

When the ligament is exposed to extended loading, it will increase in mass and failure load, especially if the load is greater than the sustainable amount, causing partial or complete ligament rupture. Complete ligament rupture requires surgical reconstruction using autograft or allograft. Autograft provides a scaffold similar to the natural composition of the native ligament. Some experimental studies have evaluated the remodeling process of the autograft postoperatively, including cellular changes such as vascular growth and fibroblast proliferation. First, the inflammatory phase will happen from within minutes up until 48 to 72 hours postsurgery; followed by the repairing phase, which initiates fibroblast proliferation signals to rebuild the ligament's tissue matrix. The final phase is remodeling, which can last for years, where the graft begins to resemble normal ligament tissue. Moreover, some scientists believe that ligamentization occurs only in the outer portion of the graft, early revascularization on graft surface will occur within 2 to 4 weeks, and the avascular zone in the mid-substance of the graft remains even after 6 to 12 months. According to some researchers, autograft will begin to appear as "normal" ligament tissue within 9 months. A key advantage on autograft is the absence of foreign body reaction, as the graft was taken from the same body tissue. Regardless of this advantage, autograft is also associated with some morbidity, such as discomfort and decreased range of motion over donor area, which may affect postoperative rehabilitation.[5–7]

Alternatively, allograft is a tissue taken from donor of the same species. There are some advantages for using allograft, such as shorter surgery time and lack of donor-site morbidity. The major disadvantage is the risk of disease transmission.[8] Despite this, some studies consider allograft as the best substitute to autograft.[6]

A standard method to evaluate remodeling process of bone tendon graft healing is a histologic examination of graft tissue.[9,10] Because of the difficulties getting human histologic examination due to research ethics, there are a limited number of experimental studies that directly compared autograft and allograft ligamentization, and some contradiction studies over which one is the best graft option for ACL reconstruction. To advance it further, a thorough analysis of previous experimental studies on the histological process of autograft and allograft should be performed. The aim of this review is to systematically analyze the autograft and allograft healing process based on histological findings.

Materials and Methods

Search Strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11,12] The search for studies was done in the PubMed, Science Direct, and Cochrane Library databases on May 23, 2020, to identify all of the published studies reporting ligament healing based on histological process, comparing autograft and allograft for ACL reconstruction. We extracted the eligibility criteria into keywords of the Boolean Operator. The keywords used were "ligamentization" OR "ligament healing process" OR "re-modelling" AND "autograft-tendon" OR "auto transplant tendon" OR "autologous graft" AND "allograft-tendon" OR "allotransplant tendon" AND "ACL reconstruction" OR "Anterior Cruciate Ligament reconstruction" OR "ACL surgery" OR "Anterior Cruciate Ligament surgery."

All the inherent aspects of each study, including study quality, objective, study selection, data variables, risk of bias assessment, and irrelevant data were analyzed by the first authors. All studies' abstracts and titles were read and selected appropriately by decision of the first author. Duplicate records and irrelevant studies were removed in this phase. Subsequently, the second author decided whether the studies should be further analyzed, as an expert in Orthopedic Sports Surgery. Furthermore, studies that underwent the first screening were evaluated by both authors using the inclusion and exclusion criteria.

Inclusion and Exclusion Criteria

We used the PICO (Population, Intervention, Comparison and Outcome) method. Inclusion criteria were population (animal studies) with the intervention being ACL reconstruction surgery using autograft and allograft. The comparison was cellular healing based on the histological findings between autograft and allograft.

We excluded case reports, case series, review articles, and all articles with level of evidence bigger than II (►**Table 1**). All studies that underwent ACL reconstruction using only autograft or allograft were also excluded.

Adequate study protocols for result verification as well as comprehensible documentation of the remodeling process.

Study Quality Assessments

Authors searched the studies for titles and abstracts based on inclusion criteria. Then, full articles were extracted from all databases that were suitable for the subject. The authors had a meeting and discussed which relevant studies should be included. The quality and content from studies were assessed, and any disagreements were discussed to finalize a highly qualified and eligible study.

All aspects of the studies, including methodological quality, data variables, and risk of bias assessment, were appraised by filling up forms (►**Fig. 1**), which were then collected by the main author. Finally, the authors gathered to discuss any contradicting points.

Statistical Analysis

We measured the results of the meta-analysis using the Review Manager (RevMan. The Nordic Cochrane Center, Cochrane Collaboration. Odense, Denmark) software, version 5.3. The interstudy heterogeneity was computed with the $\chi 2$ test, with results being considered heterogeneous if $I^2 < 50\%$. For the continuous outcome, we used the mean difference (MD) and odds ratio (OR) for dichotomous outcomes. The authors also

Table 1 Studies used in this meta-analysis

Authors	Journal	Country	Procedure Date Range	Study Design	Level of Evidence
Razi et al., 2009	Journal of Orthopaedic Surgery and Research	Iran	2006–2012	Cohort Prospective Study	III
Barber et al., 2014	The Arthroscopy Association of North America	USA	2001–2012	Retrospective Comparative Study	III
Larson et al., 2016	The Arthroscopy Association of North America	USA	2002–2007	Case Series	IV
Li et al., 2012	The American Journal of Sports Medicine	China	NA	Cohort Prospective Study	III
Engelman et al., 2014	The American Journal of Sports Medicine	USA	2005–2009	Case Control Study	III
Sun et al., 2011	The Journal of Arthroscopic and Related Surgery	China	2005–2008	Prospective Comparative Study	II
Tian et al., 2016	The American Jorunal of Sports Medicine	China	2008–2009	Randomized Controlled Trial	II

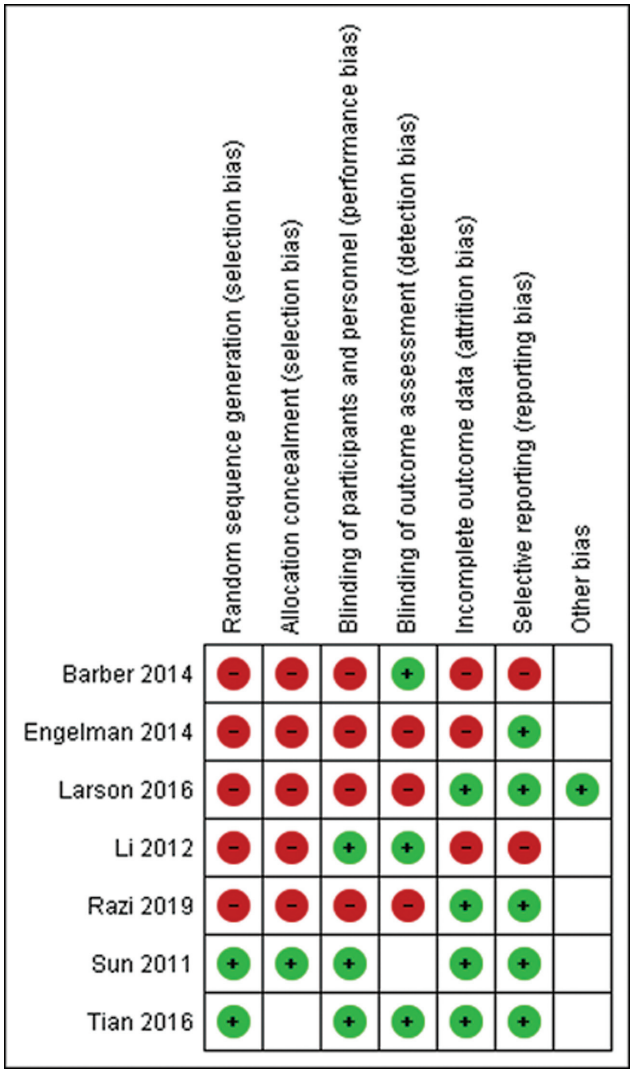

Fig. 1 Flow diagram describing the strategy for conducting this study based on the PRISMA guidelines.

assessed the clinical impact of this meta-analysis review using a trial sequential analysis (TSA) with the statistical software of TSA (Copenhagen Trial Unit. Copenhagen, Denmark), beta version 0.9. The results is considered significant if the Z-curve crosses the boundary of futility.

Result

Search Result

Initial search through PubMed, MEDLINE, and Cochrane Library revealed 412 potential articles. After the duplicates were removed, 246 articles remained. From those, 14 articles were obtained and screened for relevance and eligibility. The relevant articles were searched manually, eligibility was checked, and details were studied in order not to miss included reports. Subsequently, 5 studies were included in this meta-analysis, reporting biopsied results with quantitative histology of ligament healing between allograft and autograft. The 9 excluded studies did not provide ligamentization comparison between allograft and autograft, or ligamentization time frame. At the end of the selection process, 5 studies with animal models were included, as shown in ►**Fig. 2**. The total sample of all studies is 232 animal models.[7,13–16] All of studies were prospective, with designated time points for histology examination..

All articles had varied level of evidence, ranging from level I to II (►**Table 1**). Duration of follow-up started as early as post-operative until a maximum of 54 weeks. The animal models used were mammals such as Merino sheep, goats, and New Zealand rabbit. Each study criteria were listed in ►**Table 2**.

ACL Reconstruction

All included studies had autograft and allograft transplantation groups, with four of them using the flexor tendon as an allograft and autograft. Types of autograft and allograft

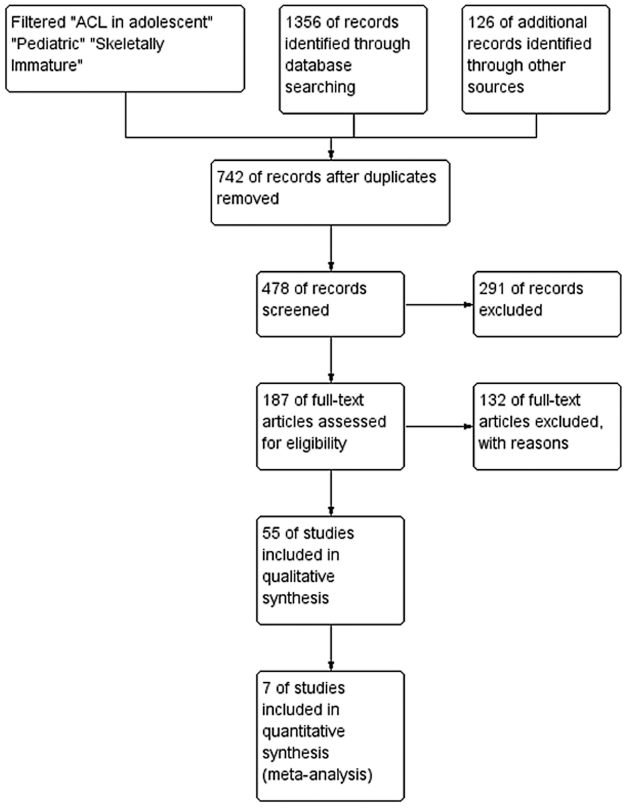

Fig. 2 Risk of bias summary: review of authors' judgements about each risk of bias item for each included study.

preparations were varied. All studies were using graft transplantation with a diameter of 6 to7 mm. Those studies performed both arthrotomy and excised native ACL, followed by ACL reconstruction. Graft fixations also varied from femoral, tibia fixation button, cancellous screw, and Krakow stitches. After the surgical procedure, each animal was immobilized in individual cages.

Graft Examination

Animals were euthanized at fixed time points ranging from 2 to 52 weeks, and the healing process was evaluated by histomorphometry. Only one study evaluated the macroscopic gross on graft treatment, starting from two weeks after surgery, and found accumulation of synovial fluid over the graft insertion.[13] Tissue samples were taken from midsubstance tissue of graft bundle until graft insertion sites; only three studies showed specimen size on biopsy site ranging from free cut at around 7 to 8 µm.[14–16] They also performed H&E staining followed by histologic analysis performed under conventional light and/or high electron microscopes.

Ligamentization Process

To document ligamentization process, all studies evaluated different aspects, such as cellular distribution and morphology, appearance of inflammatory cells, vascularization, extracellular matrix, phases of healing, and length of healing process. The aspects that all of those studies evaluated are cellular distribution of the remodeling graft, phase of healing, and length of healing process. A second look at the arthroscopy and histology evaluation started as early as 2 weeks, up until 54 weeks, as seen in ►**Figs. 1** and **2**.[7,13–16] The initial remodeling changes and degenerative process could be seen at 2 weeks postoperatively. At the peripheral tendon, the regular matrix was replaced with dense connective tissue.[13] At 6 weeks postoperatively, there was cellular proliferation of osteoblasts and newly formed blood vessels, with a marked difference between allograft and autograft, with less cellularity in the first one.[7,14,15] Collagen crimp begins to reorganize toward center of the graft, and the endochondral ossification begins in the bone tendon junction throughout 12 weeks in both graft types.[7] Cellular formation and vascular components will resemble an intact ACL at 48 weeks in autograft. Myofibroblast density will continue to increase up to 52 weeks, when cellular distribution and morphology was improved in each graft.[7,15]

Of the articles included in this research, 4 evaluated that there was less cellular and vascular proliferation in tendon allografts rather than in autografts. Furthermore, 4 of the 5 included studies have been evaluated in different ligamentization stages than those already observed up until 54 weeks.[7,14–16] Only one study had observed within short period until 8 weeks.[13] The 4 other reports have mentioned three different stages of ligamentization with similar characteristics of histologic changes.[7,14–16] Allograft and autograft healing have similar phases and ligamentization time frame, with the exception of cells density, cellular distribution in each phase, and tendon graft vascularization, which will never reach the level of native ACL.[10]

We performed a meta-analysis on the cellular count from 6 to 8 weeks with a statistically significant result between autograft and allograft (Heterogeneity, $I^2 = 89\%$; MD, 95% confidence interval [CI] = −34.92, −54.90, −14.93; $p = 0.0006$). The cellular count at over 24 weeks is also statistically significant between both grafts (Heterogeneity, $I^2 = 26\%$; MD, 95% CI = −14.59, −16.24, −12.94; $p < 0.00001$) (►**Fig. 3**).

Discussion

Nowadays, the allograft has gained more popularity than autograft in ACL reconstruction, since it has decreased surgical time, low donor morbidity, and unaltered patellofemoral tracking.[2] However, there was a debate over the issue of radiated allograft, which uses gamma irradiation and has a greater impact to graft healing. Several studies on the process of allograft healing found it happened similarly to autograft, but with a slower rate of healing. Gulotta et al.[3] found that freezing allograft components during graft preparation will also denature the cell surface components, resulting in a decreased graft immunogenicity and causing hypocellular allograft ligament and limitation of immune response during the initial healing stages.[3,9] Conversely, autograft has some advantages over allograft, including a decrease in the risk of disease transmission during ACL

Table 2 Outcome characteristics of the included studies

Parameters	Razi et al. 2019			Barber et al. 2014			Larson et al. 2016			Li et al. 2012			Engelman et al. 2014		
	Allograft (n = 13)	Autograft (n = 18)	*p*-value	Allograft (n = 28)	Autograft (n = 53)	*p*-value	Allograft (n = 8)	Autograft (n = 22)	*p*-value	Allograft (n = 30)	Autograft (n = 22)	*p*-value	Allograft (n = 38)	Autograft (n = 35)	*p*-value
Primary Outcomes															
Graft Failure	6 (46.2%)	7 (38.9%)		2 (7.1%)	5 (9.4%)	0.85	3 (37.5%)	2 (9%)	0.10	0	0	> 0.99	11 (28.95%)	4 (11.43%)	0.3756
Lachman Test Positive	6 (46.2%)	7 (38.9%)	0.68	3 pt (gr 1 +)	3 pt (gr 1 +)		3 (37.5%)	2 (9%)		6 (20%) gr 1+	4 (18.2%) gr 1+		0	0	
Positive Pivot Shift Test	0	0		2 pt	4 pt		0	0					0	0	
Knee Joint Translation (KT Arthrometer, MRI)	Side to side: -	Side to side: -		Side to side: 0.59 mm (SD = 1.5) < 3 mm: 22 pt 3–5 mm: 3 pt > 5 mm: 0	Side to side: 0.34 mm (SD = 1.9) < 3 mm: 43 pt 3–5 mm: 6 pt > 5 mm: 1	0.58	Mean side to side: 0.4 ± 2.4 mm		<0.01	0.42 ± 0.04 mm	0.43 ± 0.02 mm	0.5908	10.81% pt	15.63% pt	0.5538
IKDC scores	84.3 ± 3.2	85.6 ± 4.4	0.39	1.9–2.9 (pre-post-op) (2.4 ± 0.5)	3.3–3.1 (pre-post-op) (3.2 ± 0.09)	0.32	68.2–91.8 (−27.7–−18.0) 95% CI Mean: 80 ± 11.8		<0.01	92.6 ± 5.9	93.3 ± 5.2	0.644	94 ± 5	88 ± 10	0.4817
Cincinnati Scores				54.6–86.2 (pre-post-op) (70.4 ± 15.8)	39.5–85.1 (pre-post-op) (62.3 ± 22.8)	0.76	75–93.1 (−26.4 (−12.1) 95% CI (94 ± 9.05)		<0.01						
KOOS	78 ± 7.2	75 ± 7.4	> 0.05												
Lysholm Scores				60.3–89.9 (pre-post-op) (75.1 ± 14.8)	44.8–87.0 (pre-post-op) (65.9 ± 21.1)	0.43	79.3–91.5(−20.1 (−6.4) 95% CI (85.4 ± 6.09)		<0.01	93.4 ± 5.2	94.3 ± 5.4	0.543	91.5 ± 6.5	84.5 ± 6.5	0.465
Secondary Outcomes															
Revision surgery	6 pt	7 pt		2 pt	5 pt		3 pt	2 pt		0	0		11 pt	4 pt	
Infection	0	1 pt (5.6)													

Abbreviations: IKDC, International Knee Documentation Committee; MRI, magnetic resonance imaging. **Notes:** *Values in Graft Failures and Lachman Test are reported as number (percentage). Values in IKDC, Cincinnati and Lysholm are reported as median (Interquartile range).

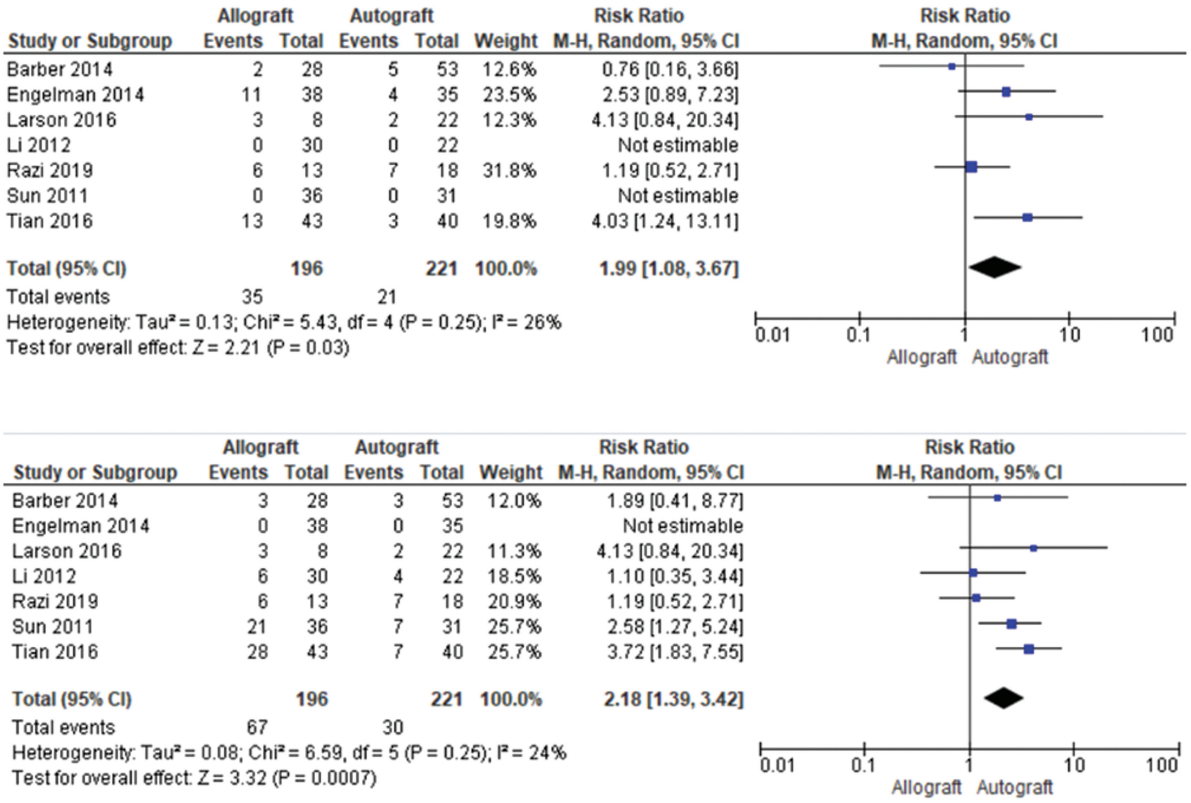

Fig. 3 Comparison: Allograft vs. Autograft; Outcome: Graft Failure, Lachman Test > +1, IKDC Score, Revision Surgery.

reconstruction; some authors also demonstrated that graft incorporation between tendon graft to bone insertion showed a higher rate compared with allograft.[6,13]

According to the included studies, based on cellular distribution, vascularization, and other histology signs of graft maturation, there are three consecutive distinguishable phases of ligamentization. Pauzenberger et al.,[10] in a review based on four studies, found that the initial phase of healing start from 2 up until 12 weeks, followed by remodeling from 12 to 48 weeks, to the final maturation phase, which will be ongoing up until 48 months.[6,10] Primarily using animal models to evaluate ligamentization process in allograft and autograft, Gulotta et al.[3] reveals that the intra-articular healing of both grafts has the same process, from the initial phase until progressive remodeling and maturation, the difference being that allograft relies on bone to tendon healing and heal through fibrovascular tissue with anchoring of formation Sharpey's Fiber and new bone production, first healing of allograft will undergo osteonecrosis over tendon bone graft insertion, followed by incorporation graft to tunnel.[3,10] Several experimental studies also found no differences in ACL reconstruction using allograft or patellar tendon autograft. Conversely, Jackson et al.[14] used patellar goat tendons to demonstrate that there were slower healing rate and less complete incorporation of tendon grafts to an insertion tunnel when compared to autograft. The ACL reconstruction with allograft should be protected from maximum load for a longer period of time.[14,17] Another report has demonstrated myofibroblast formation and collagen crimp; myofibroblast expression was higher, and the restoration and organization of collagen crimp was better in autograft; this process happens in the early healing phase of autograft.[5,7,18] Another study, by Nikolaou et al.,[8] used cryopreserved allograft (−80° C) in canines as a study model and found there was no healing disruption and no effect on the biomechanical properties, so the allograft structures were still similar to autograft. Shino et al.,[19] who used deep freezing allograft (−20° C) in dog models, also found a similar healing process with autograft. Over 30 weeks, allografts will have the same mechanical properties as the previous native ACL, and over 52 weeks the anterior cruciate ligament will be similar to its normal composition.

Furthermore, this review shows the concept of general ligamentization between autograft and allograft proposed in animal models. Ligamentization of graft is a biological continuous and time-dependent process. The difference in graft healing between autograft and allograft is useful to choose the graft technique preoperatively and to determine the rehabilitation period postoperatively. However, there is no consensus in the current review regarding the ligamentization process' time frame, as each study has a different quantitative histology of graft healing.

Parameters	Tian et al. 2016			Sun et al. 2011		
	Allograft (n = 43)	Autograft (n = 40)	*p*-value	Allograft (n = 36)	Autograft (n = 31)	*p*-value
Primary Outcomes						
Graft Failure	(13) 30.2%	(3) 7.5%	0.001	0	0	NA
Lachman Test Positive	Gr 0: 15 (34.9%) Gr I: 16 (37.2%) Gr II: 12 (27.9%) Gr III: 0	Gr 0: 33 (82.5%) Gr I: 4 (10%) Gr II: 3 (7.5%) Gr III: 0	0.001	Gr 0: 29 (80.6%) Gr I: 11 (35.5%) Gr II: 10 (32.3%) Gr III:0	Gr 0: m10 (32.3%) Gr I: 4 (11.1%) Gr II: 3 (8.3%)	0.00011
Positive Pivot Shift Test	Gr 0: 27 (62.5%) Gr I: 11 (25.6%) Gr II: 5 (11.6%) Gr III: 0	Gr 0: 37 (92.5%) Gr I: 3 (7.5%) Gr II: 0 Gr III: 0	0.004	19 (61.3%) gr 0 8 (25.8%) gr 1 4 (12.9%) gr 2	33 (91.7%) gr 0 3 (8.3%) gr 1	0.008
Translation (KT Arthrometer, MRI)	Side to side: 5.5 mm (SD = 1)	Side to side: 2.4 mm (0.7)	0.04	Side to side: 5.6 mm (SD = 3.1) < 3 mm: 10 (32.3%) > 5mm: 10 (32.3%)	Side to side: 2.5 mm (SD = 0.7) < 3 mm: 31 (86.1%) > 5mm: 3 (8.3%)	0.00017
IKDC scores	85 ± 11	89 ± 9	0.0748	83 + 10	87 + 10	0.208
Cincinnati Scores	87 ± 12	90 ± 10	0.2214	85 + 13	88 + 11	0.212
Lysholm Scores	86 ± 9	90 ± 11	0.0727	87 + 11	89 + 8	0.353
Secondary Outcomes						
Revision surgery	0	0		0	0	
Infection				0	0	

Abbreviations: IKDC, International Knee Documentation Committee; MRI, magnetic resonance imaging. **Notes:** *Values in Graft Failures and Lachman Test are reported as number (percentage). Values in IKDC, Cincinnati and Lysholm are reported as median (Interquartile range).

Limitations

The validity of this review is determined by the quality of the included studies, which have a publication range from 1993 to 2012. As different surgical techniques for ACL reconstruction were progressively developed, various animal models have been used, but none of the studies analyzed here used human models. Meanwhile, animals had a higher rate of graft healing compared to humans. However, none of the previous studies in humans have compared ligament healing for each type of graft, as a second invasive procedure was hardly done. Those studies with animal models can be an initial benchmark to compare ligament healing with studies which used bigger populations and humans as a study model. Inter-study heterogeneity with different parameters could interfere with the results, such as various histology study methods and quantitative histology results. Moreover, there is still a limited number of studies which compared ligamentization between allograft and autograft. Further clinical studies are needed to compare the best healing between autograft and allograft, based on histology reviews, to increase the success rate of ACL reconstruction. Those clinical studies seem to be important regarding the failure rate, which has increased.

The healing processes of autograft and allograft were similarly composed, resembling the native ACL as early as 48 weeks in the maturation phase. The major difference of both ligamentization processes is the cellular distribution, which is worse in allograft than autograft. We recommend autograft for ACL reconstruction, because it shows more cellular accumulation and faster remodeling response when compared to allograft, with significant results. Thus, both autograft and allograft healing have similar time duration and three chronological and distinguishable phases, beginning with early inflammatory phase, remodeling phase, and maturation phase. However, larger clinical trials will be needed to emphasize this literature's result.

Conclusion

In ACL reconstruction, both autograft and allograft can be considered as the treatment of choice. However, we concluded that autograft is better than allograft when comparing the healing rates. Furthermore, in autograft, the cellular distribution is different from allograft, in which there is a lower cellular accumulation, meaning autograft has better outcomes with faster remodeling response. Assessment of patients' activity level and postoperative rehabilitation are also important for better outcomes.

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Conflict of Interests
The authors have no conflict of interests to declare.

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