Hamstring tendon regeneration after harvesting: a systematic review

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ABSTRACT

Background: Hamstring tendons are often used as autografts for anterior cruciate ligament (ACL) reconstruction. However, no systematic review has been performed describing consequences, such as hamstring tendon regeneration rate and determinants of hamstring tendon regeneration.

Purpose: To summarize the current literature regarding hamstring tendon regeneration rate, the time course of regeneration, and determinants of hamstring regeneration.

Study design: Systematic review.

Methods: A search was performed in the Embase, Medline (OvidSP), Web-of-Science, Cochrane, PubMed and Google Scholar databases up to June 2014 to identify relevant articles. A study was eligible if it met the following inclusion criteria: tendons were harvested, regeneration at harvest site was assessed, population size was at least 10 human subjects, full-text article was available and the study design was either a randomized controlled trial, prospective cohort study, retrospective cohort study or case control study. A risk of bias assessment of the eligible articles was determined. Data describing hamstring tendon regeneration rates were pooled per time period.

Results: A total of 18 publications met the inclusion criteria. The mean regeneration rate for the semitendinosus and gracilis was, in all cases, 70%, or higher. More than 1 year after harvesting, 79% (median [IQR], 80 [75.5-90]) of the semitendinosus tendons and 72% (median [IQR], 80 [61-88.5]) of the gracilis tendons were regenerated. No significant differences in regeneration rate could be found considering patient sex, age, height, weight or duration of immobilization. Results did not clearly show whether absence of regeneration disadvantages the subsequent hamstring function. Five studies measured the regeneration rate at different moments in time.

Conclusion: Hamstring tendons regenerated in the majority of patients after ACL reconstruction. The majority of the hamstring tendon regeneration was found to occur between 1 month and 1 year after harvest. No significant determinants for hamstring tendon regeneration could be identified because of a lack of research. The function and strength of the regenerated hamstring remained unclear.

Clinical relevance: Insight into hamstring tendon regeneration is of clinical relevance as it may influence the choice of ACL graft and it may alter the current rehabilitation after harvesting the tendon.

Key terms: hamstring tendon regeneration; determinants; time course; clinical outcome.

INTRODUCTION

The hamstring has become one of the most often harvested tendons used to reconstruct the anterior cruciate ligament (ACL) after rupture[18]. Hamstring tendon autografts are used more often for primary ACL reconstruction compared with bone-patellar tendon-bone (BPTB) autografts[1,12,17]. This may be the result of several advantages to using hamstring tendons, such as less donor-site morbidity, fewer kneeling problems, and fewer patellar tendon ruptures[8,9,32,33].

In 1992, Cross et al[5] were the first to describe the potential of hamstring tendons to regenerate after harvesting for ACL reconstruction. However, in the following years, after observing neotendons by histology or visual means, investigators found that some hamstring tendons seemed to lack the ability to regenerate[16,27].

Several predictive factors have been identified for tendon regeneration in general. Some examples of determinants that may negatively influence tendon regeneration are the use of nonsteroidal anti-inflammatory drugs[25], the use of nicotine[22], and diabetes mellitus[10,11]. However, no systematic review has described determinants for hamstring tendon regeneration before.

Knowledge of regeneration of hamstring tendons is of clinical importance, as it may influence the choice of ACL graft and may even change rehabilitation programs after surgery[13]. In addition, some patients voice concerns about the consequences of removing native tendons and the functional deficits that may result as a consequence. This systematic review aimed to answer these questions.

No systematic review has been performed concerning the regeneration of harvested hamstring tendons previously, nor has a review been performed to describe determinants for hamstring tendon regeneration. The aim of this systematic review was to summarize (1) hamstring regeneration rate after harvesting, (2) the time course of regeneration, (3) the morbidity and function loss of nonregenerated harvested hamstrings, and (4) determinants that may influence the process of regeneration.

METHODS

Search strategy

The search strategy (Supplementary Table 1) was carried out on published literature from the following electronic databases: Embase, Medline (OvidSP), Web-of-Science, Cochrane, PubMed and Google Scholar. These databases were searched from their inception to June 1, 2014. Additionally, the reference list of each included study was reviewed.

Eligibility criteria

A publication was eligible if (1) a surgical procedure that entailed hamstring tendon harvesting was used, (2) an evaluation of hamstring regeneration at harvest site was performed, (3) the study population consisted of a minimum of 10 patients, (4) the study was performed on humans, (5) full-text article was available, and (6) the study design was a randomized controlled trial, prospective cohort study, retrospective cohort study, or case control study.

Studies were excluded when (1) the outcome was other than specified in the inclusion criteria (e.g. evaluation of the hamstring tendon autograft), (2) there was no information about the regeneration, or (3) previous hamstring injuries were reported.

Animal studies were also excluded. The search was limited for language (English, Dutch, French, German, or Spanish).

Identification of eligible studies

Identified studies were screened, based on title and/or abstract, independently by 2 reviewers (M.S., D.M.). Full-text versions of the selected studies were reviewed, and if they met the eligibility criteria, the study was included in the current systematic review. Disagreements were solved by consensus.

Data extraction

Three independent reviewers (M.S., S.L., and J.P.) performed data extraction from each included publication. Extracted characteristics of the included studies were as follows: number of included subjects, sex, average age, time between surgery and evaluation, imaging technique and experience of examiner. The outcome measures were percentages of tendon regeneration, the time course of regeneration, the morbidity of harvested hamstrings not regenerated, and determinants predicting the regeneration potential of the hamstring tendon. Hamstring tendon regeneration rates are displayed in percentages based on their follow-up periods (less than or more than 1 year).

Risk-of-bias assessment

We assessed the risk of bias of studies using a quality assessment list (Table 1), based on modified questions of existing quality assessment tools[6, 7, 29]. The purposes of this systematic review were of a different nature. Studies reporting the rate of tendon regeneration were considered to have a low risk of bias if consecutive patients were included and if the imaging technique used was valid and reliable. Next to these criteria, in order to be considered to have a low risk of bias, articles investigating a relationship between tendon regeneration and determinants of regeneration or clinical outcome had to use valid determinants as well as an unbiased assessment of the study outcome and

determinants. Two independent researchers performed the risk-of-bias assessment. Disagreement was solved by consensus.

Table 1. Criteria for the risk-of-bias assessment.

Question	Response
1. Is there a clearly stated aim?	The study must have a study question, main aim or objective. The question addressed must be precise and relevant in light of the available literature. To be judged as *adequate*, the aim of the study must be consistent with the description given in the introduction of the paper.
2. Were consecutive patients included?[a, b]	The investigators must state 'consecutive patients' or 'all patients during period from *X* to *X*.'
3. Are inclusion and exclusion criteria described?	Inclusion and exclusion criteria must be reported.
4. Is the inclusion of patients described?	The number of eligible patients who agreed to participate (ie. gave consent) must be reported.
5. Was data collection prospective? That is, were data collected according to a protocol established before the beginning of the study?	The investigators should state 'prospective' or 'follow-up'. A study is not prospective when the study design is a chart review or database review.
6. Was the imaging technique used to confirm regeneration valid and reliable?[a, b]	To be judged as *adequate*, at least 1 of the following imaging techniques must be used: histological biopsy, magnetic resonance imaging, echo / ultrasound, computed tomography. All other imaging techniques are judged as inadequate.
7. Was assessment of the study outcome and determinants unbiased?[b]	To be judged as *adequate*, outcome(s) and determinants have to be measured independently of each other.
8. Were the determinants measures used accurate (valid and reliable)?[b]	To be judged as *adequate*, the determinant measures must be shown to be valid and reliable, or the investigators must refer to other work that demonstrates the determinant measures to be accurate.
9. Was the follow-up period appropriate for the aim of the study?	To be judged as *adequate,* the study must report the follow-up period, and a study must entail 3 months' minimal follow-up.
10. Was loss of follow-up reported and acceptable?	To be judged as *adequate*, the study must report the loss of follow-up, and the loss of follow-up must be ≥20%.
11. Was the sample size calculated before the study was initiated?	To be judged as *adequate,* calculation of the sample size must have been made before the study was initiated.
12. Were the statistical analyses adequate?	To be judged as *adequate,* the following aspects must be met: - The relationship between the determinant and the primary outcome was described. - There was an adjustment for age and/or sex. A study was inadequate if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses. - The variance of the outcome was reported (e.g. standard deviation, confidence interval)

[a] *Judged as adequate for studies investigating the rate of hamstring tendon regeneration.*
[b] *Judged as adequate for studies investigating a relationship between hamstring tendon regeneration and determinants or clinical outcome.*

When the article met the criterion, 1 point was granted, if the criterion was not met, 0 points were given. If the information concerning the specific criterion was not available in the study and information was not available after contacting the authors, 0 points were given.

Statistical analysis

In this systematic review, data for hamstring tendon regeneration were pooled. Regeneration rates less than 1 year after harvesting were pooled, and regeneration rates more than 1 year after harvesting were pooled. Distribution of the pooled data are displayed as median and interquartile range (IQR).

RESULTS

Literature search

From initial 2957 relevant articles identified, 2939 publications were excluded based on title and abstract, because they did not meet the inclusion criteria. Consequently, a total of 18 studies were included. A flow chart of the literature search is presented in Figure 1. Hamstring tendon regeneration rates were reported in 17 of the included studies, and 6 of the included studies reported possible determinants for hamstring regeneration or clinical outcome.

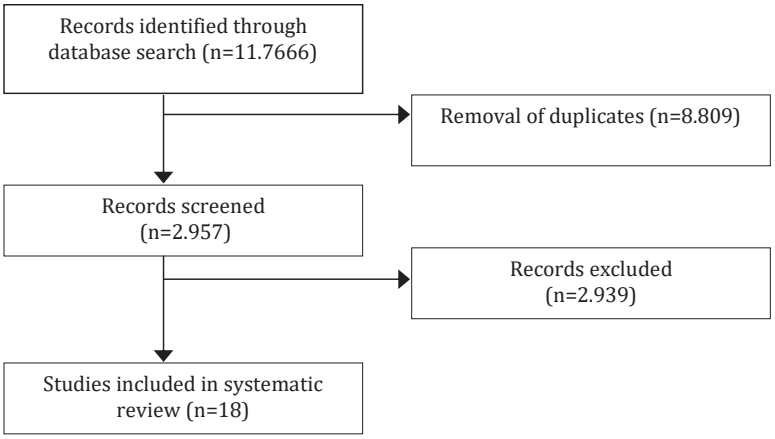

Figure 1. Flow chart.

Risk-of-bias assessment

According to the predefined criteria, 6 articles that considered the rate of hamstring tendon regeneration had a low risk of bias[4, 11, 15, 26, 27, 30]. Three studies investigating

possible determinants for hamstring regeneration or clinical outcome had a low risk of bias[4, 11, 26] (Supplementary Table 2). Other studies did not meet the criteria and were therefore considered to have a high risk of bias.

Study characteristics

The study sizes ranged from 10 to 50 patients. The average age of the included patients varied from 20 to 37 years. Male participation ranged from 27% to 100%. Follow-up time ranged from 1 week to 10 years. Table 2 shows the data extraction of the studies evaluating hamstring tendon regeneration after harvesting.

Measuring methods

The included studies used different imaging techniques to determine regeneration of the hamstring tendons. Magnetic Resonance Imaging (MRI) was the most common used technique (12/18)[2, 4, 9, 11, 15, 19, 23, 24, 28, 30, 34, 35]. Other techniques used were 3-dimensional computed tomography (2/18)[20, 21], histological biopsy (3/18)[9, 26, 31] and ultrasound (3/18)[3, 27, 31].

To be assessed as regeneration, all the included studies demanded at least regrowth of tendon tissue. Next to this, different studies used their own scoring system with additional points of interest (e.g. cross-sectional area of muscles and tendons, muscle volume, muscle length, proximal shift of the musculotendinous junction, pixel value, and insertion site) to assess the presence or absence of regeneration.

Tendon regeneration

All included studies reported their exact regeneration rates except from Rispoli et al[28]. The regeneration rates varied overall from 50% to 100% for the semitendinosus tendon and from 46% to 100% for the gracilis tendon (Table 3). Regeneration of the gracilis tendon was only measured by use of MRI. After the data were pooled, the overall mean regeneration rate in the first year after harvesting was 91% (median [IQR], 97[74-100]) for the semitendinosus and 100% for the gracilis tendon. The overall mean regeneration rate more than 1 year after harvesting was 79% (median [IQR], 80 [75.5-90]) for the semitendinosus and 72% (median [IQR], 80 [61-88.5]) for the gracilis.

Time path of tendon regeneration

Five studies determined the regeneration rate at different points in the first year after ACL reconstruction. Eriksson et al.[11] described that no tendon regeneration could be observed 2 weeks after surgery, but 6 months after surgery, the majority of the patients (73%) showed regeneration.

Table 2. Data extraction.

		Study participants					
Author (Year)	**Study design**	**No.**	**Sex, % male**	**Age at start study, y, (mean or median (± SD[b])**	**Follow-up time, mo (mean or median (± SD[b])**	**Imaging technique**	**Experience examiner (No. of examiners)**
Eriksson et al.[11](1999)	Prospective study	11	73	24	6-12	MRI	MRI radiologist (1)
Papandrea et al.[27] (2000)	Prospective study	40	73	28	24	US	Orthopaedic surgeon (1)
Eriksson et al.[9] (2001)	Case series	16	88	26	MRI, median: 7 Histology, median: 10	MRI / Histology	MRI: MRI radiologist (1) Histology: unknown
Rispoli et al.[28] (2001)	Case series	20	65	37	32	MRI	Musculoskeletal radiologist (2)
Tadokoro et al.[34] (2004)	Retrospective study	28	36	22	67.2	MRI	NR
Nakamae et al.[21](2005)	Prospective study	29	52	28	12	3D-CT	Orthopaedic surgeon (2)
Nishino et al.[23] (2006)	Prospective study	23	43	22 (±4)	23	MRI	NR
Okahashi et al.[26] (2006)	Prospective study	11	27	23	12	Histology	Orthopaedic surgeon (1)
Takeda et al.[35] (2006)	Prospective study	11	55	21	12.7	MRI	NR
Ahldén et al.[1] (2012)	Case series	19	53	Median: 23	Median: 102	MRI	Musculoskeletal radiologist(1)
Bedi et al.[3] (2012)	Case series	15	40	27	96.3	US	Musculoskeletal radiologist (1)
Choi et al.[4] (2012)	Case series	45	100	33 (±7)	36.4 (±7.4)	MRI	Musculoskeletal radiologist (1)
Janssen et al.[15] (2012)	Prospective study	22	77	28 (±5)	12	MRI	Orthopaedic surgeon (1) and Radiologist (1)
Murakami et al.[19] (2012)	Prospective study	20	55	23*	15	MRI	Orthopaedic surgeon (3)
Nakamae et al.[20] (2012)	Retrospective study	39	56	Group 1: 30 (±12) Group 2: 27.1 (±11.4)	6 and/or 12	3D-CT	Orthopaedic surgeon (2)
Snow et al.[30] (2012)	Retrospective study	10	70	33	129	MRI	Orthopaedic surgeon (2)
Stevanović et al.[31] (2013)	Prospective study	50	70	25 (±4)	US: 24 Histology: unknown	US / histology	NR
Nomura et al.[24] (2014)	Prosepective study	24	58	21 (±2)	28 ± 18	MRI	Orthopaedic surgeon (1)

[a] *3D-CT, three-dimensional computed tomography; MRI, magnetic resonance imaging; US, ultrasound; NR, not reported.*
[b] *Standard deviation given if reported in the original study.*

Table 3. Regeneration rates before and after 1 year of follow-up.

		Regeneration rate, % (n/N)			
		≤1-y follow-up		>1-y follow-up	
Author (Year)	**Imaging technique**	**Semitendinosus**	**Gracilis**	**Semitendinosus**	**Gracilis**
Eriksson et al.[11] (1999)	MRI	73 (8/11)			
Papandrea et al.[27] (2000)	US	100 (40/40)			
Eriksson et al.[9] (2001)	MRI/ Histology	75 (12/16)			
Rispoli et al.[28] (2001)	MRI	100 (20/20)			
Tadokoro et al.[34] (2004)	MRI			79 (22/28)	46 (13/28)
Nakamae et al.[21] (2005)	3D-CT	100 (20/20)			
Nishino et al.[23] (2006)	MRI			91 (21/23)	
Okahashi et al.[26] (2006)	Histology	82 (9/11)			
Takeda et al.[35] (2006)	MRI			100 (11/11)	82 (9/11)
Åhldén et al.[1] (2012)	MRI			89 (17/19)	95 (18/19)
Bedi et al.[3] (2012)	US			50 (9/18)	
Choi et al.[4] (2012)	MRI			80 (36/45)	76 (34/45)
Janssen et al.[15] (2012)	MRI	64 (14/22)	100 (22/22)		
Murakami et al.[19] (2012)	MRI	100 (16/16)			
Nakamae et al.[20] (2012)	3D-CT	97 (38/39)			
Snow et al.[30] (2012)	MRI			80% (8/10)	
Stevanović et al.[31] (2013)	US/ Histology			72 (18/25)	
Nomura et al.[24] (2014)	MRI			88 (21/24)	
Total		91 (177/195)	100 (22/22)	79 (142/179)	72 (74/103)
Median (Interquartile range)		97 (74-100)		80 (75.5-90)	80 (61-88.5)

[a]*Data are reported as percentage (absolute values) unless otherwhise indicated. 3D-CT, three-dimensional computed tomography; MRI, magnetic resonance imaging; US, ultrasound.*

Nakamae et al.[21] reported that no regeneration could be observed 1 month after surgery. However, 90% of the patients showed regeneration at 9 months after ACL reconstruction, and all the patients showed regeneration after 1 year[21].

In accordance with Eriksson et al.[11], Papandrea et al.[27] did not report any regeneration after 2 weeks. Papandrea et al.[27] reported that after 12 months, all fibers of the regenerated tendon were attached to the medial popliteal fascia.

Rispoli et al.[28] made no differentiation between regeneration of the semitendinosus and gracilis tendon, but the authors reported fluid or edema in the semitendinosus and gracilis tract 2 weeks after harvesting. Although a neotendon seemed to be present after 12 months, the most distal 3 to 4 cm of this neotendon remained ill defined[28].

Murakami et al.[19] used an inducer technique meaning that the gastrocnemius branch of the harvested semitendinosus was used as a graft to improve the regeneration process. This study reported tendon regeneration in all patients 1 month after ACL reconstruction.

These five studies show that the process of regeneration took place the first year after harvesting and that the regeneration rate could be 100% after one year. However, none of these studies reported a clearly defined time period of regeneration. Other studies, with only one evaluation moment, reported regeneration rates for the semitendinosus ranging from 64% to 97%[15, 20].

Determinants for tendon regeneration

Six publications reported possible determinants, such as sex, demographic data, and duration of immobilization[4, 9, 11, 20, 26, 35].

Patient sex Only 5 publications made a distinction in regeneration rated based on sex[4, 9, 11, 26, 35]. In these publications collectively, regeneration in men could be observed in 85.5% of the cases and in women in 83.3% of the cases. No study reported a significant difference in regeneration rate between men and women.

Demographic data Choi et al.[4] and Nakamae et al.[20] investigated the effect of several demographic factors on hamstring tendon regeneration. No significant difference in hamstring tendon regeneration could be found based on age, weight, or height.

Duration of immobilization Nakamae et al. described the effect of duration of immobilization after ACL reconstruction on tendon regeneration. They divided the study population into 2 groups: a control group with a standard rehabilitation protocol with 3 days of immobilization (short immobilization) and the intervention group with of 10 to 14 days of immobilization (long immobilization). In the short immobilization group, all patients but one showed tendon regeneration. In the long immobilization group, a tendon-like structure was confirmed in all cases. The difference in regeneration rate was not statistically significant ($p=0.42$)[20].

Tendon regeneration in relationship with clinical outcome

Seven studies determined whether tendon regeneration influenced the clinical outcome[4, 9, 15, 19, 20, 23, 34]. Clinical outcome was defined as hamstring function and hamstring strength.

Choi et al.[4] noted that patients without regenerated tendons had more than 4 times as much flexor strength deficit compared with patients with 2 regenerated tendons ($p<0.05$). Furthermore, a correlation ($\rho=-0.443$) was noted between the number of regenerated tendons and the amount of functional deficit. This contradicts the results of Janssen et al.[15] who did not report a significant difference in flexion and extension strength between the patients with both hamstring tendons regenerated and the patients with 1 regenerated tendon.

Eriksson et al.[9] performed several functional performance tests. The Lysholm scores showed no statistical difference between the regeneration and no-regeneration group.

Furthermore, regarding hamstring strength, no statistical difference between the regenerated group and non-regenerated group could be found.
Nakamae et al.[20] considered hamstring strength and reported no significant correlation between hamstring peak torque and the types of regenerated tendon.
Nishino et al.[23] showed that hamstring strength was greatest when the semitendinosus tendon regenerated and had a normal length. Hamstring strength was lowest when no semintendinosus tendon-like structure could be identified. Unfortunately, no p-values were reported.
Using ultrasound, Tadokoro et al.[34] were able to differentiate between different morphologic regeneration (hypertrophic, atrophic, and unidentifiable regeneration) of semitendinosus and gracilis tendons. The hamstring strength of the operated leg was compared with the hamstring strength in the nonoperated side. The nonoperated side had significantly greater hamstring strength in all cases, except for the hypertrophic gracilis tendon group (p=0.077).

DISCUSSION

This systematic review aimed to provide an overview of the current evidence regarding hamstring tendon regeneration after harvesting.
The mean regeneration rate less than 1 year and at least 1 year after harvesting for the semitendinosus tendon was 91% (median [IQR], 97 [74-100]) and 79% (median [IQR], 80 [75.5-90]), respectively; for the gracilis tendon, it was 100% and 72% (median [IQR], 80 [61-88.5]), respectively. The majority of the hamstring tendon regeneration was found to occur between 1 month and 1 year after harvest. No determinants for tendon regeneration are described. Six studies determined whether tendon regeneration influenced the clinical outcome. However, results of these studies are contradictory.
The included studies reported a wide range of regeneration rates. Several explanations can be found for this variation. First, all the included studies used other points of interest to assess the rate of regeneration. Second, the assessments are mostly dichotomous, which is not in accordance with a gradual, continuous process expected in tendon regeneration. Third, studies used different imaging techniques to visualize tendon regeneration. It is unlikely that these techniques are equal in all aspects to determine the hamstring regeneration. Fourth, patient characteristics such as sample size, age, and sex differed. In short, the wide range in reported regeneration rates might be due to the heterogeneity in study designs and how tendon regeneration was assessed.
We found counterintuitive results when comparing the high regeneration rates less than 1 year after harvesting and the relatively low regeneration rates more than 1 year after harvesting. Our aim is to identify the time course of regeneration. This could be

established best if only prospective studies were included, measuring regeneration rates at different points in time. Studies measuring regeneration only once are less accurate, as it is unknown whether regeneration was present before. Considering the included studies in this systematic review, it becomes clear that a majority of the studies reporting regeneration rates in the first year only had 1 measurement moment[9, 19, 21, 27, 28]. This may have contributed to an overestimation in studies measuring regeneration rates less than 1 year after harvesting.

The current systematic review aims to clarify the time course of regeneration. Janssen and Scheffler[14] described in a systematic review 3 different stages of a regenerating hamstring; however, the time course of these stages remained unclear. Five studies assessed the regeneration rates in patients at different chronological moments the first year after harvesting for ACL reconstruction[11, 19, 21, 27, 28]. Four of these studies reported a regeneration rate of 100% after one year[19, 21, 27, 28]. This result was contradictory to studies that used one measure point in time, as several studies reported regeneration rates less than 100% in the first year after surgery. Therefore, it remains unclear when regeneration is completed and whether reported regeneration rates in the first year after harvesting are an overestimation or an underestimation, respectively, due to studies with several measurement moments and with a single measurement moment. Studies that used more than 1 evaluation point measured a different number of patients at each evaluation point. It was not reported whether these patients were the same individuals as the ones who were evaluated before[11, 21, 28]. So the exact time course of regeneration could not be exactly clarified, but the majority of hamstring tendon regeneration was found to occur between 1 month and 1 year after harvest.

Another aim of this systematic review was to identify predictive factors for regeneration. Some studies mentioned regeneration rates in men and women separately, but sex as a determinant for hamstring tendon regeneration has never been researched. Vourazeris et al. considered the possibility of fatty infiltration as an inhibiting factor for tendon regeneration in rabbits. However, no fatty infiltration could be found over time after hamstring tendon harvesting[36]. Fatty infiltration cannot be considered as a determinant. Altogether, we conclude that neither positive nor negative predictors for hamstring tendon regeneration have been described in current literature.

Only 7 studies investigated the relationship between regeneration and clinical outcome[4, 9, 15, 19, 20, 23, 34]. However, these results were contradictory. Choi et al.[4] reported that the number of regenerated tendons influenced hamstring function. Thus, the clinical consequences of the absence of regeneration remain unclear.

In future, more research is required to identify determinants of hamstring tendon regeneration. This is important, because if any determinants can be specified, a risk profile for regeneration failure could be developed. Based on this risk profile, it will be possible to assess whether reharvesting may be possible in the future. Further, more knowledge

about the clinical outcome in terms of hamstring strength and hamstring function after regeneration may influence the type of surgery chosen. However, because the clinical consequences of absence of regeneration remain unclear, better studies are needed to clarify this. Rehabilitation programs should be redesigned if it is found that mechanical load is a positive or negative predictive factor for regeneration. Further, knowledge about the time course of regeneration can change rehabilitation programs, because without hamstring regeneration these muscles cannot be rehabilitated or exercised.

The risk-of-bias assessment that we performed showed that the probability of bias is high. Six studies that examined hamstring tendon regeneration were considered to have a low risk of bias[4, 11, 15, 26, 27, 30]. Only Choi et al.[4], Eriksson et al.[11], and Okahashi et al.[26], investigating the relationship between hamstring tendon regeneration and determinants of regeneration and clinical outcome, met the criteria described in the methods section[4, 11, 26]. The strength of evidence is therefore limited because of the quality of the available studies. Another weakness of this systematic review is the population size in the included studies. Only 2 studies performed a calculation of sample size, and other studies were underpowered to allow firm conclusions. However, this systematic review pooled data concerning hamstring regeneration and therefore approximated real regeneration rates. For this reason, we conclude that hamstring tendons regenerate after harvesting in at least 70% of the cases.

In conclusion, the results of this systematic review indicate that the semitendinosus and gracilis tendon regenerate in the majority of the patients after harvesting for ACL reconstruction. The pooled regeneration rate for the semitendinosus tendon and for the gracilis tendon is at least 70% in all cases. While the exact time couse of regeneration could not be determined exactly due to heterogeneity of the study designs, the majority of hamstring tendon regeneration was found to occur between 1 month and 1 year after harvest. No positive or negative determinants for tendon regeneration have been described yet. Because of conflicting evidence, no correlation could be described between tendon regeneration and clinical outcome. Considering the possible potential clinical effect, it is of vital importance to perform more prospective research concerning hamstring tendon regeneration after harvesting, its functional deficit, and determinants that influence regeneration.

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SUPPLEMENTARY DATA

Supplementary Table 1. Search terms.

(Hamstring/de OR 'semitendinous muscle'/de OR 'gracilis muscle'/de OR (hamstring* OR semitendin* OR gracilis* OR ((single OR double) NEAR/3 bundle*)):ab,ti) AND (harvesting/de OR autograft/de OR 'tendon graft'/de OR 'anterior cruciate ligament reconstruction'/de OR 'anterior cruciate ligament'/de/dm_su OR 'anterior cruciate ligament injury'/de/dm_su OR 'anterior cruciate ligament rupture'/de/dm_su OR (('anterior cruciate ligament'/de) AND ('ligament surgery'/de)) OR (harvest* OR autograft* OR autotransplant* OR gathering* OR transect* OR ((acl OR 'anterior cruciate') NEAR/3 (surg* OR repair* OR reconstruct*))):ab,ti) AND (regeneration/exp OR evaluation/de OR 'muscle function'/de OR strength/de OR 'muscle strength'/de OR 'tensile strength'/de OR torque/de OR 'knee function'/de OR 'neuromuscular function'/de OR 'range of motion'/de OR 'muscle contraction'/de OR 'physical examination'/de OR 'medical examination'/exp OR 'function test'/de OR 'joint laxity'/de OR 'knee instability'/de OR 'joint instability'/de OR biomechanics/de OR (recover* OR regenerat* OR evaluat* OR function* OR strength* OR torque* OR torsion* OR force* OR flexion* OR (range NEAR/3 motion*) OR (physical* NEAR/3 examin*) OR stabilit* OR instab* OR laxit* OR rotat* OR biomechanic*):ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND ([english]/lim OR [dutch]/lim) NOT ([meta analysis]/lim OR [systematic review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [review]/lim)

SUPPLEMENTARY DATA

Supplementary Table 2. Risk-of-bias assessment.

Author (Year)	1	2[a, b]	3	4	5	6[a, b]	7[b]	8[b]	9	10	11	12	Risk of bias
Eriksson et al.(1999)	1	1	0	0	1	1	1	1	0	0	0	0	Low
Papandrea et al. (2000)	1	1	0	0	1	1	0	0	1	0	0	0	Low
Eriksson et al. (2001)	1	0	1	0	1	1	1	1	1	1	0	0	High
Rispoli et al. (2001)	1	0	0	1	1	1	0	0	1	0	0	0	High
Tadokoro et al. (2004)	1	0	1	0	0	1	0	0	1	0	0	0	High
Nakamae et al.(2005)	1	0	1	0	1	1	0	0	1	0	0	0	High
Nishino et al. (2006)	1	0	0	0	1	1	0	0	1	0	0	0	High
Okahashi et al. (2006)	0	1	0	1	1	1	1	1	1	0	0	0	Low
Takeda et al. (2006)	1	0	0	0	1	1	0	1	1	0	0	0	High
Ahlen et al. (2012)	1	0	0	0	0	1	0	0	1	0	1	0	High
Bedi et al. (2012)	1	0	1	0	1	1	0	0	0	0	0	0	High
Choi et al. (2012)	1	1	1	0	1	1	1	1	1	0	0	1	Low
Janssen et al. (2012)	1	1	1	0	1	1	0	0	1	0	1	0	Low
Murakami et al. (2012)	1	0	0	0	1	1	0	0	1	0	0	0	High
Nakamae et al. (2012)	1	0	1	0	0	1	0	0	1	0	1	0	High
Snow et al. (2012)	1	1	1	0	1	1	0	0	1	0	0	0	Low
Stevanovic et al.(2013)	1	0	1	1	1	1	0	0	1	0	0	0	High
Nomura et al. (2014)	1	0	1	0	1	1	0	0	1	0	1	0	High

The numbers 1 to 12 represent questions from the risk of bias assessment.
[a]studies reporting about hamstring tendon regeneration rate should obtain 1 point to decrease the risk of bias.
[b]studies investigating relationship between tendon regeneration and determinants should obtain 1 point to decrease the risk of bias.