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The Effect of L-Carnitine on Experimental Achilles Tendon Injury

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SUMMARY

Background. L-carnitine (LC), which has anti-inflammatory and antioxidant effect, is especially consumed by sportmans to increase muscle mass recently. Therefore, the functional, histopathological effects of LC on experimental Achilles tendon injury were investigated in this study.

Methods. Forty male Wistar Albino rats were randomly divided into four groups (n = 10). A tendon injury model was created by clamping the left Achilles tendon of all rats except the control group. Tendon Injury Group (TIG) and the Control group did not receive LC treatment. LC (100 mg/kg/day, intraperitoneally) was started to administer one week before the injury model in pre-LC group and the same day of injury in post-LC group following the establishment of model for four weeks. After the tendon injury and at the end of the experiment, rats in all groups were subjected to a Gait test (GT) twice. On the 30th day of injury, the rats were sacrificed, and left Achilles tendons were dissected for histopathological analysis.

Results. Initial GT data were significantly different between the control and other groups ($p < 0.001$). The final GT data were significantly different only between the Control and TIG ($p = 0.002$). Histopathological examination revealed that neovascularization, fibroblastic activity, and collagen fibril sequencing parameters were found to be significantly different amongst the TIG and pre-LC group, and post-LC group ($p < 0.05$).

Conclusions. LC contributes to the tendon healing by histopathologically and functionally.

KEY WORDS

Gait test; histology; inflammatory; rat; tendinopathy.

INTRODUCTION

Tendons are the body's strongest soft tissue structures. However, they can easily be damaged by frequent repetitive movements, degeneration and sudden traumas. Although being the Achilles tendon is the strongest and thickest tendon in the human body, it is commonly susceptible to damage and ruptures due to sudden strain and overload (1). At the present time Achilles tendon injury is frequently seen in professional athletes and 30-49 aged amateur athletes to the increasing interest in sports (2). Achilles tendinopathy is especially common in elderly patients accompanied by degenerative processes due to decreased vascularization (3). The delay in the healing period of the tendon causes them to be immobilized for a long time. Prolonged immobilization negatively affects the anatomical and physiological properties of the tendon, and also the risk of re-injury. The prolongation of the immobilization period of the tendon in the healing process causes restriction in the daily life activities of patients, and especially active and productive people causes losses in the workforce. For this reason, many experimental studies have been conducted to investigate new treatment modalities such as glucosamineand chondroitin sulphate, vitamin C or ascorbate, hydrolyzed type I collagen, L-arginine-alpha-keto-glutarate, curcumin, boswellic acid, methylsulfonylmethane, and bromelain (4) related to healthy and rapid healing of tendons (3, 5-7).

LC was synthesized in the liver and kidney is an unmodified amino acid. In the transport of long-chain fatty acids into the mitochondrial matrix, where the beta-oxidation process takes place, it functions as a cofactor (8). The three phases of the local healing process following tendon injury are inflammatory, proliferative, and remodeling, respectively. Therefore, anti-inflammatory and antioxidant agents are expected to promote tendon repair (9).
Experimental studies have shown that LC is a powerful antioxidant molecule with anti-inflammatory effects (10, 11). Consequently, the purpose of this study is researched the functional and histological effects of LC on tendon recovery following experimental Achilles tendon injury.

MATERIALS AND METHODS

Ethical statement

This study was approved by the Aydin Adnan Menderes University for Animal Experiments Local Ethics Committee (Approval no: HADYEK 64583101/2022/027 – Date of approval: April 18, 2022).

Tendinopathy procedure

A preliminary study was performed to determine the experimental Achilles tendon injury model. Rats were anesthetized with ketamine hydrochloride before the Achilles tendons were clamped (10 mg/kg, Ketalar®, Pfizer, Istanbul, Turkey) and Xylazine hydrochloride (5 mg/mL, Rompun®, Bayer, Istanbul, Turkey). Four different tendon injury models were carried out to the four rat Achilles tendons, with the different degree of clamp level, clamp compression and relaxation time, and the number of compression repetitions (**table I**). The rats were euthanized under the general anesthesia at the end of 30th day. Four Achilles tendons were surgically dissected and taken into 10% formaldehyde fixation solution for Hematoxylen-Eosin staining. The evaluation was conducted by a single pathologist who was blind to the tendon injury procedure based on modified the Curtis *et al's* (12) scoring on histological recovery. The separameters are fibroblastic activity, inflammation, neovascularization, collagen fiber sequencing, and calcification. As a result of histopathological scoring, it has been decided that the sample of model IV has the most obvious inflammation and the least healing.

Experimental procedure

This experimental animal study was conducted in Faculty of Medicine Animal Experiments Laboratory. In this study, 40 male Wistar albino rats weighing 400-530 g at 36 weeks of age were employed. Four groups of ten rats each were created by randomly dividing the animals. The rats were traced the standard conditions of 12-hour light/12-hour darkness cycle and three to four animals were kept in each cage. They were provided to access *ad libitum*, unlimited feed and water. Daily injection of LC (100 mg/kg, Lekarnitin ampoule 1 g/5 cc, Pharmada, Istanbul, Turkey) in the pre-LC group was started one week before the tendon injury. Injection of LC in the post-LC group was started following the tendon injury (**figure 1B**). One group with tendon injury (TIG) was left without LC treatment. The control group was not applied a tendon injury or LC treatment. Under the anesthesia, tendon injury model IV was chosen as previously decided on preliminary study to the TIG, pre-LC group, and post-LC group (**figure 1A**). The weights of all rats were recorded each Monday throughout the study to adjust the LC doses weekly (**figure 1C**). On the day of 30th post experimental tendon injury, the rats were decapitated under the anesthesia of Ketamin and Xylasine and the left Achilles tendons were dissected for histopathologic analysis.

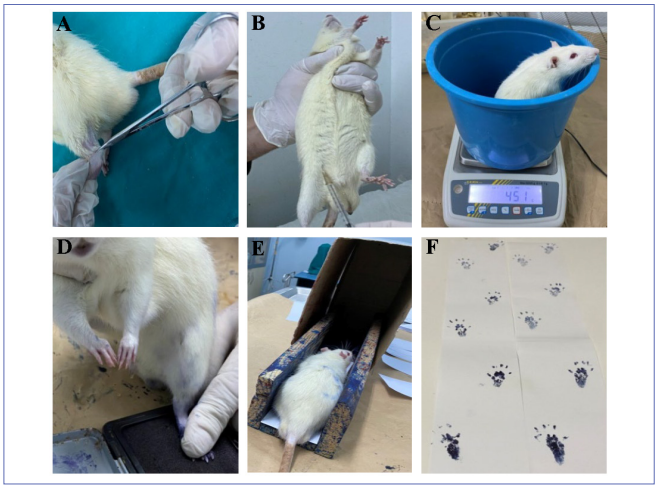

Figure 1. Application of tendon injury **(A)**; Injection of LC intraperitoneal **(B)**; Rat weight measurement **(C)**; Process of gait test **(D-F)**.

Table I. Tendon injury models of preliminary study.

	Model I	Model II	Model III	Model IV
Clamp level degree	2	2	3	3
Clamp compression time (minutes)	1	2	2	2
Clamp relaxation time (minutes)	3	1	1	1
Compression repetition number	4	4	4	5

Gait test

Murrell *et al*. (13) described the Achilles Functional Index (AFI) that measures how well the Achilles tendon functions. GT was applied to all rats in twice, consequently after compressed the tendon and at the end of the experiment. A walking track (width of 7.5 cm, height of 8 cm, and length of 42 cm) was used for GT. The plantar surfaces of the back legs of the rats were stained with blue ink and they were ensured walking on a wide 7 cm and a long 42 cm white paper placed on the walking track floor (**figure 1D-F**). The footprints measurements of rats were made using the image J program. AFI was calculated using the formula which was base upon the distinction in the footprint between the healthy and the injury side during walking. A single numerical value was obtained. The formulas are:

1) PLF = (healthy PL - injury PL) / injury PL
2) TSF = (injury TS -healthy TS) / healthy TS
3) ITF = (injury IT - healthy IT) / healthy IT
4) AFI = 74 (PLF) + 161 (TSF) + 48 (ITF) - 5

where Print length (PL) is the distance between the heel and the third toe; Toe-spread length (TS) is the distance between the first to fifth fingers; Intermediary toe-spread length (IT) is the distance between the second and fourth toes. PLF, TSF and ITF values were used for the AFI calculation on this formula.

Data from the first GT that was performed following a tendon injury was used to calculate the initial AFI result. The last AFI value was obtained from data the last GT that was applied at the end of the experiment. In healthy rats, the AFI value is expected to be close to zero. The negative increase in AFI value points out loss of function on the injured side.

Histopathological analysis

After the experiment was completed, all rats were sacrificed under the anesthesia (10 mg/kg xylazine and 90 mg/kg ketamine-hydrochloride) and the left Achilles tendons were fixed 10% formaldehyde solution and then embedded in paraffin blocks. Following this process, longitudinal serial sections were cut 5-6 micrometer thickness and stained with Hematoxylin-Eosin and then, evaluated based on modified the Curtis *et al.* (12) scoring. The degree of inflammation was scored based on the density of the lymphocyte cells: 0 – no, 1 mild, 2 – moderate, 3 – considerable. The fibroblastic activity was scored based on the density of the fibroblast cells: 0 – no, 1 slight, 2 – moderate, and 3 – considerable. The degree of neovascularization was graded as follows: 1 – slight if there were 0-5 capillaries, 2 – moderate if there were 5-10 capillaries, and 3 – considerable if there were more than 10 capillaries. The collagen fibers sequencing scored as: 0 if irregular, 1 if regular. The samples were scored as: 1 if there was calcification, or 0 if not. An experienced pathologist who was blind to the rat groups performed the histological evaluation. The tendon samples were examined under an (Olympus BX53, Olympus Corparation, Tokyo, Japan) binocular double-head light microscope.

Statistical assessment

Shapiro-Wilk test analysis was performed to determine whether quantitative variables conformed to a normal distribution. One-way analysis of variance was employed in independent groups for variables with normal distributions and the Kruskal Wallis test was used for variables with non-normal distributions. Dependent measures were comparisoned with the paired t test. In order to examine the main effect of time and groups and the effect of time × group interaction on weight (g), factorial ANOVA test was applied in repeated measures. When describing a variable that does not follow a normal distribution, descriptive statistics are expressed as the median (25^{th}-75^{th} percentile) and when describing a variable that follows a normal distribution, as the mean and standard deviation. Statistics were considered significant for values below 0.05 ($p < 0.05$).

RESULTS

The results of the rats weight

In the first week, there was no statistically significant difference amongst the weight measurement values of the groups ($p > 0.05$). However, there was a significantly difference between the 2^{nd} week weight measurement values of the control group and post-LC group ($p = 0.218$). The third week of the study's weight measurement findings revealed a significant difference amongst the control group and the pre-LC group ($p = 0.035$) and the post-LC group ($p = 0.011$), respectively. It was determined that the weight measurement results at the fourth week were significantly difference between the pre-LC group ($p = 0.045$) and the control group, higher significantly difference between the control group and the post-LC group ($p = 0.005$). As reported by the weight measurement results were performed in the fifth week, there was only significantly difference between the post-LC group and the control group ($p = 0.012$) (**table II**).

The results of GT

As comparison to the control group, the first AFI readings were considerably lower in the TIG, the pre-LC group, and the post-LC group ($p < 0.001$). The TIG and

Table II. Comparison of the experimental groups weights.

Groups	1st week	2nd week	3rd week	4th week	5th week
Control	494.70 ± 45.32	500.50 ± 48.32	505.20 ± 45.07	508.90 ± 43.98	518.20 ± 41.53
TIG	481.20 ± 43.68	475.50 ± 44.07	488.90 ± 43.93	486.80 ± 45.81	489.40 ± 51.31
Pre-LC	460.80 ± 22.01	469.70 ± 14.01	458.40 ± 29.17*[a]	463.70 ± 28.00*[a]	473.10 ± 34.33
Post-LC	450.10 ± 28.90	452.60 ± 27.47*[a]	450.80 ± 23.35*[a]	450.10 ± 25.33**[a]	459.80 ± 26.19**[a]

[a]Control group between significantly difference; $p < 0.05$; **$p < 0.001$

Table III. First AFI and final AFI values of experimental groups.

Groups	First AFI	Final AFI
Control	-6.59 ± 2.49	-6.50 ± 2.50
TIG	-23.99 ± 5.99***[a]	-9.89 ± 10.02**[a]
Pre-LC	-24.97 ± 7.41***[a]	-8.70 ± 1.72
Post-LC	-25.39 ± 7.75***[a]	-9.34 ± 1.81

[a]Control group between significantly difference; **$p = 0.002$; ***$p < 0.001$.

the control groups differed between them in a moderately significant way, according to the final AFI data ($p = 0.002$). The final AFI values did not significantly different amongst the control group, the pre-LC group, and the post-LC group ($p = 0.576$, $p = 0.111$). Between the control group and the TIG, the final AFI values showed a statistically significant difference ($p < 0.05$). AFI values within-group comparisons revealed statistically significant differences between the pre-LC and post-LC groups ($p = 0.006$ and $p = 0.033$, respectively). The first AFI values of the pre-LC and post-LC groups were considerably lower than the final AFI values. Both the control group ($p > 0.05$) and the TIG ($p = 0.501$) did not indicate a significant difference in the first-final AFI values intra-groups (**table I**).

The results of the histopathologic assessment

Significant variations in the histological parameters of inflammation ($p = 0.010$), neovascularization ($p = 0.005$), and fibrotic proliferation ($p = 0.005$) were determined amongst the groups in our investigation. The control group's inflammatory score was considerably lower than that of the TIG and post-LC group ($p < 0.05$). Both the pre-LC group and the post-LC group had significantly higher neovascularization scores than the control group ($p < 0.05$). In the TIG group compared to the post-LC group, the neovascularization score was considerably lower ($p < 0.05$). In the post-LC group compared to the TIG, the fibroblastic activity score was considerably greater ($p < 0.05$). Except for the TIG group, collagen fibril sequencing was regular in the control, pre-LC, and post-LC groups. The calcification was present in all the samples of pre-LC group and post-LC group (**figure 2**).

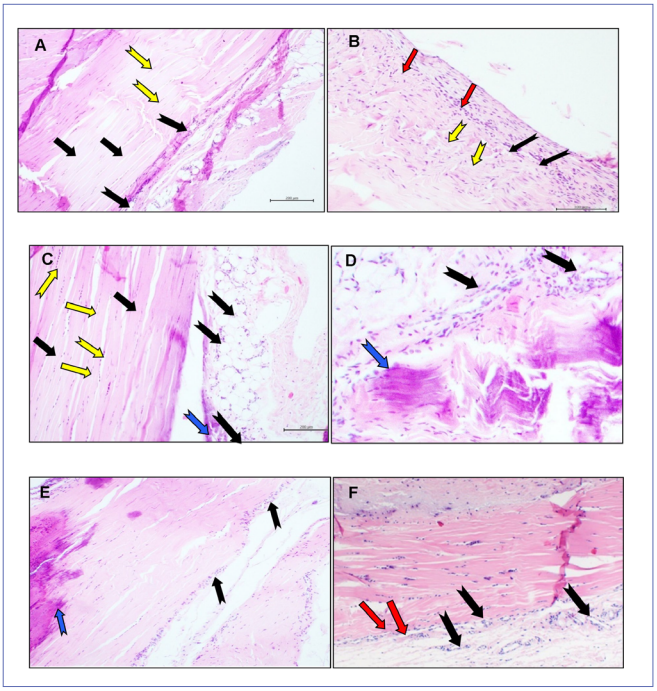

Figure 2. Histopathological appearances of studied groups: control group **(A)**; TIG **(B)**; pre-LC group **(C, D)**; post-LC group **(E, F)** (H&E, X200).

Lymphocytes (red arrow), fusiform-shaped inactive fibroblasts (yellow arrow), circular-shaped active fibroblasts (yellow-tailed arrow), neovascularization (black-tailed arrow), collagen fibers sequence (black arrow), calcification (blue-tailed arrow).

DISCUSSION

Because tendons have a limited ability to heal, there is a risk of re-injury and re-rupture, making tendon diseases a significant problem for physicians. For this reason, the researches on histologic and functional restoration of the tendon are important for patients and physicians. Inflammation, proliferation and remodelling stages of tendon healing process are similar to wound healing (3). So, there are many investigational studies about biomechanical and histological healing of the tendon using different nutraceuticals supplements, biomaterials, cellular therapies, bioprinting, gene therapy and anti-inflammatory agents (4, 14-16). Currently, there is still no commonly accepted treatment (agent-subtance) that will provide the best and fastest healing of the tendon damage.

As a cofactor, LC involved in medium and long-chain fatty acids to pass into the mitochondrial matrix. Also, studies demonstrated that LC is an antioxidant and anti-inflammatory aspects in tissues without any side effect (10, 11, 17-19). Since there are so little studies on the effects of LC tendon recovery, we aimed to research the effects of LC on an Achilles tendon injury model. It has been reported that the most effective dose of LC is 100 mg/kg/day (19-21). For this reason, LC was preferred to administer once daily at dose of 100 mg/kg intraperitoneally in our study. Considering that it is similar to Achilles tendinopathy, we preferred to create an inflammation by appling a crush ischemic injury model with a clamp. We determined the model with a preliminary work. The rats were weighed once per week during the experiment to research the impact of LC on body metabolism. The weight measurements of groups indicated no significant variation in the first week. This finding demonstrates the homogeneous distribution in the experimental groups. According to the 2nd week weight measurement results, a significant difference was found only between the control group and the post-LC group ($p = 0.218$). The post-LC group gained statistically less weight than the control group. In both the pre-LC group ($p = 0.035$) and post-LC group ($p = 0.011$), as compared to the control group, the mean weight results at the third and fourth weeks were shown to be statistically substantially lower. Only between the control group and the post-LC group did the mean weights at the fifth week differ statistically substantially ($p = 0.005$). In our opinion, this is because LC is effective in beta oxidation by facilitating the transfer of long chain fatty acids to the mitochondrial matrix (8). The lack of a statistically significant difference between the control group and the TIG shows that that tendon damage has no effect on weight gain of the rats. However, weight gain in the TIG was less than in the control group. We think that this might be due to the negative effect of pain due to tendon injury on the eating behavior of rats. Contrary to the results we obtained, there are studies providing that LC is not as effective as calorie restriction and exercise in weight loss in literature (22). The meta-analysis study examining the effect of carnitine on weight loss in adult humans ($n = 911$) revealed that the groups receiving LC had a significantly lower body mass index compared to the control group, and LC was effective in weight loss (23). Also, the results of a meta-analysis of 37 research including 2,292 participants revealed that LC supplementation significantly decreased body weight (24). The results of these two studies are consistent with agreement with our data. The findings of research investigating the effect of LC supplementation on weight gain due to fat oxidation are inconsistent. Therefore, more works are needed to clear up this issue.

Researches have revealed that functional and biomechanical healing of the tendon is parallel process (25). Functional evaluation of tendon healing is essential for determining whether the substance employed in treatment was effective. For this purpose in our study, GT was performed twice on all rats, after injury and at the end of the experiment. A single numerical value was obtained by using the GT data in the AFI equality. The AFI value approaching zero indicates functional recovery of the Achilles tendon. A more negative value of the AFI points out lack of function on the injured side. The first AFI values are lower than the last AFI in the TIG, pre-LC, post-LC groups, as expected after injury. The first AFI value was not significantly different amongst the TIG, the pre-LC and the post-LC groups ($p > 0.05$). According to this result, experimental tendon injury is proved by functional evaluation as well as histopathological assessment. The last AFI value was significantly different between the control group and the TIG, due to insufficient functional recovery in the TIG. The final AFI value was no significant difference between the control group and the pre-LC group and the post-LC group. When the subtraction of the first AFI and the last AFI values was compared, there was a significant difference only in the pre-LC and post-LC groups. According to these results, our study is the first to show that LC supplementation contributes to the functional recovery of the tendon. In addition, there is no statistically significant difference in the last AFI value between the pre-LC and post-LC groups, which indicates that the use of LC before tendon injury does not have a more positive effect on tendon healing.

Examined histopathological parameters were inflammation, neovascularization, fibroblastic activity, collagen fibril sequencing and calcification in our study. There was an inflammation in the etiology of acute tendon pathology (injury). Positive markers of tendon healing in the injury site are more fibroblastic activity, new formations of collagen fibril, new vascular structures (26).

Kuşcu *et al.* (27) investigated the effect of LC on experimental Achilles tendon repairment histopathologically. In this study, it was performed that control group was applied nothing, but after surgical repair of the Achilles tendon, the sham group was given to nothing, the serum physiologic (SF) group was given one week SF, and LC group was given intraperitoneally for one week. LC group rats were given 300 mg/kg/day intraperitoneally for one week. Ten rats in each group were sacrificed at the end of 6 weeks of the study. As a result of the histopathological examination, it was determined that there was no statistically significant difference between the groups in the parameters of inflammation ($p = 0.687$), neovascularization ($p = 0.409$), fibroblastic activity ($p = 0.389$). Contrary, significant differences were found between the groups in histopathological parameters of inflammation ($p = 0.010$), neovascularization ($p = 0.005$), and fibroblastic activity ($p = 0.005$) in our study. The reason of Kuşcu *et al.* (27) results may be the short-period of application of LC. However, they did not determine LC detrimental effect on tendon healing.

Yildiz and Turalıoğlu (20) researched histopathological effect of LC on Achilles tendon healing in postmenopausal period of rats. In that study, after tendon repaired, LC was administered in postmenopausal period rats and control group two different doses as 100 mg/kg at low dose and 200 mg/kg at high dose. According to the results of that study, a significant difference was found in fibrosis (marker of excessive fibroblastic activity) ($p = 0.44$) and neovascularization ($p = 0.26$), parametres between the healthy control group and the injured group after the administration of high and low doses of LC. But they stated that there is no significant difference between the groups administered low and high-dose LC and the optimal dose is 100 mg/kg. Any treatment that inflammation is reduced and induces fibroblast proliferation will accelerate tendon healing. In our study, although the inflammation score was lower in the pre-LC and post-LC groups compared to the TIG, there was no statistically significant difference ($p > 0.05$). This result indicates that LC dose or administration period does not sufficiently reduce inflammation. Besides, there was a statistically significant difference in fibroblastic activity and neovascularization parameters amongst TIG with pre-LC group and post-LC groups ($p < 0.05$) in our study. In addition, collagen fibrils sequence was regular in all tendon sections of the control, the pre-LC and the post-LC groups. According to these data, LC has a positive effect on the regular organization of the sequence of collagen fibers by increasing fibroblasts proliferation. Histopathological parameters were not statistically different between the pre-LC group and the post-LC group ($p > 0.05$). This result shows that LC has no prophylactic effect against tendon injury.

In addition, there was a calcification in all tendon samples except the control group. After tendon injuries, ossification and calcification, called mineralization, may occur in the tendon. Parallel to the formation of calcification after tendon injuries and tendon repair, calcification has also been detected especially during the healing process of rotator cuff tendonopathy (28, 29). This condition may have a negative effect on tendon healing. In our study, while we observed calcification foci in all preparations of the pre-LC and post-LC groups, we did not detect calcification foci in the preparations of the control group. This may be explained by the fact that the LC molecule activates mineralisation pathways in injured tissues. According to the results of our study, although LC has a positive effect on the functional healing of the tendon, it does not have a complete effect on histological healing. These results we have obtained will be guiding for future studies with larger sample sizes that will clarify this issue. There strictions of our investigation are the absence of evaluation of the short-term effect of LC, and rats are old and male.

CONCLUSIONS

In conclusion, the findings of our investigation demonstrated that LC was conducted functional and histological recovery of the injured tendon by affecting organization of the sequence of collagen fibers, fibroblastic activity and neovascularization parameters. Further studies of its effect about various time sequence, age and sex differences are needed to evaluate.

FUNDINGS

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DATA AVAILABILITY

Data are available under reasonable request to the corresponding author.

CONTRIBUTIONS

ZSK, BD: study design. ZSK, BD, HH, HB: data collection, data analysis and interpretation, writing – orginal draft. ZSK, BD: writing – review & editing.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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