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Abstract

Background The aim of the study was to develop a standardized rat model for chronic rotator cuff tears. Therefore, a time point of degenerative changes that shows comparable histological changes to the chronic tendon tears in humans had to be determined. The rat shoulder has already been described as a standardized model for investigation of the healing behavior in acute supraspinatus lesions. Little data exist about the possibility of generating a chronic rotator cuff lesion.

Methods We performed a complete detachment of the supraspinatus tendon in 45 Sprague-Dawley rats. After an interval of 3, 6 and 9 weeks (15 rats in each group), the macroscopic and histological changes were analyzed. The histological investigation included atrophy and fatty muscle degeneration, tendon degeneration and the grade of inflammatory changes. For evaluation of tendon degeneration, a modified MOVIN-Score was used. The contralateral shoulder provided as control group.

Results Macroscopically the defect showed an increasing coverage with scar tissue over time with a complete closure in 73% after 9 weeks. The 3 week group showed the highest rate of persisting defects (80%). The atrophy of the supraspinatus muscle decreased from initial slight atrophy to a nearly normal muscle status in the 9 week group. Fatty infiltration was found in three animals per

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group regardless of the time interval after detachment. Tendon degeneration (modified MOVIN-Score) showed no significant difference between 3 and 6 weeks ($p = 0.93$) whereas after 9 weeks a significant increased degeneration was found ($p < 0.01$). In the early phase (3 and 6 weeks), inflammatory cells could be detected more frequently.

Conclusions The results show that a chronic tear of the human rotator cuff can be imitated in the rat model with some exclusion. The rapid self-healing response in the rat and the fatty infiltration of the human muscle are the main differences. However, tendon degeneration, inflammation and muscle atrophy combined with a persisting defect at 3 weeks after detachment are comparable to the chronic tendon tears in humans. This model can serve as a basis for further research in the field of rotator cuff repair for chronic lesions.

Keywords Rat model · Rotator cuff changes · Chronic tear · Human rotator cuff · Histology

Background

Lesions of the rotator cuff tendons are a common cause for pain and weakness of the shoulder [1]. The technical approach to surgical repair of these tears experienced a vast progress in the last two decades [2]. Nevertheless, there is still a recurrent tear rate between 25 and 68 percent [3–5]. Apart from defect size and primary fixation stability, there are further important factors to influence the outcome after reconstruction [6]. Especially, the age of the patient and tissue quality play an important role. In the clinical setting, a delayed treatment of the rotator cuff tear is a common situation [7]. According to various studies, the healing of an acute tendon defect after immediate repair seems to differ essential to the healing behavior of chronic lesions after repair [8, 9]. Therefore, the healing capacity of these chronic lesions gains increasing importance.

In current concepts for improving the tendon healing, biological factors (e.g. stem cells, growth factors, transcription factors) play an increasingly important role [10–12]. In 1996, Soslowsky et al. [13] established the rat model for acute rotator cuff disease.

Referring to this, the goal of this study was to develop a rat model for chronic rotator cuff tears that could be used in further investigations (e.g. biologic augmentation techniques in chronic tears).

We hypothesized that a short period of 3 or 6 weeks will result in degenerative changes in muscle and tendon while a longer period will present a partial regeneration due to the increased healing potential of rat tissue.

Methods

Surgical technique

Forty-Six 12-week-old Sprague–Dawley rats (mean weight 427 g SD 27.9) were used in this study. The contralateral left shoulders served as normal, non-operated control group. The right shoulder was operated under general anesthesia to completely detach the supraspinatus tendon from its insertion site on the humerus. The supraspinatus tendon was exposed by creating a 2 cm skin incision in a proximal to distal direction over the antero-lateral corner of the acromion. A deltasplit without detachment of the acromial insertion was performed in the anterior part of the pars acromialis. The split was extended up to 15 mm distal to the acromion. Under adduction, retroversion and slight internal rotation the supraspinatus insertion on the greater tuberosity of the proximal humerus was visualized. The supraspinatus tendon was marked with a 5-0 prolene suture (Ethicon) approximately 3 mm medial from the insertion. Under tension of the suture, the tendon was detached sharply from the rotator interval anterior to the insertion of the infraspinatus posterior. Finally, the adhesions to the anterior and posterior tissue where released by longitudinal incisions, parallel to the fiber orientation of the supraspinatus tendon. The suture was knotted with three simple knots to facilitate the localization of the tendon stump at time of scarification. The overlying deltoid muscle and skin was then closed and the rats were allowed unrestricted cage activity. For 3 days postoperatively, the rats received weight adapted pain medication (metamizole oral and buprenorphine subcutaneous) every 12 h.

Macroscopic assessment

The animals were killed at 3 ($n = 15$), 6 ($n = 15$) and 9 ($n = 15$) weeks postoperatively. After exposure of the greater tuberosity, the defect was photo documented and classified in three groups: defect, partial defect closure (more than 50% of the supraspinatus footprint covered by tissue) and complete defect closure.

Histological assessment

At killing, the musculotendinous unit of the supraspinatus was exposed and removed proximally from the supraspinatus fossa and distally from the bony insertion of the humeral head for histological analysis and stored in 4% buffered formalin solution. For analysis, 5 µm sections from each group and both shoulders were stained with hematoxylin and eosin (H&E). The sections were cut parallel to the tendon fibers and included the supraspinatus muscle and tendon, and any scar tissue that filled the gap

between the tendon and bone. The sections were qualitatively evaluated in a blinded fashion for the evaluating pathologist. Microscopy was performed on a digital microscope (Leica Microsystems, Jena, Germany). Image acquisition and analysis was carried out using a digital camera system (Nikon Inc., Duesseldorf, Germany). Six high-powered fields were analyzed per muscle and tendon cross-section to determine the proportion of degeneration, fatty infiltration, cell number, and chronic or florid inflammation within the probes. A semi-quantitative analysis was performed for each section (N = normal or no infiltration/ inflammation, + = mild and ++ = severe). For evaluation of tendon degeneration, a modified MOVIN Score was used [14]. The subcategories (fiber structure, fiber arrangement, rounding of the nuclei, regional variations in cellularity, increased vascularity and hyalinization) were scored between 0 and 3, with 0 being normal, 1 slightly abnormal, 2 abnormal, and 3 markedly abnormal. The results of the subcategories and the score sum were evaluated.

Statistics

Between group differences were compared using Wilcoxon Test (Software R, Version 2.10.0). Statistical significance was set at $p < 0.05$.

Ethics

The animal research request has been approved by the local government.

Results

The surgical intervention was tolerated without complications in all but one of the animals. One rat died directly postoperatively due to a kidney disease that has been diagnosed post mortem. For the first 3 days postoperatively, the animals used their right arm carefully but after this period no difference could have been detected.

Macroscopic results

The macroscopic evaluation revealed scar formation in all animals. With detection of the marking suture, medial retraction of the tendon could be measured (approximately 3 mm). The subacromial space presented multiple adhesions of scar tissue to the acromion, the coraco-acromial ligament and the remaining rotator cuff.

Group 1 (3 weeks) revealed a persisting complete defect in nine animals, in Group 2 (6 weeks) the number decreased to three and in Group 3 (9 weeks) there was none. A partial defect closure was documented in three times in Group 1, five times in Group 2 and four times in Group 3. Whereas a complete defect closure with scar tissue was revealed by 3 animals in Group 1, 7 in Group 2 and 11 in Group 3. The contralateral control group showed no defects.

Histological results

Muscle exhibited an obvious loss of mass and showed early degeneration with an increased fiber size and number of fibres per high powered field. As a sign of muscle degeneration, an increased amount of intermuscular fibrotic tissue could be observed whereas there was no difference between Group 3 and the control group. Consequently, the muscle degeneration decreased and returned nearly to control levels after 9 weeks postoperatively (Fig. 1). In conclusion, a rapid but transient degeneration of the muscle could be observed after detachment of the supraspinatus tendon.

The further investigation of the muscle showed a fatty infiltration only in few cases (3 cases in each group) without specific distribution pattern (Fig. 2). There was no significant difference between the groups (Fig. 3).

The histological evaluation of the tendon properties was performed with the well-established MOVIN Score [14] modified according to Maffulli et al. [13]. The subcategories "fiber structure", "fiber arrangement", "rounding of the nuclei" and "hyalinization" revealed a higher median score after 9 weeks compared to 3 and 6 weeks (Fig. 4). Whereas the subcategories "regional variations in cellularity" and "increased vascularity" showed no difference in the median. The statistical evaluation of the total tendon score revealed no significant difference between 3 and

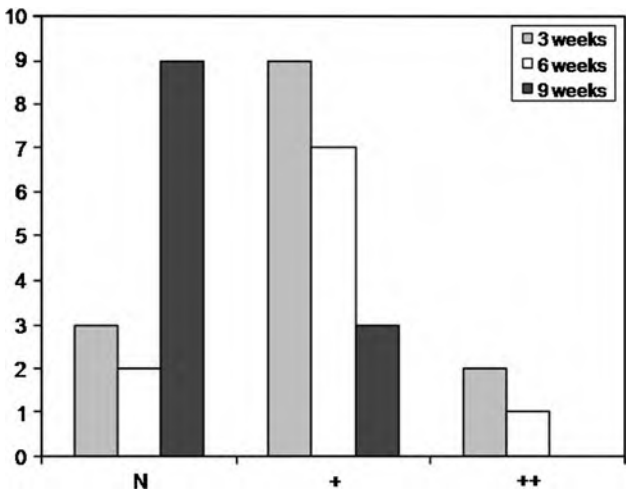

Fig. 1 Muscle degeneration (N = normal, + = mild, ++ = severe)

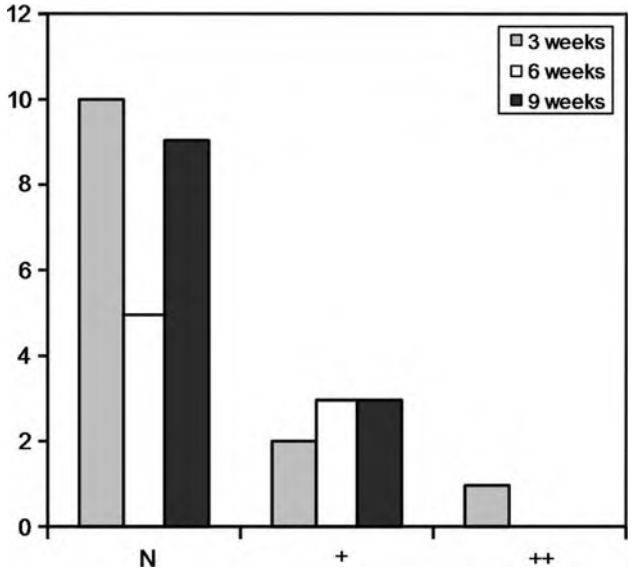

Fig. 2 Fatty infiltration of the muscle (N = normal, + = mild, ++ = severe)

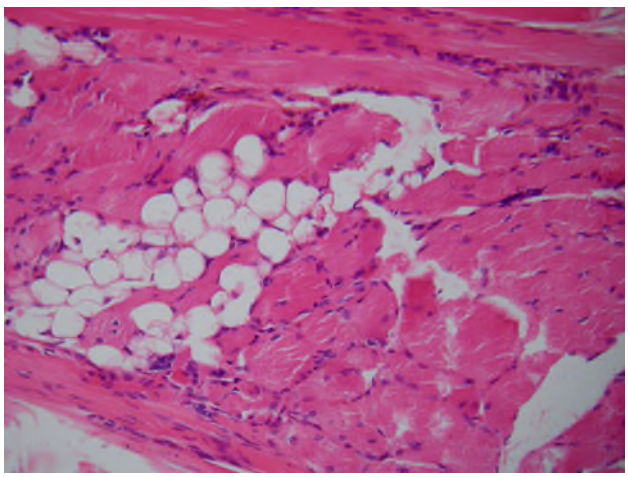

Fig. 3 Histologic example—Fatty infiltration of the muscle. Assessment of fat infiltration after tendon detachment by HE staining: Fatty infiltration after 6 weeks

6 weeks ($p = 0.93$) but there was a highly significant difference between 6 and 9 weeks ($p > 0.01$). The shape of the cells changed from round cells in the early phase (3 and 6 weeks) to spindle shaped cells (Fig. 5).

Finally, the presence of inflammatory cells has been investigated. None of the animals showed signs of an acute inflammatory process. After 3 weeks the majority of the animals (11+/2++) showed a slight increase of chronic inflammatory cells in the tendon/muscle area whereas this inflammatory process decreased after 6 weeks (8+/0++) animals and after 9 weeks postoperatively there were only three animals (3+/0++) with an increased number of inflammatory cells.

Discussion

In our study, we investigated the histological changes to the rat supraspinatus tendon and muscle after tendon detachment. We hypothesized that we have a regeneration of the tendon and muscle tissue after 9 weeks in comparison to the shorter interval of 3 and 6 weeks. This hypothesis has been supported only partially. The muscle underwent a rapid change with degeneration and loss of muscle mass in the first weeks, but this change was reversible and the muscle showed recovery after 9 weeks. In contrast, the tendon degeneration increased with time following tendon detachment especially between 6 and 9 weeks.

The macroscopic evaluation of the defects correlated with the study of Carpenter et al. [16] from 1998 where they found persisting defects of all specimens after 3 weeks and defect closure in 3/8 after 6 weeks and 2/8 after 9 weeks. In contrast to our study, they did not divide into three subdivisions with no defect closure, partial and complete closure. In the human tendon defect, there is no self-healing of full thickness or intraarticular partial thickness tears of the rotator cuff [17]. A clinical study by Yamaguchi et al. [18] showed in a sonographical investigation that the size of existing rotator cuff tears with a conservative treatment increased in size in 39 per cent of the patients after 2.8 years. There was no patient with a decrease of the tear size.

In summary, the healing situation of the rat supraspinatus tendon differs in some aspects from the human tendon. The role of the synovial fluid as healing barrier may be an important factor for the absent healing respond of the human rotator cuff. For a comparable animal model for chronic tears, we summarize that the early stage (3 and 6 weeks) should be preferred due to the persisting defect that is typical for human tendon tears.

The histological changes of the muscle including fatty infiltration and accumulation of fibrotic tissue are a specific reaction of the human muscle to a full thickness tear of the supraspinatus tendon. The accumulation of fat within the muscle is described as irreversible even after repair of the defect [19]. Despite a small percentage of the rats (3 per group) without evidence of uniform appearance across the groups, there was no significant accumulation of fat in the rat muscle in our study. These data confirm the findings of Barton et al. when they investigated the supraspinatus muscle of the rat after detachment [20]. Their specimen showed no significant difference in fatty infiltration to the control group for all time intervals. It could be stated that fatty infiltration within the muscle seems to be species dependent. In sheep, there is a significant fatty infiltration of the muscle whereas [21] it is less apparent in the rabbit [22]. Concluding the fatty degeneration in rats is not

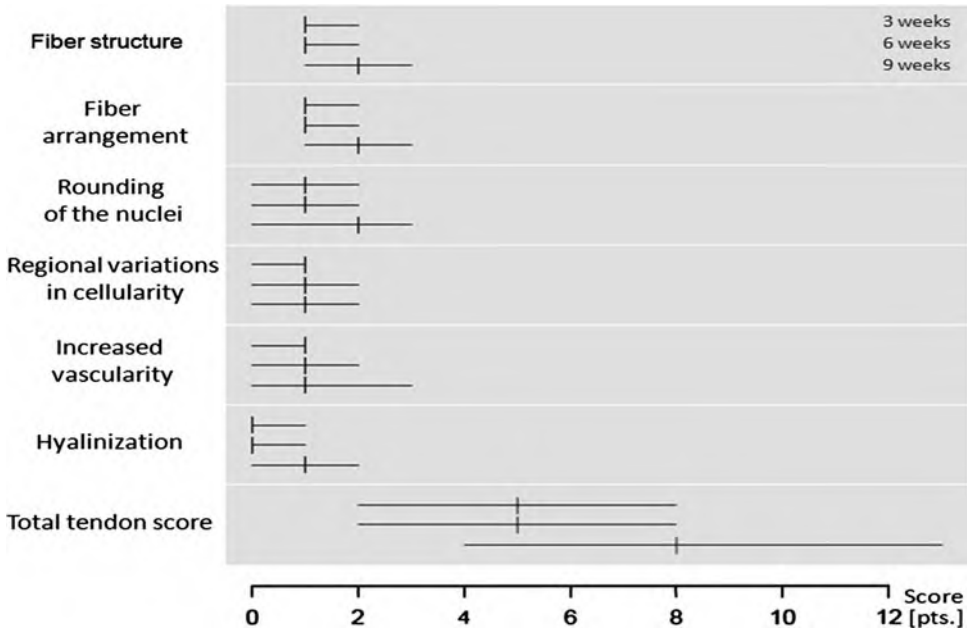

Fig. 4 MOVIN-Score. Histological findings on the treated side median and range in week 3, 6, and 9

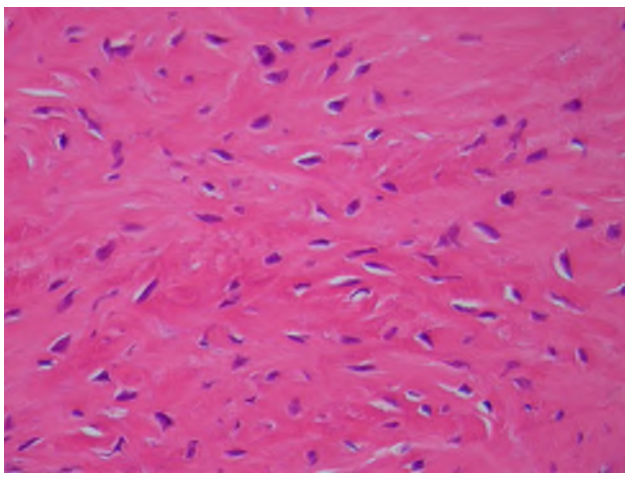

Fig. 5 Histologic example—Tendon degeneration. Assessment of after tendon detachment by HE staining: Loss of fiber orientation after 9 weeks

comparable to the human muscle and therefore not considered to determine the time interval for the chronic tear model. But a comparable fatty infiltration to the human muscle can also not be found in other small animal models.

The loss of supraspinatus muscle volume in MRI is described by Thomazeau et al. [23] for the human shoulder in chronic rotator cuff tears. In human rotator cuff repair, the atrophy of the muscle can recover with time but this process takes at least half a year [24]. In our rat model, the level of atrophy showed a peak in the early group (3 weeks) and decreased with time. Equivalent findings have been documented by Barton et al. [20]. They found the highest level of atrophy after 4 weeks with a following recovery of the muscle. For the rabbit model, a contractile response experiment showed comparable results with a continuous recovery of the muscle until the contraction values reached the level of the control group after 12 weeks [25].

There is little data about muscle biopsies in human rotator cuffs. A current study showed elevated levels of mRNA for atrophy related genes (CAPN1, UBE2B, UBE3A) in massive tears, but to our knowledge there is no description of the structural muscular changes [26]. In the rat model of Barton et al. 1 week after detachment an increase of intramuscular collagen content is reported [20]. Recovery with a decrease of the accumulation of fibrotic tissue began after eight weeks. In our results, the muscle degeneration showed the highest level after 3 weeks and decreased in a similar way in the following weeks.

In fact, the reversibility as well as the quick onset of the atrophy and degeneration is different to the behavior in the human supraspinatus muscle. This phenomenon could be explained by the defect covering and the extensive scar tissue with adhesions to the remaining rotator cuff and the acromion so that a load transmission to the surrounding tissue is possible. To obtain a comparable muscle atrophy to the human setting the early phase after detachment has to be chosen for a chronic rotator cuff model.

In the work of Longo et al. [27], the MOVIN-Score was used for intact and ruptured human supraspinatus tendons. They found a significant higher score for the ruptured tendons in all subgroups compared to the intact group. Their highly pathologic score in human tendons in the subgroups “rounding of the nuclei”, “regional variations in cellularity” and “increased vascularity” cannot be attained

in any of our groups. "Hyalinization", "Fiber structure" and "Fiber arrangement" where comparable to their degenerative changes in the human tendons. The 9 weeks group showed the highest degeneration but in means of feasibility of a reconstruction model these changes where combined with a very high rate of defect coverage and hypertrophic scar tissue.

A work of Hashimoto et al. [28] also described histological changes in human rotator cuff tears in a group of 80 tendon stumps. The orientation of the fibers was also significantly altered especially in the deep layers of the tendon. In addition, a myxoid degeneration in deep layers and hyaline degeneration in the middle layers took place. A chondroid metaplasia has been found in 21% of the patients. In a rat model, Yokota et al. [29] also found fibrocartilage as a sign of chondroid metaplasia 16 weeks after detachment.

The fiber orientation of the tendon has been investigated in detail by Gimbel et al. [30] whereas after a rapid decrease of orientation the tendon recovered from the 4th week on up to week 16. In comparison to our findings, we could not document a reorientation of the tendon in this early phase of healing furthermore, we found an increasing degeneration with myxoid changes and increasing loss of orientation up to 9 weeks.

In the human chronic rotator cuff tear, there are contrary reports about the presence of inflammatory cells. Hashimoto et al. [28] also examined the histological inflammatory signs in the supraspinatus tendon stumps but in none of the specimen, distinct inflammatory changes were observed. Whereas another group reported about 20 patients with arthroscopic rotator cuff surgery with evidence of inflammatory cells (leucocytes, few B or T lymphocytes) [31].

In the rat model, inflammatory cells have been described especially in the peritendinous soft tissue after setting a tendon lesion [13]. Also in the overuse model in the rat, there is an increase of inflammatory parameters with duration of the stress in the tendon itself [32]. In our results, there was a slight elevation of the inflammatory cell counts in the tendon and the surrounding tissue after 3 weeks with a decrease after 6 and nearly normalization after 9 weeks. In summary for this subcategory, we recommend the early phase to imitate the clinical situation with slight inflammatory changes.

With regard to following studies with larger groups to achieve sufficient statistical power we think that the phylogenetic smallest animal that technically allows rotator cuff reconstruction should be used for animal testing. But our current study has some limitations, which should be acknowledged. Retrospectively additional time points (2 and 4 weeks) would have been beneficial to evaluate the course of the histological changes more in detail. The evaluation of tendinous and peritendinous changes was performed in a semiquantitative, descriptive manner so that a detailed statistical evaluation for all tendon and muscle properties except the MOVIN-Score was not possible. But this histological description not based on complex measurements or scores gives us the opportunity to compare all properties to recent literature about histological rotator cuff changes.

Table 1 Comparison: Rotator cuff tear (human vs. rat)

Human rotator cuff	Rat rotator cuff		
	3 weeks	6 weeks	9 weeks
Muscle atrophy ++ [24]	++	++	+
Fatty infiltration +++ [19]	+	+	+
Tendon degeneration +++ [27]	+	+	++
Chronic inflammation + [31]	+	+	0
Defect rate +++ [18]	+++	++	+

Assessment of subcategories (0 = normal, + = mild level, ++ = distinct level, +++ = high level)

Our goal was to achieve an overview of the changes in the rat supraspinatus after detachment including macroscopic defect coverage, muscle atrophy, muscle degeneration, tendon degeneration, and inflammatory reaction and to compare them to the alterations of degenerative human tendons. We already expected that there will be no time point with all categories highly comparable to human tendons, but that a model with comparable attitudes can be found to study rotator cuff healing in the chronic tear.

Conclusions

The main differences to the human tendon are the low rate of fatty muscle infiltration in the rat and the hypertrophic scar tissue that generates a rapid closure of the defect. For investigating tendon healing in chronic rotator cuff tears, the detached supraspinatus tendon after 3 weeks is in our opinion the most feasible time point in the rat model. Right then the defect rate, muscle atrophy, degeneration of the muscle and inflammatory changes can be compared most likely to the human chronic rotator cuff tear. There is no significant difference to the six weeks group except the lower defect rate that gives a disadvantage. The higher grade of tendon degeneration after 9 weeks is for experimental reconstruction not advantageous due to the high defect coverage with scar tissue and the increased comparability in further subgroups (Table 1). For further studies in the field of rotator cuff repair and tendon healing combined with biological augmentation this model could be very useful.

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Conflict of interest None.

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