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Hamstring tendons regeneration after ACL reconstruction: an overview

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Abstract Despite the long lasting research the ideal method of reconstructing the ACL has not been found so far. The last year's attention has shifted to the use of the multistrand hamstring tendon grafts. High ultimate tensile load, multiple-bundle replacement that better approximates the anatomy of the normal ACL and low donor site morbidity are the main advantages of this ACL replacement graft. These theoretical advantages have been multiplied when surprisingly studies have shown that semitendinosus and grascillis tendons actually regenerate after harvesting for use as ACL autografts. In this review article we summarize the current knowledge concerning the hamstring regeneration and we focus on issues that have clinical relevance or issues that have not been answered so far.

Introduction

Despite the long lasting research [1] the ideal method of reconstructing the anterior cruciate ligament (ACL) has not been found so far. From the different treatment options that have been proposed the most popular surgical replacements for the ACL have been the biologic tissue because of their potential for graft remodeling and integration into the joint [2]. Among the various biologic grafts that have been used the bone–patellar tendon–bone (BPTB) autograft has been a popular ACL replacement graft because of its high ultimate tensile load and the possibility for rigid fixation with its attached bony ends. Nevertheless, many physicians criticize the high donor morbidity when using a BPTB graft [3–5] and the last years attention has shifted to the increased use of the hamstring tendon graft with its relatively low donor site morbidity. Semitendinosus and/or gracilis tendons graft use has evolved from single strand to quadruple strand graft [6, 7] that provides ultimate tensile load as high as 4,108 N [8] and also provides a multiple-bundle replacement that better approximates the anatomy and the function of the normal ACL [9]. These theoretical advantages of the hamstring grafts have been multiplied when surprisingly studies have shown that semitendinosus and grascillis tendons actually regenerate after harvesting for use as ACL autografts. In this literature review article we summarize the current knowledge concerning the hamstring regeneration and we focus on issues that have clinical relevance or issues that have not been answered so far.

Literature review

It was in 1992 when Cross et al. [10] first published his paper describing the apparent regeneration of semitendinosus and gracilis tendons in four patients after the transection for repair of the ACL. The normal tendons have been harvested from their musculoten-

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dinosus origins and retained the peripheral (tibial) attachments. The authors selected the four patients among a group of 255 patients that had examined postoperatively and a palpable thickened band of tissue was found at the anatomic place of the normal tendons. The insertion of the tendons was noted to the medial popliteal fascia. Further investigation with MRI confirmed the presence of these tendons and their more proximal insertion. Strength testing of the knees revealed a 10% decrease in strength for both flexion and extension in three patients and a slight strength increase in the fourth patient. Despite that at the time there were no data concerning the nature of the regenerated tissue and its mechanical properties, the authors suggested that regeneration of tendons occurred from the distal cut end of the muscle belly, following the fascial planes of the popliteal fossa.

Five years later, in 1997, Simonian et al. [11], using MRI, retrospectively identified a more proximal insertion of the harvested gracilis and semitendinosus tendons than on the nonoperated side in six of nine patients. At the same study they evaluated the cross-sectional areas of the biceps femoris, semimembranosus and santorius muscles and they were unable to document any significant difference between the operated and the contralateral leg. The authors concluded that the tendon harvest of the semitendinosus and gracilis muscles does not significantly compromise function and strength, despite a more proximal insertion of the regenerated tendons. Additionally, they suggested that the regenerated tendons may be reharvested for revision of ACL surgery in most of the cases.

In 1999, Eriksson et al. [12] studied with MRI, 13 patients in whom only the semitendinosus tendon but not the gracilis was harvested for ACL reconstruction. In two patients that were examined 2 weeks postoperatively, there were no signs of semitendinosus tendon regeneration. In 8 of the 11 patients that were examined 6 months postoperatively the semitendinosus tendon was regenerated and the insertion site was clearly distal to the knee joint line. Further investigation more distally in three of these eight patients revealed that the semitendinosus tendon fused with the gracilis tendon 30 mm distally to the joint line before their common insertion into the pes anserinus. In three patients the semitendinosus tendon fused into the semimembranosus tendon proximal to the joint line. This study differed from the previous ones in the matter that only the semitendinosus tendon was harvested for ACL reconstruction. The results showed that regeneration of the semitendinosus tendon occurred in all 11 patients, 6 months postoperatively. However, in 8 of the 11 patients the regenerated tendon inserted distally to the level of the joint line differing from the results of Cross et al. The exact nature of the MRI-detected regenerated tendons was not proven in this study. Additionally, no explanation was given for the relative failure in three patients for the tendons to insert at the anatomical site, distally to the joint line. Furthermore, there are questions concerning the mechanism by which retaining the gracilis tendon normal insertion the regenerated semitendinosus tendon insertion was more close to its normal anatomical site.

An ultrasonographic investigation of the possible hamstring regeneration was published in 2000 by Papandrea et al. [13]. In this study, 40 patients who underwent ACL reconstruction with doubled semitendinosus and gracilis tendons were examined pre- and postoperatively with ultrasonography to investigate the anatomy of the donor site before and after the harvest of the tendons. The patients underwent ultrasonography preoperatively at 2 weeks, 1, 2, 3, 6, 12, 18 and 24 months postoperatively. The results showed that 2 weeks after surgery the semitendinosus tendon was absent in all cases and the space was occupied by an area of decreased echogenity, suggesting the presence of a traumatic oedema of soft tissue at the area of the tenotomy. One month postoperatively, a hypoexhoic mass appeared. This mass progressively matured 2–12 months postoperatively but remained hypoechoic and hypotrophic in comparison with the normal semitendinosus tendon. Not before 18 months postoperatively the regenerated tissue appeared very similar to the normal semitendinosus tendon. The authors characteristically emphasised that the regenerated tendon in all cases seemed to be attached to the medial popliteal fascia, at the level of the joint line. Additionally, they admitted that the process of regeneration investigated by ultrasonography was indeed a regeneration from muscle to something they did not really know about its nature.

An answer to the nature of the regenerated tissue was first given by Eriksson et al. [14] in 2001. Six patients that had undergone ACL reconstruction with a quadruple semitendinosus tendon autograft 7–28 months earlier were examined with MRI and surgical exploration of the semitendinosus tendon donation site. In five patients, regeneration of the semitendinosus tendon was seen at the clinical examination, the MRI study and the open surgical exploration as well. The regenerated tendons could be palpated along with the gracilis tendons in the dorsomedial aspect of the distal thigh, just proximal to the knee joint. Biopsies then obtained from the five regenerated tendons and histologic evaluation followed. The new formed tissue had the features of a normal tendon. Nevertheless, scar-like areas with irregularly oriented collagen were observed focally into the regenerated tendons. In three patients in whom biopsy was performed under local anesthesia the tension of the regenerated tendons could be assessed by asking the patients to voluntarily contract their muscle. In all three cases the tendon tension was thought to be adequate compared to the gracilis tendon. The authors of this study suggested that the extrasynovial postharvest hematoma in the tendon canal may act as a scaffold for fibroblast precursor cells from the surrounding tissue that could invade the area and start fibroblast proliferation and collagen production, thus giving an explanation for the mechanism of the semitendinosus tendon regeneration. However, the question about the mechanical properties of the regenerated tendons and their value for second time use as ACL grafts still remained unanswered.

At the same year, Rispoli et al. [15] published another MRI study concerning the direction of the hamstring tendons regeneration. Twenty-one patients that had underwent ACL reconstruction with both semitendinosus and gracilis tendon were examined with MRI, 2–32 months after surgery. The results showed that 2 weeks after surgery no regenerated tendons were seen. Six weeks post-op tissue, at the level of the superior pole of the patella tissue, was seen with the appearance of the normal tendons. Progressively, 3–32 months post-op regenerated tendons were identified at the level of the joint line, 3–4 cm above the pes anserinus and in one case 1–2 cm above the normal attachment of the hamstring tendons. The authors concluded that tendons first regenerate proximally and then proceeds distally along the fascial planes and they hypothesised that this process may be analogous to the nerve regrowth through intact neural sheaths. The real functional ability of the regenerated tendons still remained uncertain.

In another histological study, Ferretti et al. [16] described the histologic course of the regenerated tissue in three patients after ACL reconstruction with the semitendinosus and gracilis tendons. The first patient was examined 6 months after surgery and the two others 24 and 27 months postoperatively, respectively. In all patients regeneration of the semitendinosus tendon was found but the insertion of the regenerated tissue was 2–3 cm proximal to the pes anserinus. Histological evaluation of the regenerated tissue 2 months post-op revealed prominent fibroblastic proliferation together with a few vessels surrounded by fibrous tissue and only a few bundles of well-oriented collagen fibers. On contrary, in the two patients that have been examined 2 years postoperatively, the regenerated tissue presented two zones of maturation. In the peripheral zone a prominent fibroblastic proliferation was observed together with a few vessels surrounded by loose fibrous tissue, whereas in the central zone parallel bundles of collagen fibers were seen together with haphazardly arranged tenocytes like cells. The authors hypothesized that the mechanical stresses that apply on the regenerated tissue progressively support its maturation to tendon. The same was previously suggested by Eriksson et al. [14]. Additionally, before that, several papers, especially within the field of hand surgery, had shown the way collagen fiber orientation and tensile loading properties can enhance tendon healing [17–19]. It is very interesting to notice that even 27 months postoperatively the maturation process has not been totally completed. Additionally, in this study there were no data about the regeneration process of the gracilis tendon.

In 2003, Hioki et al. [20] published their MRI study concerning the intramuscular movement of hamstrings muscle after reconstruction of the ACL with a hamstrings tendon graft. Eleven patients, who underwent ACL reconstruction with the semitendinosus and gracilis tendons, were examined 10–48 months postoperatively with MRI. The knee flexion strength was measured in eight patients as well. Results showed that in six patients the semitendinosus muscle movement was similar to the movement of the intact muscle of the controlateral knee. In these patients the semitendinosus tendon appeared to be regenerated and tendonlike structures were observed distally. In the five remaining patients, no regenerated tendon was identified and the semitendinosus muscle was moving distally with active knee flexion. Additionally, the patients were divided in three groups according the knee flexion strength. In group III, in which no regenerated tendon was seen, the semitendinosus muscle was considerably smaller proximally and the knee flexion was the lowest measured. In group II, the muscle was almost one-half the size of the normal semitendinosus but tendon-like structures appeared distally. Finally, in group I, the muscle had the size of the normal semitendinosus and the knee flexion strength was near 100% of the normal. Thus, the authors of this study concluded that the effect of hamstrings tendon harvest is not uniform as far as the regeneration of the tendons and the knee muscle strength is concerned.

The first data about the biomechanical properties of the regenerated semitendinosus tendon was published by Leis et al. [21]. Ten rabbits were randomized in two groups of five and evaluated 16 and 28 weeks postoperatively. In all animals the semitendinosus tendon was harvested with a stripper. MRI evaluation was done preoperatively and postoperatively. Histological and biomechanical testing of the regenerated semitendinosus tendon was performed on all specimens using the contralateral semitendinosus tendon as control. Results showed that in all animals regeneration of the tendon occurred. The anatomical attachment site varied along the tibia. Histological evaluation revealed that 16 weeks postoperatively the regenerated tendon appeared with wavy appearing but well organized collagen tissue and near normal amount of nuclei. At 28 weeks the regenerated tendon was indistinguishable from normal appearing semitendinosus tendon. Biomechanical testing showed that in the 16 weeks specimens the load failure of the regenerated tendon was 23% of the original tendon strength, whereas in the 28 weeks specimens the load to failure was 62% of the original tendon strength. The authors of this article suggested that the semitendinosus tendon regenerates from the substance of the semitendinosus muscle and processes in the same fascial plane as the native tendon, like a lizard which regrows its tail; thus they first called the phenomenon as ''the lizard tail phenomenon''.

In another study, Gill et al. [22] in 2004 further evaluated the histology of the regenerated tendon, the physiological behavior of the musculotendinous unit and the biomechanical properties of the new tendon in a rabbit model. In this study, 9–12 months postoperatively in 26 of the 31 rabbits, regeneration of the tendon was found. Most of the regenerated tendons inserted more superficial than the native tendons. Under the microscopy the regenerate tissue had the structure of the normal tendon with normal cellularity, organization and immunolocalization of type I collagen. Nevertheless, there were areas of disorganized architecture with hypervascularity and increased cellularity and disorientation of the fibril arrangement and of the cells arrangement as well. The physiological testing revealed a significant decrease in the contraction force of the musculotendinous unit. Thus, the regenerate muscle and musculotendinous junction was capable of creating and sustaining an average of 25% of the maximum load when compared with the native side. Furthermore, biomechanical properties of the neotendon were significantly less than the control side and the tensile strength values were from 20 to 75% of the native's strength (32% average). Another observation was that when the contralateral tendon was larger, a more significant regenerate tendon was observed in a matter of size and biomechanical properties. Thus, the authors speculated that a threshold size of tendon must exist before any significant regeneration can occur.

The first indication that semitendinosus tendon regeneration can be different from the gracilis tendon regeneration came with the study of Tadokoro et al. [23] in 2004. In this study, 28 patients who underwent anterior cruciate ligament reconstruction with quadruple semitendinosus and gracilis hamstring graft were evaluated after a minimum period of 2 years. From patients, regeneration of the semitendinosus tendon was observed with MRI study in 22 (79%), whereas regeneration of the gracilis tendon was observed in 13 (46%). The authors suggested that the tissue plane is protected by the fascia for the gracilis tendon in lesser extent than for the semitendinosus tendon, thus giving an explanation for the inferior regeneration rate of the gracilis tendon. Furthermore, in this study the relative hamstring strength at the operated knee was only 49% compared with the non-operated knee in prone position and 110° of knee flexion. This deficit was not found to correlate with the morphologic regeneration of the hamstring tendons. Unfortunately, no data were given for the insertion site of the regenerated tendons and the possible correlation between hamstring strength and insertion site.

In a 3D MRI study, Nakamae et al. [24] in 2005 evaluated the regeneration of the semitendinosus tendon and the correlation of the proximal musculotendinosus junction shift with the hamstring strength. About 29 patients that had undergone ACL reconstruction with the use of only the semitendinosus tendon were examined with 3D MRI preoperatively, 6 and 12 months postoperatively. In all but two patients regeneration of the semitendinosus tendon occurred. The musculotendinosus junction had shifted 7.3 ± 2.0 cm proximally comparing with the contralateral side. Additionally, there was significant correlation between the peak torque ratio and the proximal shift of the muscle–tendon junction. Six months postoperatively the peak torque ratio was lower as the musculotendinosus junction shifted proximally, whereas 12 months postoperatively the proximal shift did not affect the peak torque ratio. In this study, the tibial insertion of the regenerated tendon was found to be into the anteromedial aspect of the proximal tibia but no specific data were given about the exact position of this insertion.

Discussion

A critical review of the so far published literature allows some conclusions about the facts concerning the hamstring regeneration in ACL reconstruction but at the same time raises still unanswered questions about the hamstring regeneration phenomenon. There is no doubt that hamstring tendons have the actual capability to regenerate to a ''tendon like'' structure after harvesting. This regeneration process has been well proven with studies in humans and animal models [10–16, 20–24]. Additionally, as first suggested by Cross et al. [10], the direction of the regeneration seems to start from the distal cut end of the muscle belly and then proceeds distally along the fascial planes. Cross et al. studied the regeneration process in patients that hamstring tendons retained their natural tibial attachment and despite this regeneration of the tendons occurred, thus giving a first indication for the direction of the regeneration process. Furthermore, the studies of Papandrea et al. [13] and especially of Rispoli et al. [15] confirmed the previous findings. Nevertheless, in a recent study of sheeps, Turhan et al. [25] have found that the harvested tendons of musculus extensor digitalis lateralis regenerated in all cases but the regeneration occurred proximally and distally at the same time, thus raising questions about the direction of the regeneration process.

Histological studies of the regenerated tissue have shown that it has many features of the normal tendon. In the first histological study by Eriksson et al. [14] focal areas of scar-like tissue were observed at the regenerated tendons. Patients of this study were examined 11–28 months postoperatively. Unfortunately, no data were given for the differences observed at the maturation process of the neotendons between the early and late examined patients. On contrary, in their study, Ferretti et al. [16] have shown that 6 months postoperatively the neotendon was still immature and that even 27 months postoperatively the maturation process still continued. In the animal study, Leis et al. [21] found similar maturation process and they concluded that 28 weeks postoperatively this process have been completed and the histological appearance of the regenerated tendons was indistinguishable from the normal. On contrary, in another animal study, Gill et al. [22] found that 9–12 months postoperatively the regenerated tendons still appeared with areas of hypervascularity, increased cellularity and disorganized architecture. So, from these studies in humans and animals, the time the maturation process of the regenerated tendon will be completed is still unclear but the first indications are that this process lasts for more than 2 years.

Another issue that is still unanswered is the exact mechanism of the regeneration process. Cross et al. [10] hypothesized that the regeneration occurred following the fascial planes of the popliteal fossa. Similarly, Rispoli et al. [15] suggested that the regeneration occurs in a proximal to distal fashion along the fascial planes in a process analogous to the nerve regrowth through intact neural sheaths. Correspondingly, in their animal study, Leis et al. [21] suggested that the semitendinosus tendon regenerates from the substance of the semitendinosus muscle and processes in the same fascial plane as the native tendon. They named this process ''the lizard tail phenomenon''. Giving a different explanation, Eriksson et al. suggested that the extrasynovial postharvest hematoma in the tendon canal may act as a scaffold for fibrobroblast precursor cells from the surrounding tissue that could invade the area and start fibroblast proliferation and collagen production. Moreover, they speculated that initially extrinsic mechanisms of healing must be involved and after the fibroblasts are established in the organized hematoma intrinsic healing mechanism possibly initiates. Furthermore, Tadakoro et al. [23] claimed that the lesser coverage at the tissue plane by the fascia for the gracilis tendon explains its inferior regeneration rate. Nevertheless, these theories remain to be proven and there are still some unanswered questions. For example, by which mechanism two different tendons developing in the cases that both semitendinosus and gracilis tendons have been harvested and in any case why in some patients no regeneration at all occurs?

In the so far published literature in humans regeneration of the hamstring tendons occurred in 146 of the 164 studied patients (89%) [10–16, 20, 23, 24, 26, 27] and in the animal models regeneration occurred in 36 of the 41 animals (87%) [21, 22]. Jarvinen et al. [26] even published a case report article presenting a failed regrowth of the harvested semitendinosus tendon in a patient. In this article it was stated that such a failure to regeneration of the harvested tendon can cause clinical problems to the patient but there was no explanation about the etiology of the regeneration failure. In a cadaveric study, Irie et al. [28] suggested that if the remaining muscle stumps of tenotomized semitendinosus and gracilis muscles are located beyond the knee joint line and close to the popliteal fascia or other fibrous tissue, it is possible that a new functional myotendinous junction and thus tendon regeneration could occur. The authors speculated that in the cases where the tenotomized muscle stump does not reach the joint line level and is not close to the popliteal fascia, regrowth of the functional myotendinous junction between the muscle stump and the adjacent tissue seems to be unlikely. Nevertheless, in this cadaveric study there is no answer about the factor that determines the level of the remaining muscle stump. Although there are no sufficient data to support any theory at the time, it seems logical that if the tendon regeneration follows the fascia planes and the postharvesting hematoma formation between the fascia planes plays a role on this, the surgical technique, in the matter of preserving the anatomy of the surrounding tissue is probably an important factor. In our opinion the more meticulous and non traumatic the harvesting technique, the more probable the tendon regeneration is.

Impressive though it may be the hamstring regeneration phenomenon, is clinically significant in only two cases: either the regenerated tendon is useful for revision of ACL reconstruction surgery, or the regeneration process allows full recovery of the natural hamstring function. In a recent paper, Yoshiya et al. [27] reported a semitendinosus tendon reharvest in one ACL reconstruction revision case. The patient had undergone rerupture of the posterolateral band of his reconstructed ACL 7 months after the primary surgery. One month later the regenerated semitendinosus tendon was used with the gracilis tendon to reconstruct the posterolateral band of the graft. Nevertheless, under electron microscopy the regenerated tendon appeared with significantly smaller fibril diameters than the normal tendon suggesting inferior mechanical properties. Additionally, the reharvested tendon was used with the augmentation of the normal gracilis tendon. From previous histologic studies we know that the maturation process of the neotendon continues much longer than 8 months and even 27 months postoperatively has not been completed yet [16]. In the two biomechanical studies in rabbits [21, 22] the biomechanical strength of the neotendons were found to be 62 and 32% (on average) of the native's strength, 28 weeks and 9–12 months postoperatively, respectively. These findings in animals suggest that even 12 months postoperatively the regenerated tendons in humans have significantly inferior strength in an amount that we simply do not know yet.

As far as the restoration of the initial hamstring function is concern the findings from many different studies are controversial and rather confusing. Previous reported series [29–34] have shown almost full recovery of the knee flexor strength and many authors suggested that this functional recovery of the hamstring muscles can be attributed to the regenerative capability of the hamstring tendons [10, 12, 14, 16]. Other authors attributed the restoration of the muscle strength to the hypertrophy of the other knee flexors, like semimembranosus and biceps femoralis [35, 36]. In their study, Eriksson et al. [36] have shown that in those patients in whom regeneration of the semitendinosus tendon occurred, there was no significant decrease at the cross sectional area of the semitendinosus muscle, whereas in the patients in whom no regeneration of the semitendinosus tendon occurred there was significant decrease at the semitendinosus muscle cross sectional area that was combined with an hypertrophy of the semimembranosus muscle. In both patient groups there was significant reduction at the isokinetic strength of the hamstrings in the operated leg than in the nonoperated leg. Controversially, Simonian et al. [11] were unable to document any significant difference between the operated and the contralateral leg concerning the cross-sectional areas of the biceps femoris, semimembranosus and santorius muscles. Additionally, newer studies suggested that up to 20% knee flexor deficits are common [37, 38] and moreover other studies have proven that deep knee flexion strength was up to 30% inferior compared with the contralateral leg [23, 38–40]. Nakamura et al. [41] and Tashiro et al. [42] studied the difference in knee flexion strength in patients who had both semitendinosus and gracilis tendons harvested versus the semitendinosus alone. Nakamura found no significant strength difference between the two groups, whereas Tashimo reported greater strength deficits, especially in deep knee flexion when both tendons were harvested. It is possible that retaining the gracilis tendon normal function not only preserves a part of the knee flexion strength, but also facilitates the regeneration process of the semitendinosus tendon regeneration by preserving the anatomic fascial plane.

These controversial results in knee flexion strength studies can partly be explained by the nonuniform way the regenerated tendons re-establish their peripheral attachment. In the vast majority of the reported cases the neotendons reattach more proximally and medially to the tibia, whereas in other cases the tendons fuse with the popliteal fascia and in almost 11% of the cases no regeneration occurs as mentioned before. In their 3D MRI study, Nakamae et al. [24] have found significant correlation between the more proximal musculotendinosus junction of the neotendon and the strength deficit of knee flexion. It is also possible that the more proximal the peripheral attachment of the regenerated tendon is, the more inadequate the flexion strength must be, as suggested by Hioki et al. [20], but this hypothesis have to be furthermore proven with more studies. Additionally, the more medial attachment of the neotendons inevitably alters the internal rotator function of the hamstring muscles [43, 44]. Recent studies have shown that harvest of hamstring tendons for the purpose of an ACL reconstruction contributes to internal tibial rotation weakness [45–47].

In conclusion, despite the initial enthusiasm, the literature review still reveals unanswered questions about the tendons regeneration phenomenon and surgeons must be more sceptical about its clinical significance. Further, long-term studies are needed to clarify issues such as the exact mechanism of the tendons regeneration, the end time of the maturation process, the mechanical properties of the neotendons and the physiological role of the phenomenon in the matter of restoring the function of hamstring muscles.

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