Joint Diseases and Related Surgery

Jt Dis Relat Surg
2023;34(1):84-91

ORIGINAL ARTICLE

Effects of L-carnitine on healing of Achilles tendon in rats

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ABSTRACT

Objectives: In this experimental study, we aimed to analyze the effects of levocarnitine (L-carnitine) on tendon healing after surgical repair of Achilles tendon rupture in a rat model.

Materials and methods: The study included 40 Wistar Albino rats divided into four groups: Group 1, neither surgical intervention nor substance applications were performed for the Achilles tendons. In the other groups, the right Achilles tendons were cut using a scalpel and repaired with a modified Kessler-type technique with 3/0 monofilament polydioxanone suture. In Group 2, the rats did not receive any additional treatment, except for surgical repair. In Group 3, the same volume similar to Group 4 of saline solution was administered intraperitoneally for seven days. In Group 4, each rat received 300 mg/kg of L-carnitine intraperitoneally for seven days. At Week 6, all rats were sacrificed. All right Achilles tendons were used for biomechanical tests and histopathological evaluations. Biochemical analysis of the matrix metalloproteinase was also performed using the blood specimens.

Results: There were no significant differences among the groups in terms of the histopathological parameters. Although the mean matrix metalloproteinase level was low in the L-carnitine group, it did not reach statistical significance. A significant increase in maximum force, tensile strength, and strength to 2-mm gap was observed in the L-carnitine group.

Conclusion: The significant effects of L-carnitine on biomechanical parameters may indicate favorable effects on Achilles tendon healing in rats by reducing matrix metalloproteinase 2 and 9. To improve Achilles tendon healing, further investigation for these markers is needed. Since the effects of L-carnitine on the Achilles tendon cannot be clearly distinguished histopathologically, further studies involving L-carnitine-induced effects are warranted.

Keywords: Achilles, biomechanical, levocarnitine, matrix metalloproteinase, rat, tendon, tendon healing.

Although there are no underlying metabolic diseases for reasons such as unfamiliar training patterns, anatomy and biomechanical causes with the increase of sporting activities, Achilles tendon ruptures increase in all age groups.[1] Open and percutaneous surgical and conservative techniques are used to repair ruptured Achilles tendon. The treatment goals of a ruptured Achilles tendon are to lengthen the tendon and to increase the force and power of the gastrocnemius and soleus muscles.[2] Regardless of the treatment method, a medical support independent of these treatment options is needed to reduce early complications.

Levocarnitine (L-carnitine) is an amino acid added with trimethyl that assists long-chain fatty acids to pass through the mitochondrial membrane, and it is also known to help in oxidation and energy production in the mitochondria.[3] L-carnitine has various favorable effects on the human body; however, its effects on Achilles tendon healing are still unclear.

Received: September 17, 2022
Accepted: November 15, 2022
Published online: December 27, 2022

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This study was presented as an oral presentation at the Virtual EFORT 2021 Congress on June 30th to July 02th, 2021.

Citation: Kuşcu B, Bilal Ö, Doğar F, Topak D, Gürbüz K, Dere Kİ, et al. Effects of L-carnitine on healing of Achilles tendon in rats. Jt Dis Relat Surg 2023;34(1):84-91. doi: 10.52312/jdrs.2023.853

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Many studies have focused on the Achilles tendons and on the treatment and healing of ruptured Achilles tendons to reduce the re-rupture rate and accelerate the return to social life. What all of these studies have in common is that they demonstrate the need to apply an effective medical substance to reduce early complications; i.e., most commonly re-ruptures.

Matrix metalloproteinases (MMPs) exert a delicate effect on the ruptured tendon and subsequent repair. Activities of MMP-2, MMP-9, tissue inhibitors of metalloproteinases-1 (TIMP-1), and TIMP-2 increased in the ruptured Achilles tendon.[4] The presence of MMP-2, MMP-9, and MMP-14 is a characteristic of tendon healing. However, the uneven balance between them affects the matrix integrity. The increased MMP-2 expression is a sign of Achilles tendinopathy.[5] The release of MMP-9 in the ruptured area is diagnostic, as it is mostly released from inflammatory cells; therefore, its presence in the ruptured area is associated with inflammation.[6]

Previous studies that support the idea of using L-carnitine as a candidate as a medical substance are present in the literature and are increasing in number day by day. In this experimental study, we aimed to investigate the effects of L-carnitine on Achilles tendon healing based on biomechanical, histopathological, and biochemical analyses to enhance healing of the ruptured Achilles tendon in rats.

MATERIALS AND METHODS

This study used 40 adult, male, Wistar albino rats weighing 350 to 400 g. The rats were anesthetized by ketamine (100 mg/kg; Ketalar®; Eczacıbaşı Pharmaceuticals, Istanbul, Türkiye) and xylazine chloride (5 mg/kg; Rompun®, Bayer Pharmaceuticals, Istanbul, Türkiye). All surgical procedures were completed under sterile condition. The rats were divided into four groups. No procedures were performed in Group 1, and the rats were not administered any further medication. The rats were operated and randomly assigned into three groups upon completion of all surgical operations. The second 10 rats in Group 2 did not receive any additional treatment. In Group 3, 2 mL of saline solution as placebo was administered intraperitoneally for the third 10 rats for seven days. Each rat in Group 4 received 300 mg/kg of L-carnitine intraperitoneally for seven days.

The rats in groups were housed under a 12-h day/night cycle with environmental humidity of 55% and temperature of 21 to 22°C. All rats were given *ad libitum* access to food and water.

Surgical procedure

The hairs on the right lower extremities were shaved with an electric shaver and disinfected with povidone-iodine before coating with surgical drapes (Figure 1a). A 2-cm posteromedial incision was made over the Achilles tendon, the Achilles tendon and plantaris were explored under the skin and subcutaneous tissue, and the peritendon was opened (Figure 1b). A surgical blade was used for transecting the Achilles tendon at 0.5 cm apart from its calcaneal insertion. The plantaris tendon was also transected to prevent internal splint (Figure 1c, d). The Achilles tendon was repaired with 3-0 PDS II® using a modified Kessler-type suture technique (Figure 1e) after transection. The skin was, then, sutured using 4-0 rapid Vicryl (Rapide Vicryl®) (Figure 1f). To replicate early functional rehabilitation, cast immobilization was withheld from surgical legs.

All rats were sacrificed, and their Achilles tendons were harvested from the posterior the calcaneus to the muscle belly at the end of sixth week (Figure 1g-h).

Biochemical analysis

Blood was obtained from the heart before the rats were sacrificed and, then, centrifuged at 5,000 cycles for 10 min (Hettich ROTOFIX 32A; Andreas Hettich GmbH & Co. KG, Tuttlingen, Germany). Cold chain transport was employed during transport of the prepared for biochemical analysis at MMP enzyme-linked immunosorbent assay (ELISA) kit (PicoKine™; Boster Biological Technology, Pleasanton, CA, USA). The ELISA was used to evaluate whether plasma contains MMP-2 and MMP-9.

Histopathological analysis

For histopathological assessment, we used the modified technique of Curtis et al.,[7] calculating the common quantity of cells among multiple subjects to reduce subjectivity, as assessment can range in step with the evaluator. A field was selected and enlarged four times. A round area of 6 mm diameter was marked. The horizontal and vertical widths of this area were 1.2 mm, and 25 smaller fields were created from that area. Fusiform fibroblastic cells, veins, and inflammatory cells were counted in each of the 15 randomly selected locations, and the average was calculated (Figure 2). Depending on the degree of fibroblastic proliferation and fibrosis, inflammatory cells were observed: 0, no fibroblastic proliferation and fibrosis; 1, mild; 2,

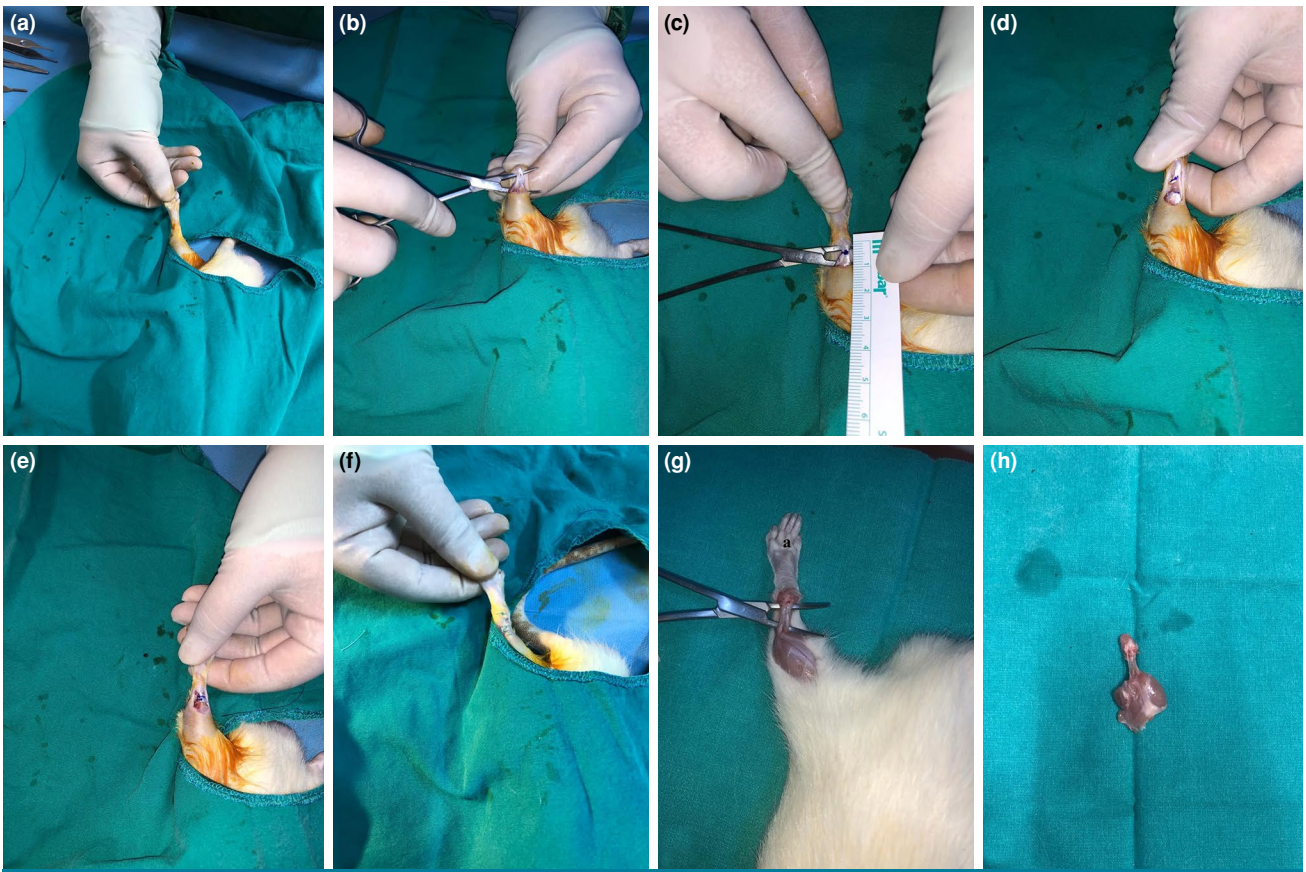


FIGURE 1. Surgical procedures step by step. **(a)** Preparation of rat before surgical intervention. **(b, c)** Dissection and determination of the Achilles tendon before transection. **(d)** Transection of the Achilles tendon at 0.5 mm apart from the calcaneal insertion. **(e)** Repair of the Achilles tendon with Modified Kessler suture technique using 3-0 PDS II suture. **(f)** Closure of the surgical side with 3-0 Vicryl suture. **(g)** Dissection of the Achilles tendon at the end of Week 6. **(h)** Excision of the dissected Achilles tendon for histopathological and biomechanical evaluation.

moderate; and 3, considerable. Neovascularization was modest when the number of capillaries was between 0 and 5, moderate when the number of capillaries was between 5 and 10, and significant when the number of capillaries was greater than 10 at a field diameter of 0.45 μm.[7]

Biomechanical testing

All harvested Achilles tendons were preserved at -80°C preclude tissue damage. Tendons were thawed at room temperature. To keep the Achilles tendons from drying out, they were all covered with a sponge soaked in saline solution.

The cross-sectional area (CSA=mm^2) of each tendon was calculated using the following formula: CSA=W×H/4 × π, where the width (W-mm) and height (H-mm) were obtained from measurements by an electronic gauge (CH-10-AT, Liuling, PRC). Using a universal testing apparatus (Z100, Zwick/Roell GmbH; Ulm, Germany) equipped with testXpert II version 3. 2 software, biomechanical testing was conducted. The tendons were placed on the testing apparatus, which included two custom and handmade tendon clamps preloaded with a force of 2 N prior to the test and subsequently loaded to failure at a displacement rate of 0.1 mm per min. We produced stress-strain curves displaying the values of tensile strength (TS), maximum force (MF), and strength to a 2-mm gap. Young's modulus (YM) values were estimated by the software of the testing apparatus. After biomechanical testing, each specimen's failure site and cause were determined and recorded macroscopically. During biomechanical testing, TS refers to the heaviest load applied prior to a catastrophic breakdown.[8] It is obtained by dividing the applied force by the diameter of a material, so that the result is independent of the diameter, when

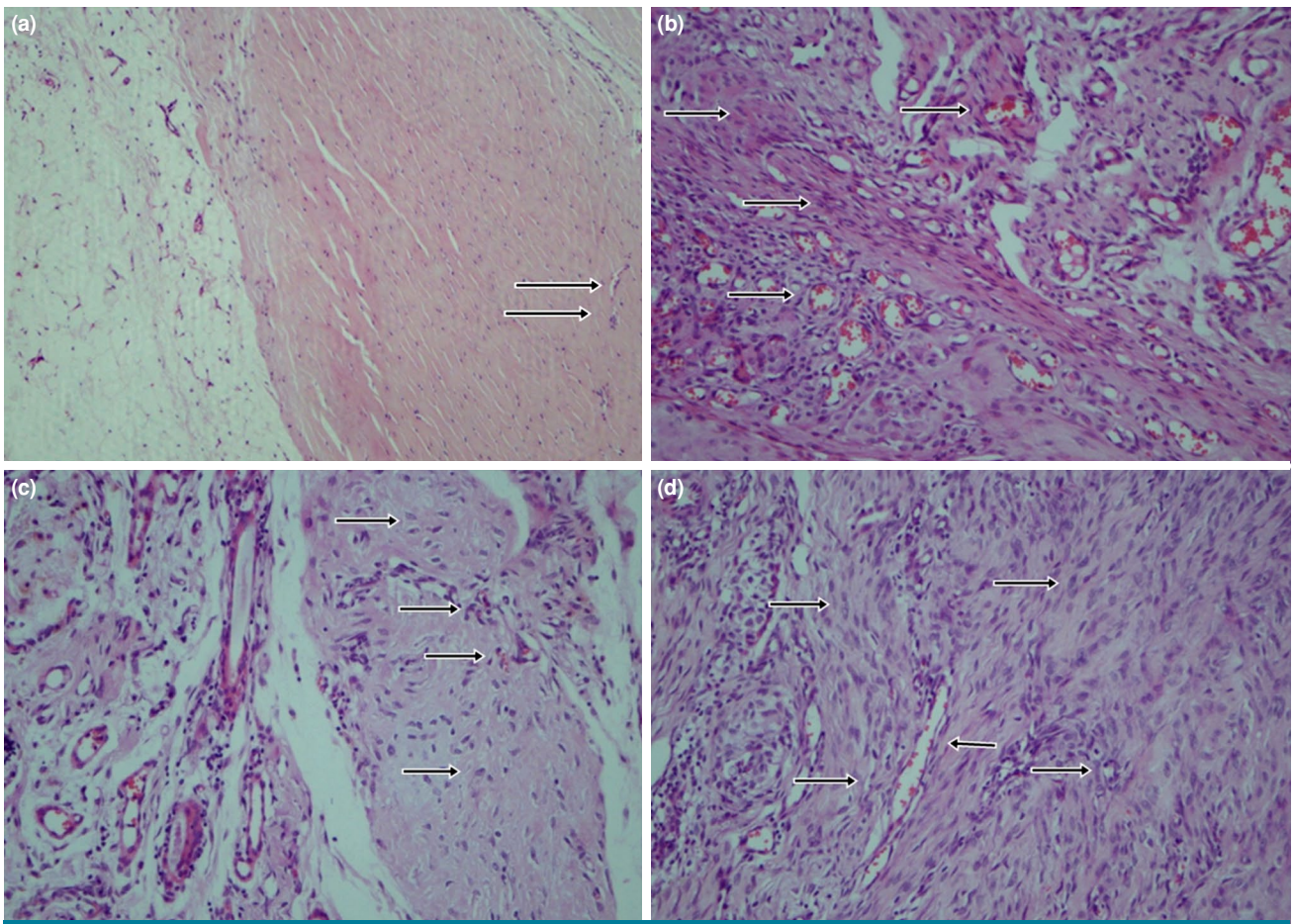


FIGURE 2. Histopathological views of each group. **(a)** Only mild neovascularization and sparse lymphocytes are observed in the section of the tendon (H&E, ×100) (Group 1). **(b)** Significant neovascularization, moderate fibroblastic proliferation, and mild inflammation and fibrosis are observed in the section of the tendon (H&E, ×100) (Group 2). **(c)** Significant neovascularization, mild fibroblastic proliferation, and mild inflammation and fibrosis are observed in the section of the tendon (H&E, ×100) (Group 3). **(d)** Moderate neovascularization, moderate fibroblastic proliferation, and mild inflammation and mild fibrosis in the section of the tendon (H&E, ×100) (Group 4).

tensile testing is applied to materials of different diameters.[8] In this measurement, the magnitude of displacement is overlooked. The strength to 2-mm gap is the amount of force required to establish a 2-mm gap at the repair location. This is regarded as a crucial characteristic for tendon healing near to the initial length.[9] The YM, which is determined by the slope of the stress-strain curve, is the measurement of elastic deformation under load.[10] The MF refers to the peak value reached in the elongation curve against the force and shows the strength of healing.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) or number and frequency, where applicable. The Shapiro-Wilk test demonstrated the normal distribution of the data, while the Levene test validated the homogeneity. Multiple group comparisons, pairwise comparisons, and independent group comparisons were conducted using one-way analysis of variance, Tukey's test, and t-test, respectively. A p value of <0.05 was considered statistically significant.

RESULTS

Biochemical results

In this current study, the ELISA method was used to detect the presence of MMP-2 and MMP-9 in the plasma. The MMP-2 and MMP-9 were significantly decreased in the L-carnitine group (Group 4; Table I). However, no significant differences were found between the groups (p=0.219 and p=0.955).

TABLE I
Comparison of the groups regarding the MMP-2 and MMP-9 values

	MMP-2	MMP-9
Parameters	Mean±SD	Mean±SD
Group 1	3391.67±1760.93	6265.4757±2649.622
Group 2	6916.76±4575. 23	6056.2015±5011.348
Group 3	4911.71±3570.58	5206.7154±3472.468
Group 4	4304.18±3410.51	5701.0067±5299.5864

MMP-2: Matrix metalloproteinase-2; MMP-9: Matrix metalloproteinase-9; SD: Standard deviation.

Histopathological results

Inflammation, neovascularization, fibrosis, and fibroblastic proliferation did not differ significantly among the groups (p=0.687, p=0.409, p=1.0, and p=0.389, respectively).

Biomechanical results

All biomechanical parameters are shown in Table II and Figures 3 and 4, respectively.

Young's modulus

The mean values of the stress-strain curve (YM) of the Achilles tendon, and the YM values among the groups were not statistically significant (p=0.350).

Tensile strength

The mean TS values in the all groups were statistically significant. The TS values were statistically significantly different between Group 1 and Group 2 (p=0.027), and between Group 1 and Group 4 (p=0.011). The TS was higher in Group 4 than in Group 2; however, no significant difference was found. The TS of Group 4 was significantly higher than those of Group 1 (p=0.011) and Group 3 (p=0.044).

Maximum force

The mean MF values of the four groups differs between the groups which were significant (p=0.030). Significant differences in MF were found between Group 1 and Group 2 (p=0.027) and between Group 1 and Group 4 (p=0.011). However, the MF value was higher in Group 4 than in Group 2, but no significant difference was found (p=0.697). The MS value was higher in Group 4 than in Group 3 (p=0.044).

TABLE II
Comparison of the groups regarding the Young's modulus, tensile strength, maximum force, and strength to 2-mm gap

	Young's modulus (kPa)	Tensil strength (N)	Maximum force (N)	S2G (N)
Parameters	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Group 1	64.33±1545.01	4856±768.57	29.61±4.89	30.42±1.51
Group 2	1481±2766.12	6855±1099.01	43.59±6.99	30.48±3.53
Group 3	1909.75±1217.14	5085±1980.09	32.33±12.59	15.92±2.55
Group 4	428.25±1534.11	7542±1656.59	46.04±10.53	37.58±11.93

kPa: Kilopascal; N: Newton; S2G: Strength to 2-mm gap; YM: Young's modulus; SD: Standard deviation.

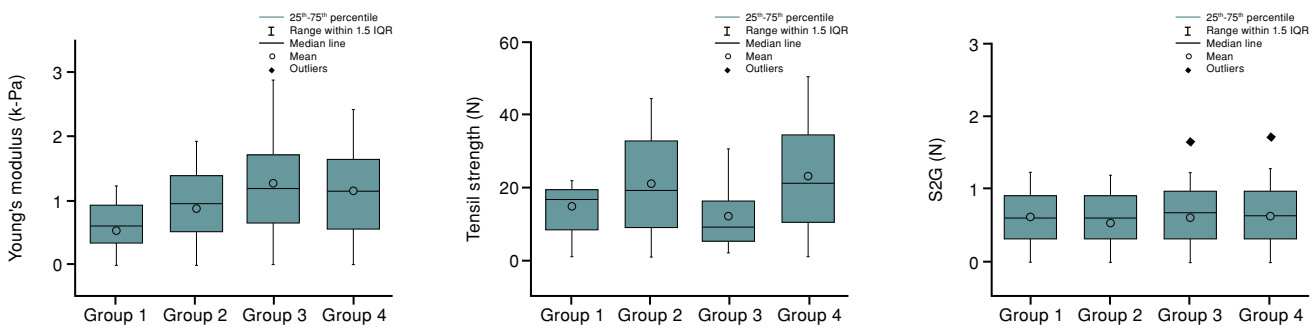


FIGURE 3. Distribution of tensile strength (TS), Strength to 2-mm Gap (S2G), Young's modulus (YM). **(a)** Comparison of YM in each group. **(b)** Comparison of TS in each group. **(c)** Comparison of S2G in each group.

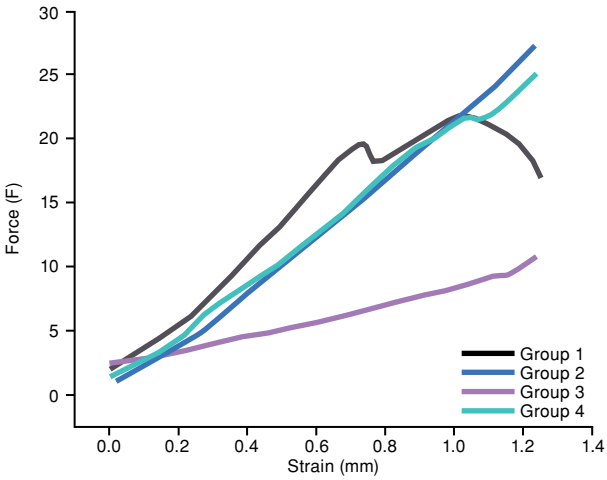


FIGURE 4. Force-strain curves of each group.

Strength to 2-mm gap

The highest mean strength to 2-mm gap value was observed in Group 4. The difference among the groups was significant. The mean strength to 2-mm gap value of Group 4 was significantly higher than that of the other groups (p=0.003).

DISCUSSION

This study firstly reveals the biomechanical, biochemical and histopathological effect of L-carnitine on tendon-tendon repair of Achilles tendons in rats. In the light of these results, further clinical trials can be carried out on this subject.

Some treatment methods showing positive effects on rat Achilles tendon healing include laser therapy, ultrasound methods, and direct current electrical methods.[11] A number of studies have also shown that autologous conditioned serum beneficial for rat Achilles tendon healing model.[12] Moreover, taurine has been demonstrated to have positive effects on rat Achilles tendon healing.[13]

Doses of 3 to 4 g of L-carnitine or glycine propionyl-L-carnitine (GPL-C) consumed between 60 and 90 min prior to exercise could increase the lactate threshold, reduce perceived exertion throughout incremental tests until exhaustion, and increase peak and average power in the Wingate cycle ergometer test.[14] In another study, the considerable effects of L-carnitine administration on preventing muscle atrophy were shown.[15] In the aforementioned study, it was concluded that acetyl L-carnitine at a dose of 1,500 mg/day had a significant effect on the reduction of neuropathic pain with promising results in compressive neuropathy caused by carpal tunnel syndrome. Also noticed is a favorable influence on nerve regeneration, particularly in the early phases of carpal tunnel syndrome.[16] A study regarding the weakness problems such as weakening of muscles showed that it could be encountered in old age and could be minimized by eliminating carnitine deficiency in the body.[17] One of the studies on L-carnitine demonstrated that it increased the bone mineral density in the musculoskeletal system.[18]

Yildiz and Turalıoglu[19] investigated histopathological effect of L-carnitine on Achilles tendon healing during the postmenopausal period. In this study, a significant difference was found in fibrosis levels between the healthy control group and the injured group after the administration of high and low doses of L-carnitine. However, no significant difference was found in the extent of fibrosis between the L-carnitine group and the other three groups in our study (p=1.0). This difference is probably caused by the dose of L-carnitine and the fact that the rat to which it was applied is male.

Güngörmüş et al.[20] also showed a significant difference in the extent of inflammation between the groups in a rat auto-tendinosis grafting at Achilles tendon repair. Moreover, significant phagocytic cells and neutrophils were observed in the experimental group. Histopathologically, no significant differences were found between the groups in terms of inflammation (p=0.0687), neovascularization (p=0.409), and fibrotic proliferation (p=0.389) in our study. Also, L-carnitine did not exert a significant effect or cause any negative effect on tendon healing. Since the effects of L-carnitine on the Achilles tendon cannot be clearly distinguished histopathologically, additional studies involving L-carnitine-induced effects are warranted.

Lehner et al.[21] reported that the contact of the blood after tendon damage with serum increased the enzymes for MMP-2 and MMP-9 that degrade the matrix. This increase had a negative effect after tendon damage. In addition, Robertson et al.[22] found that the increased release of MMP-1 and MMP-9 was highly correlated with unsuccessful healing of the rotator cuff in patients who underwent arthroscopic rotator cuff repair. In the injury group, MMP-2 and MMP-9 release was increased in both the rotator cuff and subscapularis tendon. Therefore, it is reasonable to speculate that inhibition of MMP in the damaged tendon and shoulder joint would positively affect rotator cuff and tendon healing.[22] Besides, Bedi et al.[23] showed that inhibition of MMPs in the repaired tendon positively affected the results of biomechanical tests. According to our biochemical

examination of MMP-2 and MMP-9, no significant differences were found between the groups (MMP-2, p=0.219; MMP-9, p=0.955). The mean values of MMP-2 and MMP-9 in the L-carnitine given group were low compared to the other groups, which is probably caused by the lack of sufficient specimen. Philip et al.[24] investigated 126 rats and showed the effect of amnion-derived multipotent progenitor (AMP) cells on Achilles tendon healing. The AMP group demonstrated higher YM than the amnion-derived cell cytokine solution (ACCS) group and saline group in biomechanical tests. In our study, no significant differences were found between the groups regarding the YM. In the study by Eren et al.,[25] histopathological examination revealed that both low-molecular-weight heparin and rivaroxaban had positive effects on tendon healing. However, the same positive effects were unable to be observed in biomechanical examination. In our study, the mean TS values were significantly different between Group 1 and Group 2 and between Group 1 and Group 4 ($p<0.05$). Moreover, the TS of Group 4 (L-carnitine group) was higher than that of the other groups. In our study, although significant differences were found among Group 1, Group 2, and Group 4, the mean MF value was higher in Group 2 and Group 4 ($p<0.05$). Furthermore, the mean MF was higher in the Group 4 than in Group 3 ($p<0.05$).

In a study Şahin et al.[26] investigated the effects of pentoxifylline on Achilles tendon healing in tenotomized rabbits. Pentoxifylline increased healing and strength in rabbit Achilles tendon by stimulating collagen synthesis, increasing vascularity and reducing inflammation, particularly in the early period both histopathologically and biomechanically.

Nonetheless, there are some limitations to this study. First, biomechanical testing was conducted on an *ex vivo* animal model; therefore, the effects of L-carnitine on tendon biology could not be evaluated. Second, the optimized tenotomy is not indicative of an acute Achilles tendon rupture, and linear loading is less representative of strains on the human Achilles tendon than cyclic loading. Although histopathological examinations are sufficient in our study, immunohistochemical examination could have been also added to evaluate vascularization (CD31), inflammation (MAC387), proliferation (Ki-67). Although the sample size is appropriate according to the power analysis, statistically significant differences can be demonstrated in future studies by increasing the sample size and in studies in which additional biochemical parameters are used.

In conclusion, the significant effects of L-carnitine on biomechanical parameters may indicate favorable effects on Achilles tendon healing in rats by reducing biochemical parameters such as MMP-2 and MMP-9. Since the effects of L-carnitine on the Achilles tendon cannot be clearly distinguished histopathologically, further studies involving L-carnitine-induced effects are warranted.

Acknowledgements: Thanks for Kahramanmaraş Sütçü Imam University Scientific Research Projects (Research Project Approval Number 2020/1-13 D) to funded this study.

Ethics Committee Approval: The study protocol was approved by the Kahramanmaraş Sütçü Imam University Faculty of Medicine Animal Experiments Local Ethics Committee with the approval number 2018/07-04.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conceptualization, methodology, software, data curation, writing, original draft: B.K.; Methodology, project administration: Ö.B.; Data curation: F.D.; Software: D.T.; Writing, original draft, formal analysis: K.G.; Investigation: K.İ.D.; Resources: M.T.; Validation: A.A.K.; Data curation, software: S.K.; Data curation, software: M.S.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: This study was funded by Kahramanmaras Sutcu Imam University Scientific Researchs Projects unit (Research Project Approval Number 2020/1-13 D).

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