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Repair within the first 48 h in the treatment of acute Achilles tendon ruptures achieves the best biomechanical and histological outcomes

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Abstract

Purpose To compare the biomechanical and histological properties of Achilles tendons repaired at different time points during the acute injury period.

Methods Thirty-six skeletally mature Sprague–Dawley rats underwent bilateral mid-substance Achilles tenotomy. The Achilles tendons were repaired either in the first 24 h (group 1), 24–48 h (group 2), 48–72 h (group 3), or > 72 h (mean: 120 ± 5.2 h) (group 4) after tenotomy. Six weeks after repair, nine tendons per group were assessed biomechanically and histologically. The Stoll histological scoring system was used for histological examination. The groups were compared with each other and native tendons (control group). The correlations between biomechanical and histological results were analysed.

Results There were no significant differences between groups 1, 2 and 3 regarding the mean load to failure; it was significantly lower in group 4. Healed tendons in groups 1, 2 and 3 had significantly greater stiffness than native tendons and group 4 tendons. All healed tendons had a larger cross-sectional area than native tendons. There was no significant difference in tendon length between the groups. There was no significant difference in Young's modulus between the groups; Young's modulus was lower in all the groups than in the control group. Group 1 had significantly higher extracellular matrix organization, cell alignment, cell distribution and nucleus morphology scores and total scores than group 4. Group 1 had significantly higher extracellular matrix organization, cell distribution, vascularization and inflammation scores and total scores than group 3. A significant positive correlation was detected between the maximum load to failure and total histological score.

Conclusion Repair of acute Achilles tendon rupture within 48 h, and especially in the first 24 h, provides better biomechanical and histological outcomes. In the clinical practice, the data could be used to decrease re-rupture rates, to achieve more anatomical tendon healing and to implement more effective post-operative rehabilitation programme.

Keywords Achilles tendon · Early repair · Optimal time · Tendon healing · Rat

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Introduction

Acute Achilles tendon rupture is a common injury affecting 18 per 100,000 individuals each year [22, 32]. It usually occurs during sporting activities due to forced ankle dorsiflexion against the contracted gastrosoleus muscle complex [25]. The rupture typically occurs in the midsubstance of the gastrosoleus tendon complex and is most common in men aged 30–50 years participating in recreational sports [7, 8]. Importantly, the incidence of Achilles tendon rupture is increasing globally [9, 17].

Although associated with high complication rates, surgical treatment is a more common option amongst athletic population for acute Achilles tendon ruptures [27]. Most acute Achilles tendon ruptures are treated non-operatively with the decrease in surgical incidence whilst Achilles tendon ruptures incidence increases [27].

Minimally invasive techniques have been developed to decrease complication rates [7, 10]. A higher re-rupture risk was previously reported following non-operative treatment. However, studies with a high level of evidence have shown that clinical outcomes similar to those of surgical treatment may be possible with standardized non-operative treatment, controlled range of motion exercises, and early weight bearing [13, 20, 25]. More evidence-based treatment protocols are needed due to the increasing incidence of Achilles tendon rupture.

Previous clinical studies have described various repair timepoints, ranging from as soon as possible to within 48 h or 1 week [21]. No differences in functional outcomes have been reported for repairs performed after delays of up to 1 month [3, 18]. In current clinical practice, most Achilles tendon repairs are performed within 1 week after injury [12].

Surgical intervention during the inflammatory phase may negatively impact tendon healing and the post-operative healing period [21]. The clinical effects of delayed repair were previously investigated [1, 21, 29]. However, the effect of early and delayed repair on the biomechanical and histological properties of the healed tendon is unknown. It was hypothesized that tendon healing may be affected by repair time. With the above in mind, the purpose of this study was to evaluate the effect of different repair times on Achilles tendon healing in a rat model.

Materials and methods

Animal model

Thirty-six 16-week-old male Sprague–Dawley rats weighing 400–600 g were included in the experiment. The entire procedure was performed by one orthopaedic surgeon. Bilateral percutaneous achillotomy was performed in all animals. Achilles tendon healing was studied biomechanically in nine tendons per group and nine tendons per group were examined histologically at 6 weeks in the post-repair period. Ten "native tendons" from five rats were used as a control group. Bilateral percutaneous achillotomy was performed 1 cm proximal to the calcaneal tuberosity under general anaesthesia (ketamine and xylazine) with a No. 11 scalpel. Bilateral Achilles tendon repair was performed in the first 24 h in group 1, at 24–48 h in group 2, at 48–72 h in group 3, and at >72 h in group 4 (mean 120 ± 5.2 h). The repair was performed under general anaesthesia. After a longitudinal skin incision was made, the paratenon was gently opened longitudinally with a No. 15 scalpel. The ruptured Achilles tendon was repaired with a 4-0 Vicryl suture (Ethicon, Sommerville, USA) using the Urbaniak variant of the Kessler technique [19, 26]. Tendon length and cross-sectional area were measured using a high-precision calliper (Fig. 1). Then, the paratenon was repaired primarily (single stitch) with a 4-0 Vicryl suture (Ethicon, Sommerville, USA). The skin was closed using 4-0 Vicryl single stitches. Animals were allowed to move freely in their cages without any immobilization applied to their ankle joints [15]. Animals were euthanized 6 weeks after repair. Bilateral tendons from the study and control rats were harvested with the gastrosoleus muscle and a 5-mm part of calcaneal bone for biomechanical and histological examination (Fig. 1). Tendon lengths were measured and the cross-sectional area was calculated for comparisons.

Biomechanical testing

Tendon length (mm) and diameter (mm) of the samples were measured using a high-precision calliper, and cross-sectional area (mm^2) was calculated. Maximal load to failure and stiffness were measured using a mechanical testing machine (AGS-J; Shimadzu Corp., Kyoto, Japan). The calcaneus and muscle belly were fastened to clamps. Ringer's solution was used to keep the tendons moist. The surface of the proximal and distal clamps was covered with sandpaper to hold the tissue [5]. The displacement rate was set at 1000 mm/min. The force displacement rates were digitally registered and analysed. Maximum load to failure (N), the load at the failure and there is a sudden drop in load after this point, was measured. Tendon stiffness (N/mm), resistance of the tendon to a change in length, was calculated from the linear part of the force–elongation curve and correlated to cross-sectional area (Young's modulus). Measurement accuracy was 0.1 mm for length and diameter, 0.1 mm^2 for cross-sectional area, 0.1 N for load to failure, 0.1 N/mm for tendon stiffness and 0.1 MPa for Young's modulus.

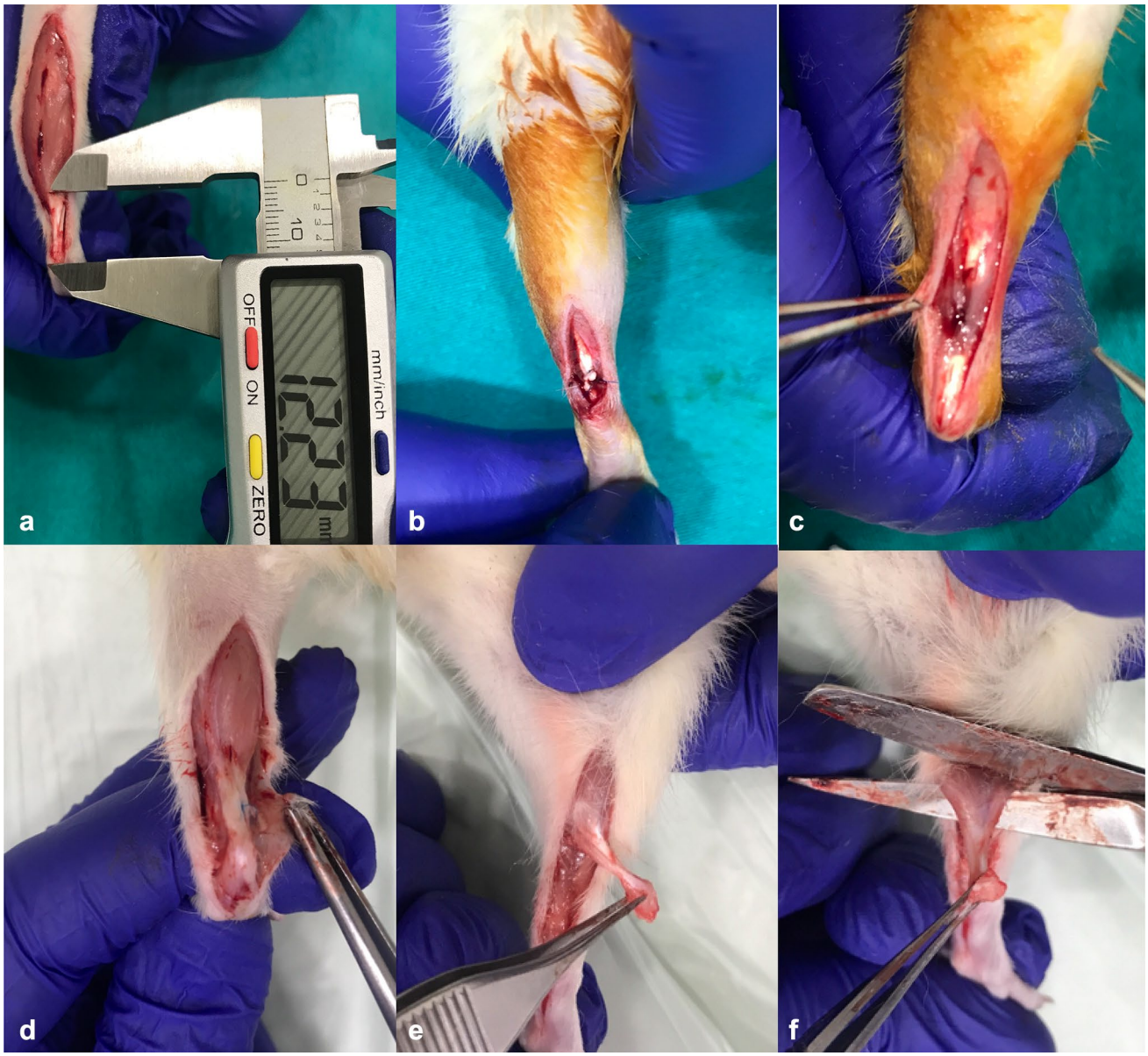


Fig. 1 Peri-operative photographs. **a** Tendon length measurement after tendon repair using high-precision calliper. **b** Repaired Achilles tendon. **c** Closure of paratenon. **d** Healed tendon before harvest. **e** Distal calcaneal bone cut. **f** Proximal gastrosoleus cut

Histological testing

Nine tendons in each group were fixed in 4% buffered formalin solution (pH 7.4) for 24 h. Then, they were dehydrated and embedded in paraffin. Parasagittal sections (4-µm thick) of the tendons were prepared and stained with haematoxylin and eosin, and Safranin O. Five different areas were examined: proximal, distal, medial, lateral and central. Extracellular matrix organization, proteoglycan content, cellularity/extracellular matrix ratio, cell alignment, cell distribution, cell nucleus morphology, metaplasia, vascularity and inflammation were evaluated and total score was calculated in each sample according to a modified Stoll histological scoring system [28]. Two blinded examiners (histology expert and an orthopaedic surgeon) performed the evaluations. A very good agreement was obtained for histological scores ($k > 0.9$ for all). The study design was approved by Acibadem Mehmet Ali Aydinlar University Experimental Animals Research Ethics Board (Approval date/number: 09.04.2018/02-13).

Statistical analysis

Results were shown as the mean ± standard deviation. The Kruskal–Wallis test (Student–Newman–Keuls method) was used to compare values amongst the groups. A p value < 0.05 was considered statistically significant. Spearman's correlation analysis was used to evaluate the correlation between biomechanical and histological results. SPSS version 22.0 (IBM corp., Armonk, NY) was used for all statistical analyses. Cohen's kappa coefficient was used to evaluate the test–retest reliability of the histological scores. A sample of nine animals per group was calculated to be necessary to detect a difference in biomechanical and histological measurements, with 0.80 statistical power. The type-1 error rate associated with the null hypothesis was 0.05.

Results

Biomechanical results

There was no significant difference in tendon length between immediately after surgery, 6 weeks after surgery and native

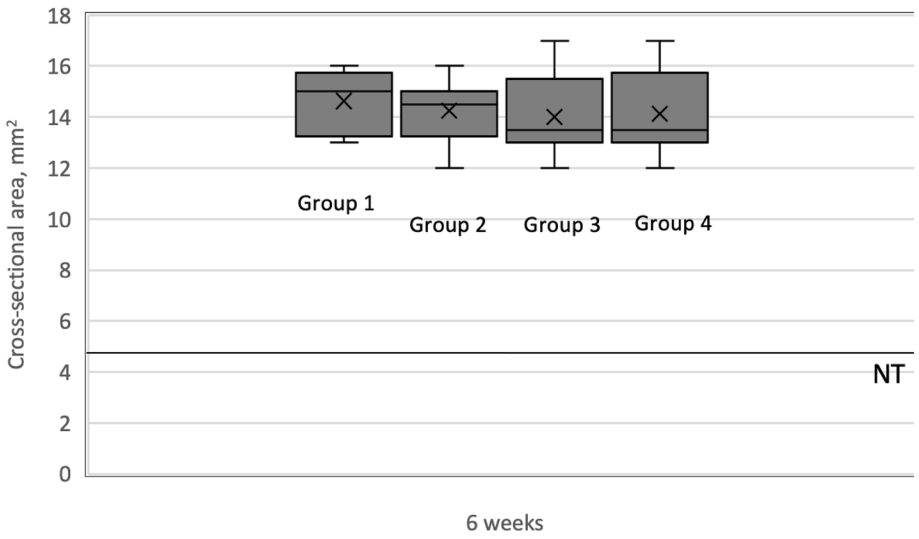


Fig. 2 Cross-sectional area (mm^2) of four groups. Boxes range from first to third quartiles. The median is shown in the boxes. Whiskers extend to values that are less than 1.5 times the interquartile range away from the first and third quartiles, respectively. The horizontal line at 5.4 mm^2 indicates the mean cross-sectional area of native contralateral tendons (NT), which was significantly smaller than all healing tendons

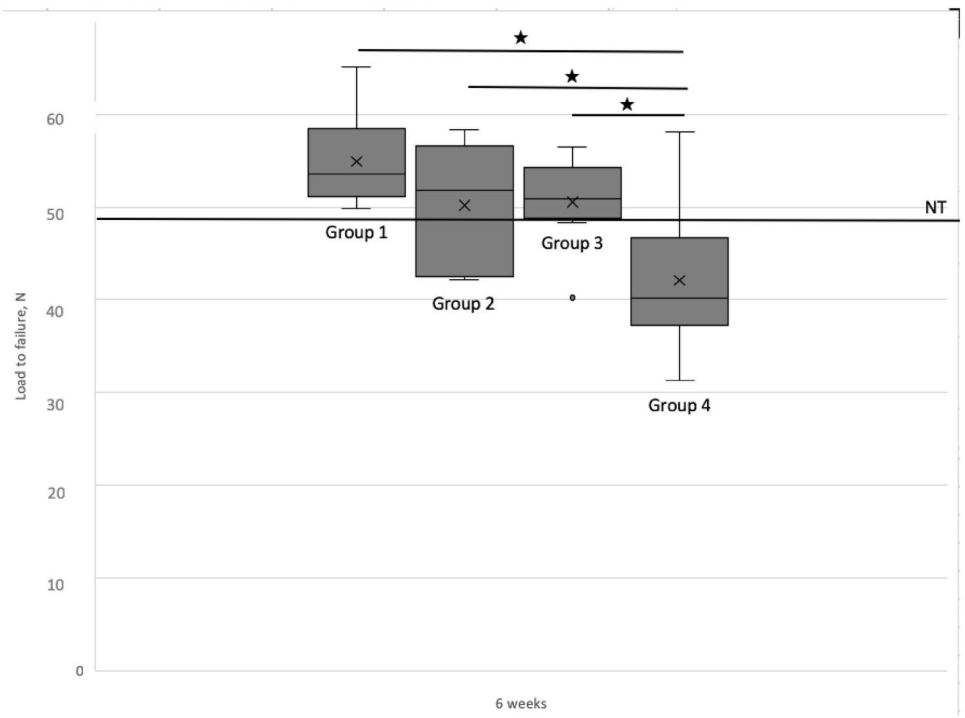


Fig. 3 Load to failure (N) of four groups. Boxes range from first to third quartiles. The median is shown in the boxes. Whiskers extend to values that are less than 1.5 times the interquartile range away from the first and third quartiles, respectively. Statistically significant differences were shown (star). The horizontal line at 49.6 N indicates the mean load to failure of native tendons (NT), which was significantly stronger than group 4

tendons (n.s. for all comparisons). At 6 weeks after surgery, the cross-sectional area was larger in all groups than in native tendons (Fig. 2). No significant difference was found between groups 1, 2, 3 and native tendons with respect to mean load to failure. Tendons in group 4 were significantly weaker than those in groups 1, 2 and 3 and native tendons at 6 weeks (Fig. 3). Tendon stiffness was significantly higher in groups 1, 2, 3 and 4 than that in native tendons (Fig. 4). No significant difference was found between the study groups when correlated to the cross-sectional area (Young's modulus). However, the cross-sectional area of native tendons remained significantly higher than that of all study groups (Fig. 5).

Histological results

In terms of the extracellular matrix organization in the tendon, the arrangement of collagen fibrils was disrupted in some places. A statistically significant decrease was observed in groups 3 and 4 compared to group 1 ($p=0.008$ and $p=0.038$) (Fig. 6).

In terms of cell alignment, the uniaxial tenocytes in the entire tendon were unable to maintain proper alignment in the middle of the tendon, especially around foreign bodies. Alignment was completely disrupted in the areas where metaplasia was observed. In group 4, the score was significantly lower than that in group 1 ($p=0.026$) (Fig. 7).

Cell distribution deteriorated in some areas secondary to repair, and focal cell clusters were observed. Group 1 had

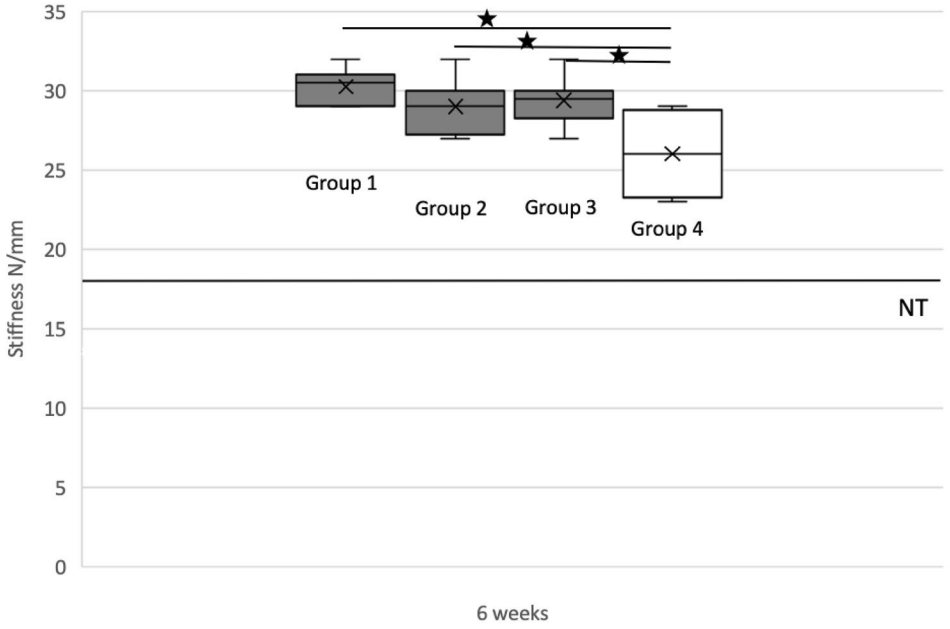


Fig. 4 Tendon stiffness (N/mm) of four groups. Boxes range from first to third quartiles. The median is given in the boxes. Whiskers extend to values that are less than 1.5 times the interquartile range away from the first and third quartiles, respectively. Statistical significance is indicated (star). The horizontal line at 18.9 N/mm indicates the mean stiffness of native tendons (NT), which was significantly lower than four groups

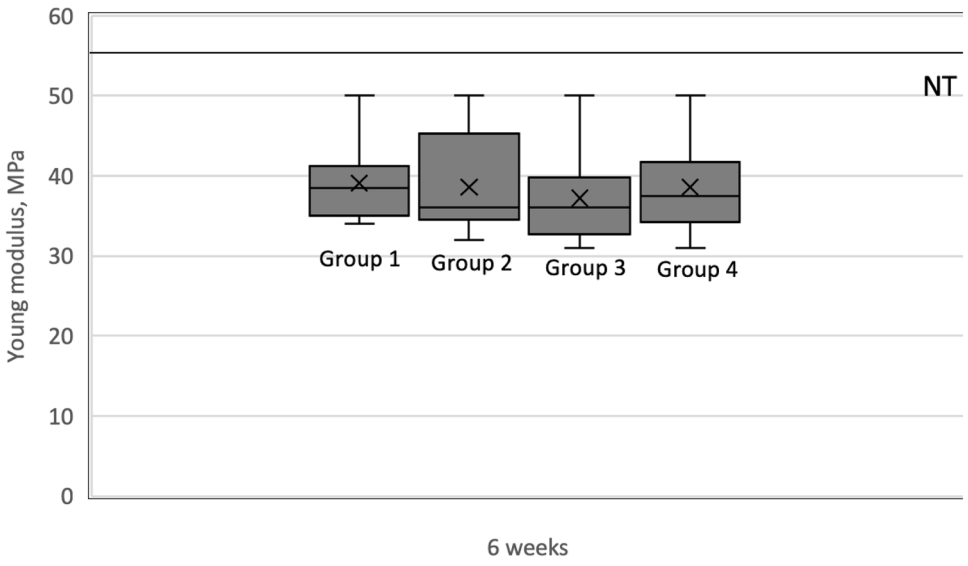


Fig. 5 Young's modulus (MPa). Boxes range from first to third quartiles. The median is given in the boxes. Whiskers extend to values that are less than 1.5 times the interquartile range away from the first and third quartiles, respectively. The horizontal line at 55.8 MPa indicates the mean elastic modulus of native tendons (NT), which was significantly greater than the Young's modulus of all study group tendons

significantly higher scores than the other groups ($p=0.014$, $p<0.001$, and $p<0.001$ regarding group 2, group 3 and group 4, respectively) (Fig. 7).

Changes in cell nucleus morphology were observed at the repair sites, especially in the areas with metaplasia. The score in group 1 was significantly higher than that in group 4 ($p=0.021$) (Fig. 7).

In the evaluation of vascularity after tendon repair, an increase in vascularity was found especially in the regions of foreign bodies and bone metaplasia. The score in group 1 was significantly higher than that in group 3 ($p=0.045$) (Fig. 6).

Inflammatory cell infiltration was observed as focal infiltrations that were more pronounced around the foreign body residues. The score in group 1 was significantly higher than that in group 3 ($p=0.032$). There was also a significantly higher score in group 4 than in group 3 ($p=0.022$) (Fig. 6). When total scores were evaluated, group 1 had a significantly higher total score than both group 3 and group 4. When all parameters were evaluated together, the histological structure was closer to the native tendon in repairs performed in the first 24 h (Fig. 6). A significant positive correlation was detected between the maximum load to failure and total histological scores ($p=0.020$, $r=0.756$).

Fig. 7 Histological sample images from 7.1 (Group 1) to 7.4 (Group 4). Pathological changes in certain areas and surrounding normal tissues were shown. 7.1, Sample images from group 1 (**a** haematoxylin–eosin, **b**, **c** Safranin O). A larger image of the area surrounded by a rectangle in **b** image is shown in **c** image. The metaplasic areas where lacunas are seen are marked with an asterisk. Cells in these areas are observed in the polymorphic structure. It is seen that the parallel and uniaxial structures of the cellular arrangement are disrupted. Foreign body residues are marked with (x). Vascular structures are indicated by arrows. An increase in cell density is observed in the neighbourhood of vascular structures and foreign body residues. 7.2, Sample images from group 2 (**a** haematoxylin–eosin, **b**, **c** Safranin O). A larger image of the area surrounded by a rectangle in **b** image is shown in **c** image. The metaplasic areas where lacunas are seen are marked with an asterisk. Cells in these areas are observed in the polymorphic structure. It is seen that the parallel and uniaxial structures of the cellular arrangement are disrupted. Cavities involving blood vessels suggest osteogenesis. The orange-stained proteoglycan-positive regions with Safranin O suggest focal cartilage metaplasia at the periphery of bone metaplasia. Vascular structures are indicated by an arrow. 7.3, Sample images from group 3 (**a** haematoxylin–eosin, **b**, **c** Safranin O). A larger image of the area surrounded by a rectangle in **b** image is shown in **c** image. The metaplasic areas where lacunas are seen are marked with an asterisk. Distortion is observed in the axes of regulation of tenocytes around bone metaplasia characterized by cavities containing vascular structures. Cells are polymorphic in these areas. Vascular structures are indicated by an arrow. 7.4, Sample images from group 4 (**a** haematoxylin–eosin, **b** Safranin O). The star-marked area shows cartilage metaplasia. Arrows indicate capillary structures. The proteoglycans in the matrix are orange

Discussion

The most important finding of this study was that superior biomechanical and histological outcomes were obtained when repairs were performed in the first 48 h, and especially in the first 24 h. Results significantly worsened when repairs were performed > 72 h after injury. These results show that the timing of repair significantly affects the biomechanical and histological properties of healing tendons.

Previously, concerns have been raised that surgical repair in the inflammatory period might negatively affect tendon healing [21]. The histological phases of the healing of ruptured tendons have been described previously [30, 31]. The

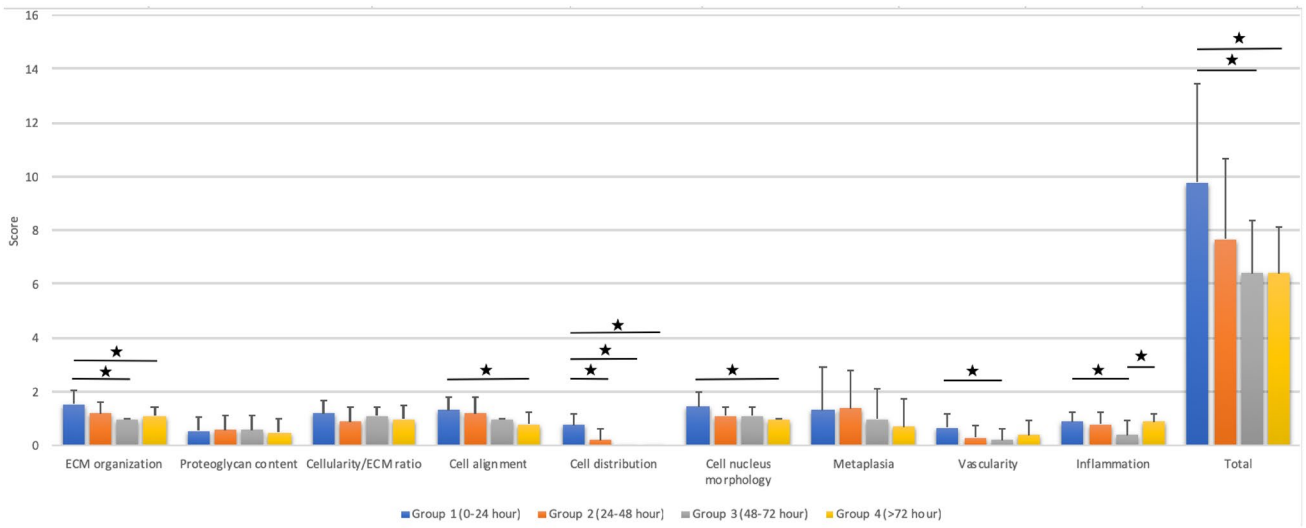
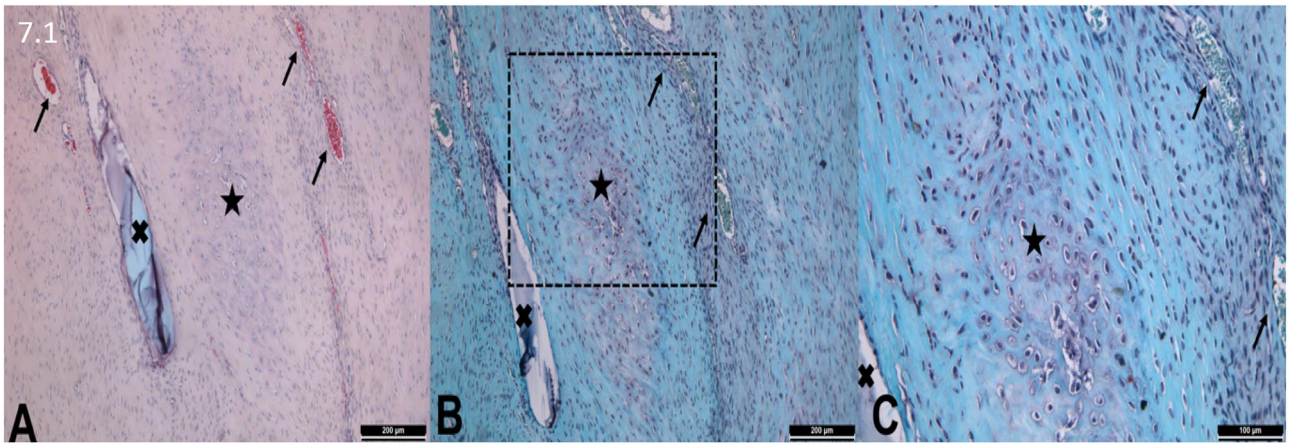
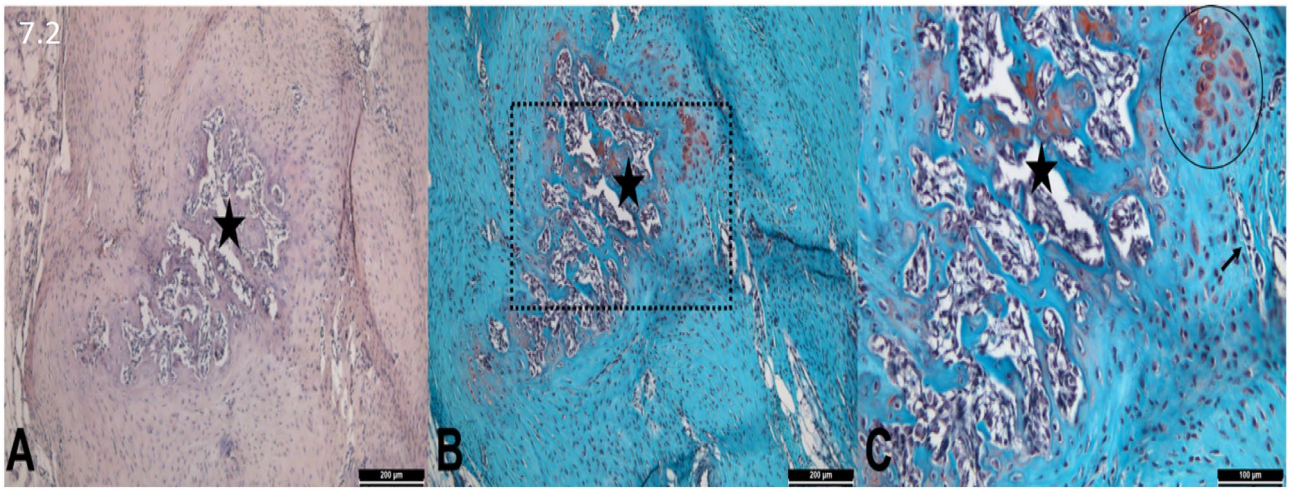


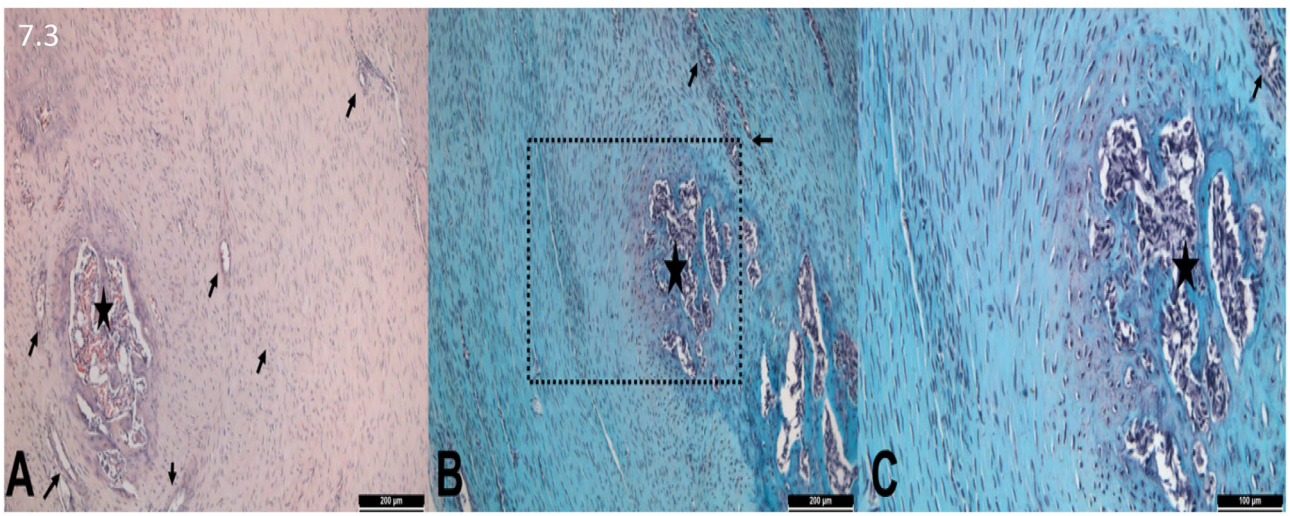
Fig. 6 The modified Stoll histological examination system scores of four groups. Statistical significance is indicated (star). *ECM* Extracellular matrix



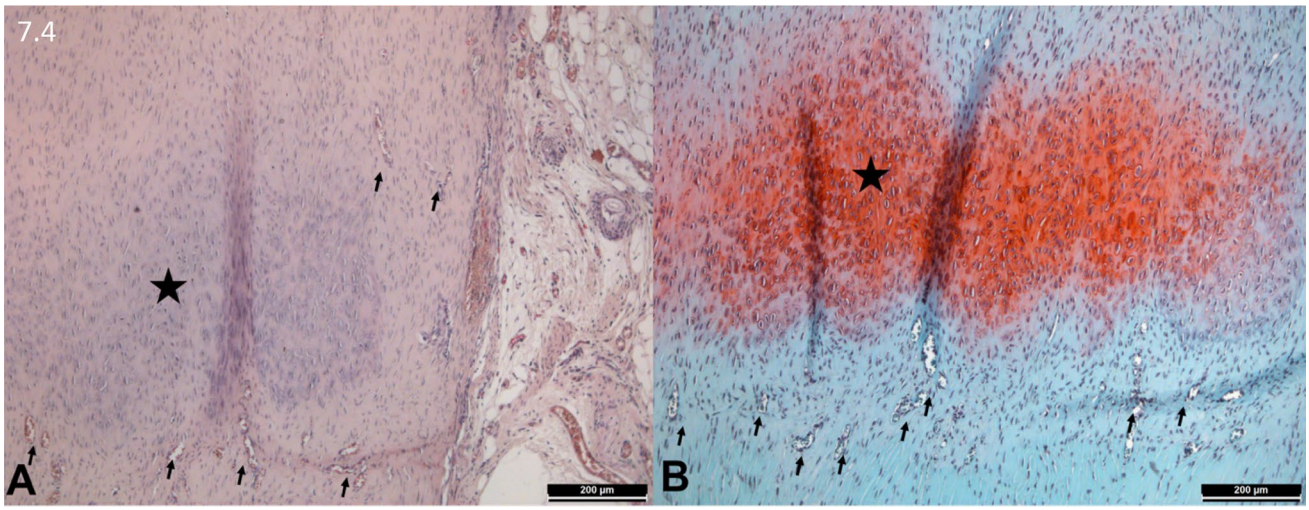
Sample images from group 1 (A: hematoxylin eosin, B and C safranin O). A larger image of the area surrounded by a rectangle in B image is shown in C image. The metaplasic areas where lacunas are seen are marked with an asterisk. Cells in these areas are observed in the polymorphic structure. It is seen that the parallel and uniaxial structure of the cellular arrangement is disrupted. Foreign body residues are marked with (x). Vascular structures are indicated by arrows. An increase in cell density is observed in the neighborhood of vascular structures and foreign body residues.



Sample images from group 2 (A: hematoxylin eosin, B and C safranin O). A larger image of the area surrounded by a rectangle in B image is shown in C image. The metaplasic areas where lacunas are seen are marked with an asterisk. Cells in these areas are observed in the polymorphic structure. It is seen that the parallel and uniaxial structure of the cellular arrangement is disrupted. Cavities involving blood vessels suggest osteogenesis. The orange-stained proteoglycan-positive regions with Safranin O suggest focal cartilage metaplasia at the periphery of bone metaplasia. Vascular structures are indicated by an arrow.



Sample images from group 3 (A: hematoxylin eosin, B and C safranin O). A larger image of the area surrounded by a rectangle in B image is shown in C image. The metaplasic areas where lacunas are seen are marked with an asterisk. Distortion is observed in the axes of regulation of tenocytes around bone metaplasia characterized by cavities containing vascular structures. Cells are polymorphic in these areas. Vascular structures are indicated by an arrow.



Sample images from group 4 (A: hematoxylin eosin, B safranin O). The star marked area shows cartilage metaplasia. Arrows indicate capillary structures. The proteoglycans in the matrix are orange.

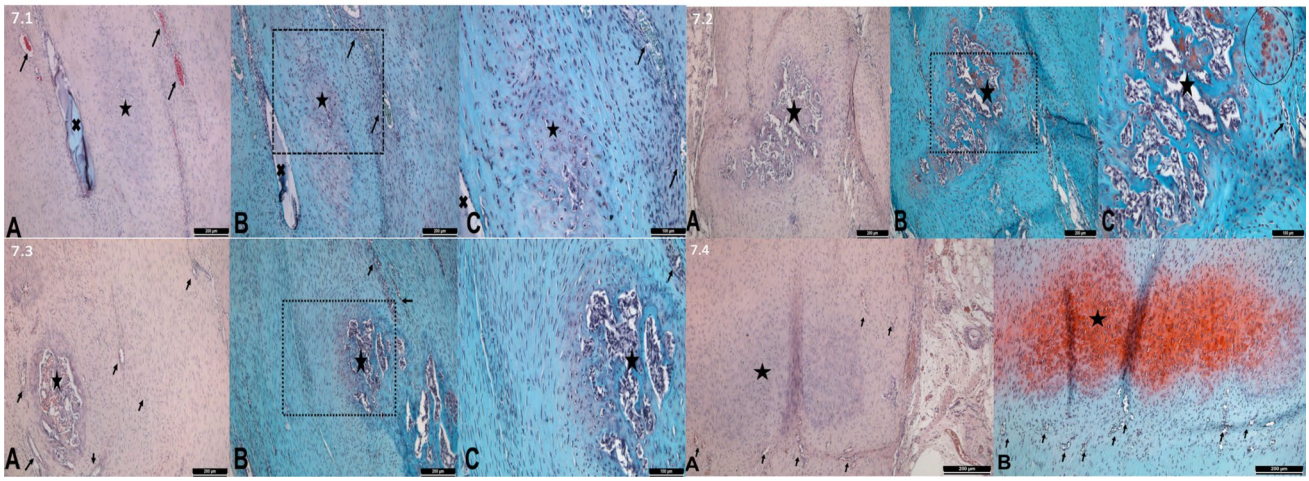


Fig. 7 (continued)

first phase is the haemorrhagic phase, which occurs in the first few hours. The gap is filled with a fibrin clot and polymorphonuclear leucocytes and lymphocytes migrate to the area. The inflammatory phase then begins at 24–48 h and is marked by the arrival of macrophages. During the third phase, fibroblasts arrive and begin producing collagen and matrix proteins. All this takes place during the first week after the initial injury. The final phase of healing is remodelling and maturation, which can continue for months. Within 12–14 weeks, a normal collagen composition of the tendon is obtained [23]. In the present study, Achilles tendons were repaired at four time points: within 24 h from injury, 24–48 h from injury, 48–72 h from injury, and > 72 h after injury. The results showed that the best histological and biomechanical outcomes were obtained in repairs performed in the first phase of tendon healing. Performing repairs during the inflammatory phase did not significantly affect the outcomes. Histological and biomechanical properties worsened when repairs were performed during the proliferation phase. These properties deteriorated when the repair was delayed. This finding may be associated with surgery initiating a second inflammation process, disrupting cell proliferation, differentiation and collagen production [11, 14].

Hypocellularity and poor vascularity of tendons affect the healing process [19]. The paratenon is important for supplying blood to the Achilles tendon [4]. The paratenon contains progenitor cells that significantly contribute to the healing of tendons [6]. Closing the paratenon over the tendon in Achilles tendon repair has been recommended to provide better healing and avoid wound healing problems [16, 19, 24]. In the present study, the paratenon was gently opened and closed in all of our repairs to achieve healthy tendon healing and to test our hypothesis in an objective manner.

In the literature, the influence of delayed Achilles tendon repair on patient-reported outcome scores, isokinetic muscle strength and adverse events has been evaluated [21, 29].

Park et al. [21] compared clinical outcomes and isokinetic muscle strength amongst patients who underwent Achilles tendon repair at the following time points: 24 h, 24–48 h and 48 h–1 week after injury. They reported no significant difference amongst the groups in terms of ankle isokinetic muscle strength and clinical outcome scores. The complication rate was low in all groups. In contrast, Svedman et al. [29] reported better clinical outcomes with lower rates of adverse events in patients who underwent Achilles tendon repair within 48 h compared to those who underwent Achilles tendon repair after 72 h. If the biomechanical and histological superiority of repairs performed within the first 48 h compared with after 72 h are interpreted together with the clinical results of Svedman et al. [29], the results of this study appear to support their clinical results.

Some limitations of this study should be discussed. Although immobilization of plantar flexion with early rehabilitation is accepted as a standard therapy in humans, immobilization and physical therapy are not realistic in animal models [12, 15]. Thus, in this study, we did not restrict ankle joint motion or implement early functional physical therapy. As we know, more ruptures are not clear cuts in the clinical practice. Surgical cut is not representative for a typical Achilles tendon rupture, which probably occurs in silently degenerated tendon and is certainly very different from a surgical transection [2]. Biomechanical and histological evaluations were performed at only one time point. The results may have been different if we had performed assessments during earlier phases of healing.

Conclusion

Repair of acute Achilles tendon rupture within 48 h, and especially in the first 24 h, provides better biomechanical and histological outcomes. In the clinical practice, the data could be used to decrease re-rupture rates, to achieve more anatomical tendon healing and to implement more effective post-operative rehabilitation programme.

Funding None.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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