Original article
https://doi.org/10.18019/1028-4427-2024-30-4-572-580

Achilles tendon regeneration after experimental transverse tenotomy with preserved peritenon and the structures

M.V. Vlasov, N.Yu. Shirokova, I.V. Musikhina✉

Privolzhsky Research Medical University, Nizhny Novgorod, Russian Federation

Corresponding author: Irina V. Musikhina, i_musihina@mail.ru

Abstract

Introduction The Ponseti method is the first choice for congenital clubfoot with the possibilities of transverse tenotomy being underexplored in repair of the Achilles tendon in pediatric patients.

The **objective** was to identify specific features of the Achilles tendon repair after experimental transverse intersection and preserved peritenon, vessels and nerves of growing rabbits.

Material and methods The experimental study included 20 Chinchilla rabbits of both sexes aged 1.0–1.5 months used as a biomodel with a weight of 1476.0 ± 114.3 g. Rabbits were sacrificed in groups of five by air embolism under local anesthesia at 15, 30, 60 and 90 days of surgery.

Results The tendon defect zone was represented by small areas of dense fibrous scar tissue with some cellular fibroblasts, and tendon fibers of unremarkable architectonics arranged in a mutually parallel waves could be seen in the layers of connective tissue at 90 days. The thickness of the first-order collagen fibers increased to 8.9 ± 1.32 μm and comparison with the normal value of 9.2 ± 1.88 μm showed no statistically significant difference ($p = 0.38$). The thickness of the second-order collagen fibers increased to 28.1 ± 1.28 μm during the time, and comparison with the standard measurements of 28.3 ± 2.23 μm demonstrated no statistically significant difference ($p = 0.64$).

Discussion According to the literature, the ability of the tenoblast to synthesize structural proteins and regulatory biomolecules after injury decreases with age and leads to fibrous restoration of the tendon and formation of a permanent scar. Our study on growing rabbits showed that the organotypic structure of the experimental tendon restored at the intersection site at 60 days with the Achilles tendon defect being represented by the tendon-like tissue at 90 days.

Conclusion The Achilles tendon was shown to regenerate in optimal conditions after the dissection and preservation of the peritenon, vessels and nerves with tendon tissue being formed within a short time (3 months after the intervention) being identical to the original.

Keywords: congenital clubfoot, Ponseti method, Achilles tendon regeneration, micromorphometry, experiment, rabbit

For citation: Vlasov MV, Shirokova NYu, Musikhina IV. Achilles tendon regeneration after experimental transverse tenotomy with preserved peritenon and the structures. *Genij Ortopedii*. 2024;30(4):572-580. doi: 10.18019/1028-4427-2024-30-4-572-580

INTRODUCTION

Congenital clubfoot treatment has evolved throughout history: from nonoperative management reported by Kite (1972) [1] and various surgical interventions to the Ponseti approach [2–6]. The Ponseti method has become the gold standard of care for the treatment of congenital club foot. It consists of simultaneous correction of the main components of the foot deformity, application of plaster casts, Achilles tendon tenotomy and foot abduction bracing [7–14]. Moreover, in 70–85 % of cases, correction of the equinus of the foot can be corrected through percutaneous transverse Achilles tenotomy [15–19].

Tendon regeneration has been a topic of interest amongst the scientific world [20–22]. Thus, tendon regeneration can occur due to intrinsic resources through proliferation and migration of tenocytes from the epitenon and endotenon to the injury site or extrinsic resources through penetration of cells from the tendon sheath and synovium [23–24]. Tendon healing involves intrinsic and extrinsic mechanisms, with the latter being predominant earlier in the healing process while the intrinsic mechanism can be delayed [25]. The sources of regeneration are important for the synthesis of the extracellular matrix (ECM) and for the establishment of the intrinsic neovascular network [26]. Ultrastructural changes are maintained after 12 months of injury [27]. The tendon regenerate is scar-like and unable to restore the biomechanical properties it had before injury [28]. Frank, McDonald and Shrive [29] reported remodeling of tendon tissue that can continue for several years, and tendons can demonstrate a significant decrease in structural and mechanical properties immediately after injury, followed by a slow, but incomplete restoration to the original parameters.

Although Achilles lengthening is the standard treatment of congenital clubfoot in children using the Ponseti method, there is no data on the reparative processes of the transected calcaneal tendon with the preservation of the peritenon. A practicing orthopaedic surgeon aims to restore pediatric anatomy of the bone and the tendon during surgical intervention. Changes in the Achilles tendon after its intersection are essential in the treatment of congenital clubfoot. The effectiveness of the rehabilitation of the patients would depend on the quality of the calcaneal tendon recovery and the time: the length of immobilization, the safety of mechanical load and exercise therapy programme. Experiments on growing animals were produced to explore changes in the tendon with transverse achillotomy and intact peritenon, vessels and nerves.

The **objective** was to identify specific features of the Achilles tendon repair after experimental transverse intersection and preserved peritenon, vessels and nerves of growing rabbits.

MATERIAL AND METHODS

Achilles tendon repair was explored experimentally in growing animals that underwent transverse tenotomy without crossing the connective tissue sheath, peritenon. The experimental study included 20 Chinchilla rabbits as biomodels of both sexes aged 1–1.5 months with a weight of 1476.0 ± 114.3 g. Conventional animals were kept under standard conditions in the vivarium of a university clinic in accordance with the rules of the European Convention on protection of vertebrate animals used for experiments or other scientific purposes (Strasbourg, 18.05.2014). The experimental part of the work was performed following the requirements set out in the Order of the Ministry of Health and Social Development of the Russian Federation No. 708n dated August 23, 2010 “On approval of the rules of proper laboratory practice.”

Rabbits were sacrificed in groups of five by air embolism under local anesthesia on days 15, 30, 60 and 90 after achillotomy. The timings for the study of the tendon reparative regeneration were selected based on literature data [30]. An Achilles tendon preparation of the intact rabbit

limb was examined in all series of the experiment to determine the parameters of the age norm. The regenerated Achilles area was histologically examined, and collagen fibers of the first and second order were counted.

The experiment reproduced a subcutaneous transverse section of the Achilles tendon with intact peritenon, vessels and nerves. Under general anesthesia, the skin and subcutaneous tissue were dissected longitudinally 0.3–0.5 cm on the posterior tibia at a distance of 1 cm off the attachment of the Achilles tendon to the calcaneal tubercle. Then the tendon sheath and the peritenon were longitudinally dissected with the intersection of all the layers including paratenon and epitenon to the length of the skin incision. The calcaneal tendon was isolated subperitenonially and transected transversely with a scalpel No. 11 causing no injury to the peritenon. Then the animal's paw was dorsiflexed with the ends of the transected tendon diverging by 0.5–0.7 cm inside the connective tissue sheath. The skin wound was not sutured. The limb was fixed with a plaster cast from the upper third of the thigh to the foot for 2 weeks. There was no limitation to weight-bearing with the cast removed.

The tissue samples were fixed in a 10 % solution of buffered neutral formalin and decalcified using Biodec-R medium (Bio-Optica). Histological examination of the specimens was produced according to the generally accepted method using Thermo Excelsior ES Tissue Processor. Paraffin embedded tissue blocks were produced using Thermo Scientific HistoStar Embedding Workstation. Thermo Scientific Microm HM 325 Microtome was used to produce paraffin-embedded sections 4–6 μm thick that were stained with hematoxylin and eosin, and mounted in mounting medium. Microscopy and photographic recording of histological preparations were produced using the Leica DMR morphometric equipment.

Statistical analysis was performed using the Statistika 12.0 package. Normal distribution was statistically identified using the Shapiro – Wilk test. The nonparametric Wilcoxon method was used for the samples that did not correspond to the normal distribution law and had a small volume.

RESULTS

The thickness of collagen fibers of the first and second order measured normally and at the regeneration site of sacrificed animals at different points in time is presented in Table 1.

Table 1

Comparative analysis of the thickness of collagen fibers of the first and second order measured normally and at the regeneration site

Term of animal sacrifice		Thickness of collagen fibers, microns	
		I order	II order
Normal (n = 5)	M ± SD	9.2 ± 1.88	28.3 ± 2.23
14 days (n = 5)	M ± SD	4.8 ± 1.81	16.4 ± 2.27
	p-level	**p^* = 0.005**	**p^* = 0.0003**
30 days (n = 5)	M ± SD	6.9 ± 1.42	20.5 ± 2.49
	p-level	**p^* = 0.002, p^{**} = 0.04**	**p^* = 0.0003, p^{**} = 0.01**
60 days (n = 5)	M ± SD	8.5 ± 1.43	25.2 ± 2.54
	p-level	p^* = 0.13, p^{**} = 0.02	p^* = 0.07, p^{**} = 0.01
90 days (n = 5)	M ± SD	8.9 ± 1.32	28.1 ± 1.28
	p-level	p^* = 0.38, p^{**} = 0.14	p^* = 0.64, p^{**} = 0.07

Note: *M*, mean; *SD*, root-mean-square standard deviation indicating the spread of data over the interval of the characteristic value relative to the mean; p-level (p^*), level of significance (Wilcoxon signed-rank test) of differences in relation to normal parameters; p^{**}, level of significant differences in relation to measurements of the previous day.

The traumatic injury site was represented by acellular areas and lysed collagen fibers at 15 days of surgery. A significant area of the preparation was occupied by thin collagen fibers, forming a felt-like network interspersed with small foci of necrosis. The adipose tissue had a small area. A large number of fibroblastic cells, differing in shape and size, were located along the bundles of collagen fibers or formed proliferates. Tender maturing granulation tissue with predominating histiocytes and fibroblasts and a high content of thin-walled vessels in the cells was identified in some areas of the defect zone. Collagen fibers maintained axial direction in the tendon being adjacent to the injury site at a short distance, but "intercalated" bundles led to disrupted orientation of most fibers with resultant thinned and fragmented bundles of collagen fibers acquiring tortuous contours. Destruction foci or extensive cell proliferation were seen in the zone (Fig. 1).

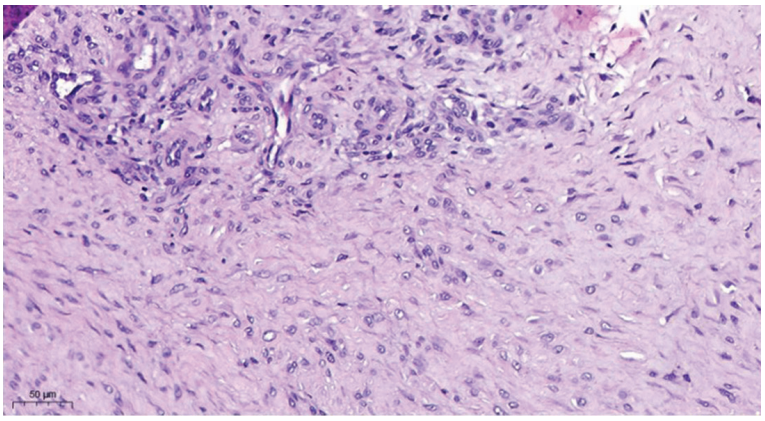

Fig. 1 Longitudinal section of the rabbit's calcaneal tendon in the defect area at 15 days showing an area of granulation tissue being replaced by scar tissue with a large number of fibroblasts. Stained by hematoxylin and eosin, magnification ×200

Areas of tendon destruction were identified at the site with loss of pink color and replacement foci, dense fibrous connective tissue and small areas of loose, abundant cellular tissue with a large number of histiocytic elements. A thinner regenerate with an ordered structure containing no excess collagen structures, was observed at the defect site at the stage of the experiment. The predominance of fibrocytic cells located between parallel bundles of collagen fibers was determined in the scar tissue. The structure of the scar tissue was identical to the original tendon tissue, which was confirmed by the presence of bundles of collagen fibers of the first and second order, tightly adjacent to each other with areas of loose connective tissue and a small number of blood vessels.

The thickness of the first order collagen fibers measured 4.80 ± 1.81 μm at 15 days and was statistically less significant than the normal value of 9.20 ± 1.88 μm, $p = 0.005$. The thickness of the second-order collagen fibers at the time was equal to 16.40 ± 2.27 μm with a statistically significant difference compared to the normal of 28.30 ± 2.23 μm, $p = 0.001$.

Extended sections of mutually parallel bundles of tendon fibers with visible tenocyte nuclei separated by endotendinium were identified in the perifocal zone of the tendon at 30 days. Increased thickness of the collagen fiber bundles was noted at the time, which acquired a wavy configuration characteristic of the normal tendon structure. However, some collagen structures remained less structured with lack of waviness. The representation of adipose tissue was more widespread in the area compared to the previous study period and appeared as focal growths. The defect site was characterized by a growth of dense fibrous connective tissue of a scar nature with a small content of capillary-type vessels and cellular fibroblast-histiocytic elements. There was no unidirectionality and orderliness in the arrangement of collagen fibers in the regenerate structure with areas of low density of fibroblasts differing in the shape and size of the nucleus (Fig. 2).

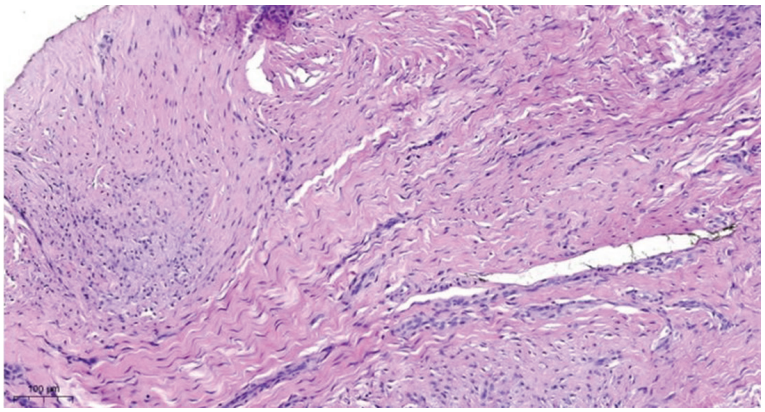

Fig. 2 Longitudinal section of a rabbit's calcaneal tendon at the defect site at 30 days showing areas of parallel bundles of tendon fibers with a wavy configuration, proliferation of scar tissue. Stained with hematoxylin and eosin, magnification ×100

The thickness of the first order collagen fibers increased to 6.90 ± 1.42 μm at 30 days compared to 4.80 ± 1.81 μm measured at 15 days with the statistically significant difference, $p = 0.04$. A significant difference remained with comparison to the normal of 9.20 ± 1.88 μm, $p = 0.002$. The thickness of collagen fibers of the second order statistically increased to 20.50 ± 2.49 μm at 30 days as compared to the parameter measuring 16.40 ± 2.27 μm on the previous day, $p = 0.01$. However, the value of the thickness of collagen fibers of the second order was statistically less in relation to the standard value, p = 0.001.

Extensive layers of preserved tendon tissue and dense bundles of collagen fibers were seen at the injury site at 60 days. Small areas of abundant cellular connective tissue, scars were found over a small area of transections (Fig. 3). The scars were characterized by a typical arrangement of collagen fibers, with some multidirectional areas of compaction and some with loose bundles and isolated degeneration areas. The scars were characterized by a decreased number of blood capillaries and vessels with an enlarged empty lumen.

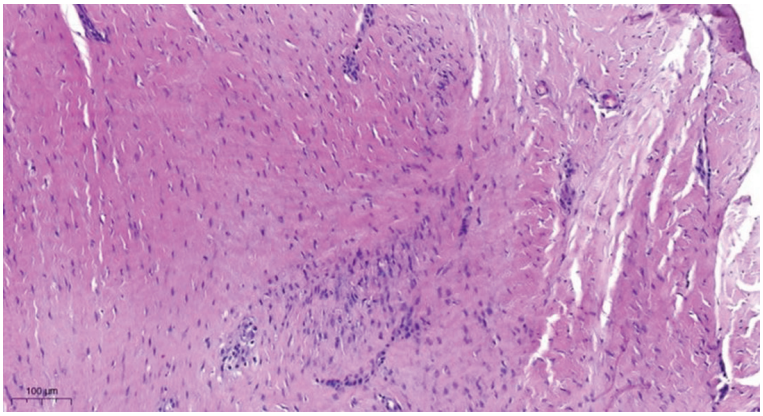

Fig. 3 Tangential section of the rabbit calcaneal tendon at the defect site at 60 days showing areas of parallel tendon fiber bundles with small inclusions of scar tissue. Stained with hematoxylin and eosin, magnification ×100

Areas of dense fibrous tissue included small foci of loose fibers and a small amount of adipose tissue, which appeared as small focal accumulations of lipocytes in the histological specimen. Tendon-like tissue developed in the healing zone over a larger area of the cut at 60 days with densely arranged dark-eosinophilic fibers and small areas of fatty and scar tissue. The bundles of collagen fibers had a unidirectional and orderly arrangement with the fiber thickness being similar to those of the normal tendon.

The thickness of the first order collagen fibers increased to 8.50 ± 1.43 μm at 60 days compared to 6.90 ± 1.42 μm measured at 30 days with a statistically significant difference (p = 0.02). There was a statistically significant increase in the thickness of collagen fibers of the second order measuring 25.20 ± 2.54 μm in comparison to the previous parameter (p = 0.07) at the time. The thickness of collagen fibers of the first and second order became similar to the normal (p = 0.13 and p = 0.07, respectively).

Extended areas of tendon tissue with wavy normally structured light-eosinophilic fibers and thickened peritenonium, small areas of loose fibrous connective tissue with a network of vessels and small foci of adipose tissue were identified in the perifocal zone of the tendon at 90 days (Fig. 4).

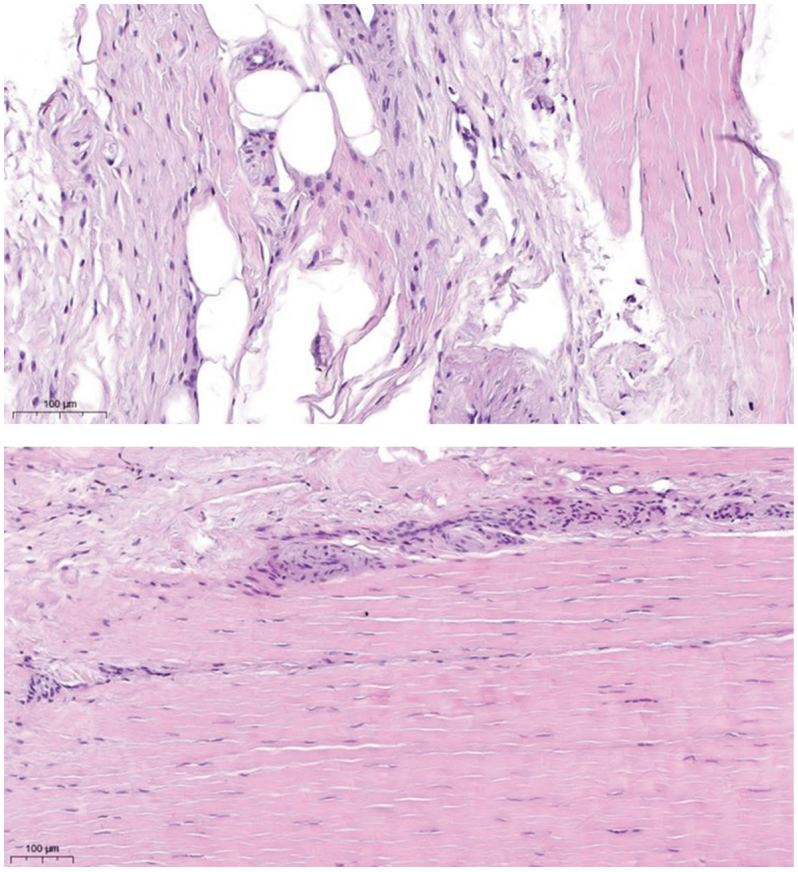

Fig. 4 Longitudinal section of the rabbit's calcaneal tendon at the defect site at 90 days showing (*a*) a fragment of a tendon-like regenerate and areas of loose connective tissue with areas of adipose tissue; (*b*) a fragment of a tendon-like regenerate with areas of vascular proliferation. Stained with hematoxylin and eosin, magnification×200

Tendon fibers of the usual architectonics with parallel wavy arrangement were found in the layers of connective tissue in the defect site at the time. Foci of loose connective tissue and a small number of small-caliber vessels were identified along the periphery in the areas adjacent to the defect zone.

The thickness of the first order collagen fibers increased to 8.9 ± 1.32 μm at 90 days as compared to the parameter measured at 60 day, p = 0.14 with no statistically significant difference (p = 0.38) when compared to the normal of 9.2 ± 1.88 μm. The thickness of the second order collagen fibers increased to 28.1 ± 1.28 μm at the time with no statistically significant difference determined in relation to the previous measurement of 25.2 ± 2.54 μm and the standard parameter of 28.3 ± 2.23 μm (p = 0.07 and p = 0.64, respectively).

DISCUSSION

According to the literature, tendons undergo numerous biochemical, cellular and mechanical changes during the aging process causing a decreased ability of the tendon to recover from injury. There is a decrease in the volumetric density of tenoblasts, decreased tenoblasts per unit surface area of the tendon [31, 32]. In general, the ability of the tenoblast to synthesize structural proteins and regulatory biomolecules after injury decreases with age.

With collagen synthesis and collagenolytic activity decreasing with age, there is a decrease in collagen fiber regeneration [33, 34]. The decrease results in an increased diameter of the collagen fibers and marked variability in thickness. Proliferating fibroblasts lead to fibrotic tendon repair and permanent scar formation in the absence of an effective number of adult tenogenic progenitor cells that would effect the cell production [35, 36].

Our experimental study on growing rabbits showed a thinner regenerate formed after tenotomy with preserved peritenonial membrane in the defect area with an ordered structure not containing excess collagen at 15 days. The predominance of fibrocytic cells located between parallel bundles of collagen fibers was determined in scar tissue. The structure of the scar tissue was almost identical to the original tendon tissue, which was confirmed by the presence of bundles of collagen fibers of the first and second order being tightly adjacent to each other with areas of loose connective tissue in-between with a small number of blood vessels. The organotypic structure of the tendon restored at the site of intersection at 30 and 60 days. The injury site was filled with tendon-like tissue and densely arranged dark eosinophilic fibers with small areas of fatty and scar tissue at 60 days. The bundles of collagen fibers had a unidirectional and orderly arrangement with the thickness of the fibers being identical to the parameters of the normal tendon. The defect zone was represented by small areas of dense fibrous scar tissue with a small number of cellular elements of fibroblasts at 90 days. Among the layers, tendon fibers of ordinary architecture were found in a parallel arrangement of collagen fiber bundles of connective tissue with the thickness being close to standard values.

It can be suggested that the intact connective tissue sheath (peritenon) can prevent the ends of the crossed calcaneal tendon from diverging over a significant distance. In this case, the intact connective tissue sheath (peritenon) actually maintains the tendon in a state of functional tension. Reparative processes in the defect area in the case with preserved functional tension of the injured tendon can occur within a short period of time. In addition to that, an intact tendon sheath (peritenon) with preserved vessels and nerves has a beneficial effect on reparative processes in the Achilles tenotomy site. The factors result in the area of the heel tendon defect being represented by tendon-like tissue over a large area with tendon fibers of ordinary architecture arranged in mutually parallel bundles of collagen fibers with the thickness being similar to standard measurements at 90 days. Based on the results of experimental work, it can be assumed that a patient with congenital clubfoot after Achillotomy performed in a sparing manner with intact peritenon can completely restore the integrity and morphological structure of the calcaneal tendon at 3 months.

CONCLUSION

The experimental study showed that tendon-like tissue with collagen fibers of adequate thickness could form at the site of Achillotomy at 3 months including small islands of fibrous scar tissue and a small number of cellular elements, fibroblasts. The Achilles tendon was shown to regenerate in optimal conditions after the dissection and preservation of the peritenon, vessels and nerves with tendon tissue being identical to the original. Therefore, Achillotomy performed for patients treated with the Ponseti method and preserved connective tissue sheath (peritenon), vessels and nerves can facilitate a positive surgical outcome.

Conflict of interest *Not declared.*

Funding *Not declared.*

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The article was submitted 01.03.2024; approved after reviewing 22.05.2024; accepted for publication 18.06.2024.

Information about the authors:

Maxim V. Vlasov — Candidate of Medical Sciences, Head of the Department, Footdoc@mail.ru;

Natal'ya Yu. Shirokova — Doctor of Biological Sciences, Senior Researcher, nush 63@mail.ru;

Irina V. Musikhina — Candidate of Medical Sciences, orthopaedic surgeon, surgeon, i_musihina@mail.ru