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ORIGINAL ARTICLE

The fluoroquinolones may positively affect tendon healing after surgical repair

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ABSTRACT

Objectives: This study aimed to evaluate the biomechanical and histological effects of fluoroquinolones on surgically repaired tendon healing.

Materials and methods: The Achilles tendons of 40 Wistar rats (mean weight: 213.5 g; range 201 to 242 g) were bilaterally surgically cut and repaired. The rats were randomly divided into four groups: the first and third groups were designated as control groups and did not receive drug therapy, whereas the second and fourth groups received 300 mg/kg ciprofloxacin for a week after the surgical procedure. The first and second groups had both tendons dissected at the end of the first week, while the third and fourth groups were dissected at the end of the third week. The left tendons were examined biomechanically, while the right tendons were examined histologically.

Results: Statistical analysis revealed that the mean maximum tensile forces of tendons in the first and second groups were 5.2±1.84 N (range, 2.9 to 8.5 N) and 11.1±2.65 N (range, 7.3 to 13.9 N), respectively, which was found to be statistically significant ($p<0.05$). At the end of the third week, mean maximum tensile forces of the third and fourth groups were determined to be 20.7±5.0 N (range, 22.1 to 29.8 N) and 28.7±4.6 N (range, 22.1 to 36.8 N), respectively, which was also statistically significant ($p<0.05$). Histologically, our results were compatible.

Conclusion: This study demonstrated that ciprofloxacin did not exhibit the expected adverse effects on surgically repaired tendon healing in the early stages but likely contributed to healing in the short term by affecting the inflammatory phase.

Keywords: Early stages, flouroquinolones, tendon healing.

Fluoroquinolone group antibiotics are commonly used in urinary tract, respiratory system, gastrointestinal system, and musculoskeletal system infections due to their favorable pharmacokinetic properties, tissue penetration, and broad antibacterial spectrum.[1] Despite their popular use, fluoroquinolones are associated with a group of side effects, primarily in the musculoskeletal system.[2] Reports of fluoroquinolone-associated tendinopathy and adverse effects on tendons have been well documented.[3]

There are numerous studies in the literature attempting to explain the underlying mechanisms of fluoroquinolone tendon toxicity. Some implicated mechanisms include mononuclear cell infiltration, effects on cytokine release, imbalance in metalloproteinases, and direct toxic effects on fibroblasts and tenocytes.[4-10] Despite all these studies, the exact mechanism of tendon toxicity of fluoroquinolones has not been fully understood.

Most of the studies on the effects of fluoroquinolones on the musculoskeletal system

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in the literature have been conducted on healthy tendons or cell cultures. There are two studies on their effects on tendon to bone healing. Fox et al.[11] reported negative effects of fluoroquinolones in rat rotator cuff repair models. They pointed out that these may be due to the effects of flouroquinolones causing alteration in tendon microstructure and their enthesis leading to degeneration. Cancienne et al.[12] reported a higher revision surgery rate in patients receiving fluoroquinolone therapy after arthroscopic repair of rotator cuff lesions.

The primary aim of this study was to evaluate the effects of ciprofloxacin, a fluoroquinolone, on surgically repaired tendon healing in the early stages using a rat model. To our knowledge, this study is the first to demonstrate the effects of fluoroquinolones on surgically repaired tendon to tendon healing in the literature, aiming to provide insight into the potential effects of this antibiotic group on clinical use following tendon repair surgery.

MATERIALS AND METHODS

Forty Wistar rats aged three months (mean weight: 213.5 g; range 201 to 242 g) were evaluated in the study. The rats were obtained from Gazi University Laboratory Animals Breeding and Experimental Research Center. All rats were fed with standardized water and food. The Achilles tendons of all 40 rats were bilaterally surgically cut and repaired, and they were randomly divided into four groups, with 10 rats in each group (one rat from first week control and flouroquinolone group were excluded from the study because of wound site infection): *(i)* no drug use after surgery, evaluated at the first week; *(ii)* oral administration of 300 mg/kg/day ciprofloxacin for one week after surgery, evaluated at the first week; *(iii)* no drug use after surgery, evaluated at the third week; *(iv)* oral administration of 300 mg/kg/day ciprofloxacin for one week after surgery, evaluated at the third week.

Ciprofloxacin was preferred since it is one of the best-known and oldest fluoroquinolones.[3] The antibiotic was administered orally via gavage every 24 h. This dose was selected as it is the potential dose that triggers the effects of ciprofloxacin on the tendon.[5] Euthanasia was performed using ketamine at the end of the first week for the first and second groups of rats, while euthanasia was performed at the end of the third week for the third and fourth groups. Both tendons of the rats were dissected from the muscle-tendon junction to the insertion on the calcaneus, leaving the calcaneus intact. The left tendons were examined biomechanically, while the right tendons were examined histologically.

Surgical technique

Surgical procedures were performed under anesthesia obtained by intravenous administration of a mixture of ketamine hydrochloride (50 mg/mL) and benzethonium chloride. Both Achilles tendons were transected through a transverse incision at the midpoint. The tendons were primarily repaired with two simple surgical sutures using 6-0 Ethilon monofilament sutures (Ethicon Inc., Raritan, NJ, USA) in the same session. Layers were closed appropriately. Weight-bearing and cage activity were not restricted. All subjects were monitored for weight loss, lethargy, and infection until euthanasia was applied. Throughout the experiment, animals were fed the same food and water. One pair of tendons from each of the first and second groups was excluded from the study due to tendon wound infection.

Biomechanical evaluation

Biomechanical tests were conducted at the Advanced Materials Research Laboratory of the Faculty of Architecture and Engineering at Gazi University. During biomechanical testing, the method described by Probst et al.[13] was used for the fixation of tendon ends. The proximal ends of the tendons were clamped into the device clamps between sandpaper, while the distal ends were



FIGURE 1. Biomechanical evaluation.

placed into wooden molds with appropriate cavities prepared for the calcaneus surface and then placed into the clamps (Figure 1). Biomechanical evaluation of Achilles tendons was performed using a Shimatsu AG-I 5 kN tensile testing machine (Shimadzu Corporation, Tokyo, Japan). Tensile force was applied at a rate of 2 mm/min.

Histological evaluation

In histopathological examination, the left Achilles tendons of each group were cut at the proximal muscle-tendon junction and distally at the attachment site to the calcaneus. Samples were placed in 10% neutral formalin (72 h), followed by dehydration through a series of ascending alcohols (70%, 80%, 96%, and 100%) and xylene, then embedded in paraffin. Sections of 5 μm thickness were obtained from paraffin blocks. Sections were first deparaffinized in xylene, then passed through decreasing alcohol series (100%, 96%, 80%, and 70%). Subsequently, sections were stained with hematoxylin, washed, and counterstained with eosin. Stained sections were dehydrated, cleared in xylene, and coverslipped with mounting medium. Hematoxylin-eosin-stained sections were examined under a light microscope.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation (SD) and (min-max). Normality was assessed using the Shapiro-Wilk test. Wilcoxon test was used to compare the pre- and post-treatment data. The statistical significance level was set at $p<0.05$.

RESULTS

Biomechanically, maximum tensile forces of the calcaneal Achilles complex were measured in Newtons. Nine samples from the first and second groups and 10 samples from the third and fourth groups were tested. It was observed that the tendon separated from the healing zone in all samples.

Statistical analysis revealed that the mean maximum tensile forces of tendons in the group using ciprofloxacin at the end of the first week were 11.1±2.65 N (range, 7.3 to 13.9 N), while in the control group without ciprofloxacin, the mean maximum tensile force was determined to be 5.2±1.84 N (range, 2.9 to 8.5 N). The difference between the two groups was found to be statistically significant ($p<0.05$), indicating that ciprofloxacin positively affected tendon healing at the end of the first week (Table I).

In the biomechanical evaluation performed at the end of the third week, the mean maximum tensile force was determined to be 28.7±1.84 N (range, 22.1 to 36.8 N) in the group using ciprofloxacin and 20.7±5.0 N (range, 22.1 to 29.8 N) in the group not using ciprofloxacin. These results were statistically significant ($p<0.05$), indicating that ciprofloxacin positively affected tendon healing at the end of the third week (Table II). However, the significant difference observed in the first week decreased at the third week.

In the histological examination of the Achilles tendon of the first group, it was observed that the incision edges mostly closed, but there were areas where closure did not occur. In the region where the incision edges met, widespread inflammatory

TABLE I
Maximum tensile forces after the first week for the control and ciprofloxacin groups

Rat	Control (N)	Ciprofloxacin N	*p*
1	8.5	12.6	
2	3.2	13.2	
3	6.7	11.4	
4	6.2	12.9	
5	4.8	8.5	
6	6.0	13.2	
7	3.5	7.5	
8	2.9	13.9	
9	5.1	7.3	
Mean	5.2	11.1	<0.05

TABLE II
Maximum tensile forces after the third week for control and ciprofloxacin groups

Rat	Control (N)	Ciprofloxacin (N)	*p*
1	20.9	26.8	
2	23.4	29.5	
3	18.4	23.5	
4	18.1	22.1	
5	19.2	32.5	
6	29.8	30.3	
7	27.9	33.1	
8	15.4	36.8	
9	14.3	25.1	
10	20.3	27.9	
Mean	20.7	28.7	<0.05

cell infiltration and angiogenesis, indicators of wound healing, were observed. New collagen fiber formation along the incision was observed (Figure 2a). It is noteworthy that the incision edges of the second group, in which ciprofloxacin was used, were completely closed. Inflammatory cell infiltration and angiogenesis in the wound healing area were significantly increased compared to the control group. Moreover, an increase in collagen fiber formation belonging to the regular connective tissue structure of the tendon was observed in the wound healing area compared to the control group (Figure 2b).

In the histological examination of the third group, inflammatory cell clusters were observed in areas adjacent to the wound edges, while inflammation decreased throughout the tissue, giving way to granulation tissue in the healing process. Numerous capillaries and newly synthesized collagen fibers were observed in the granulation tissue. It was determined that the collagen fibers did not acquire the dense connective tissue character. The general structure was similar to the group treated with ciprofloxacin in the first week (Figure 2c).

It was observed that the wound area of the fourth group treated with ciprofloxacin completely adopted a normal tendon appearance. In this group, it was found that capillaries were dense. While collagen fibers showing a regular dense connective tissue structure and tenocytes between these fibers were clearly observed, it was found that the

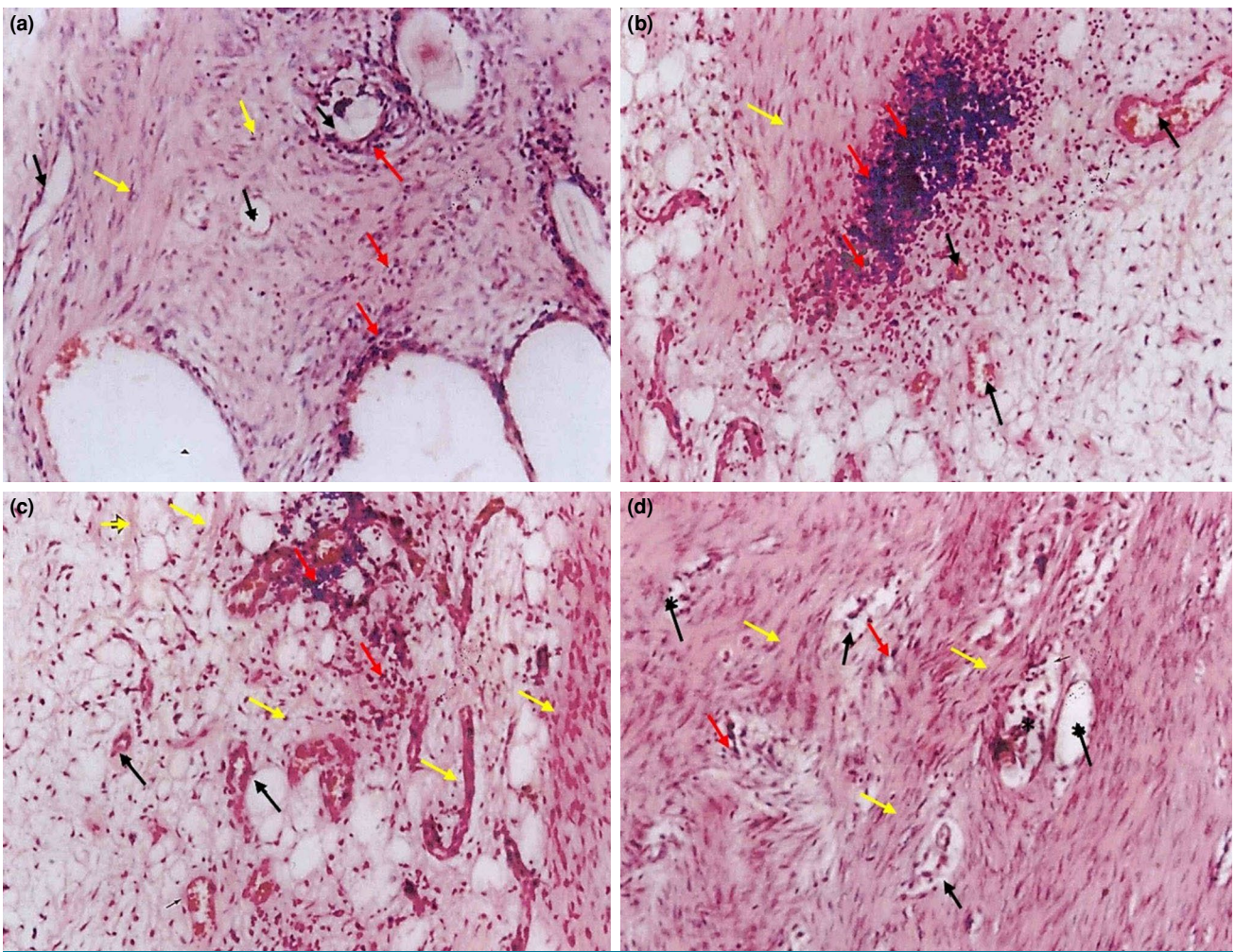


FIGURE 2. Achilles tendon sections (H-E, ×100). **(a)** Control (one week), **(b)** Ciprofloxacin (one week), **(c)** Control (three weeks), **(d)** Ciprofloxacin (three weeks).
Black arrow: Capillaries; Yellow arrow: Collagen fibers; Red arrow: Inflammatory cells.

capillaries were extremely dilated, and leukocytes infiltrated into the periphery of the capillaries in some areas (Figure 2d).

It was observed that ciprofloxacin application significantly increased inflammation compared to the control group, particularly in the normal wound healing process in the first week, while at the end of the third week, it ensured that the wound area had a normal morphology. In light of these findings, it is considered that ciprofloxacin accelerates wound healing in tendons, providing this effect by increasing inflammation and angiogenesis during the inflammatory phase of tendon healing.

DISCUSSION

In this study, the early biomechanical and histological effects of ciprofloxacin, a major fluoroquinolone antibiotic, on surgically repaired tendon healing were observed. The most important result of our study is that despite the known adverse effects of this group of antibiotics on tendons, they paradoxically contribute positively to surgically repaired tendon healing in the early stages, both biomechanically and histologically.[14]

Regarding the effects of fluoroquinolones on tendon healing after surgical repair, there is one experimental and one clinical study in the literature. Fox et al.[11] investigated the effects of fluoroquinolones on rats undergoing rotator cuff repair and reported that fluoroquinolones negatively affected healing biomechanically and histologically. Similarly, Cancienne et al.[12] reported that early use of fluoroquinolone antibiotics in patients undergoing rotator cuff repair increased the failure and revision surgery rate. These reported results contradict our findings. However, it is observed that both studies required healing at the tendon-bone junction. Leung et al.[15] demonstrated that tendon-tendon and bone-tendon healings have different biomechanical and histological characteristics. They noted that bone-tendon healing, which requires healing between two heterogeneous tissues, occurs later than tendon-to-tendon healing, and this delay may be due to the presence of a complex extracellular matrix in the bone-tendon junction. The different results in our study may be because healing occurs purely between two tendon ends.

Healing of tendons with compromised integrity is a complex process consisting of three stages without clear boundaries.[16-18] The inflammatory process lasts three to seven days and is characterized by the infiltration of red blood cells, leukocytes, important growth factors, and endothelial chemokines provided by platelets.[16,18] The second stage is the proliferation phase, managed by macrophages and tenocytes.[16,17] The third and final stage is the remodeling phase where type 1 collagen synthesis begins and the extracellular matrix is organized.[16,17] These stages are controlled by many growth factors and cytokines. Some cytokines observed to be active during tendon healing include interleukin (IL)-1 beta (β), IL-6, IL-10, tumor necrosis factor-alpha, and IL-4.[16-18] Growth factors such as platelet-derived growth factor, tissue growth factor (TGF)-β, insulin-like growth factor 1, vascular endothelial growth factor, and basic fibroblast growth factor are known to have effects at different stages of healing.[19] Enzymes called metalloproteinases, along with tissue inhibitors of metalloproteinases, are involved in regulating tendon healing.[16,17] Various studies have shown that enzymes, cytokines, and growth factors effective in tendon healing are affected by fluoroquinolones.[20] The expression of TGF-β is increased by fluoroquinolones, which plays a role in both the inflammatory and proliferation phases of tendon healing.[20,21] Increased release of TGF-β may positively affect healing.[19] The effect of fluoroquinolones on IL-1β, another cytokine that acts as an inflammatory cytokine, is controversial in the literature. While it is generally stated that IL-1β levels are adversely affected by fluoroquinolones, Fox et al.[11] reported that IL-1β was significantly upregulated by quinolones. In addition, the levels of IL-4, which acts as an anti-inflammatory cytokine in tendon healing, are reduced by fluoroquinolones.[16,22] Considering this information, the significant increase in inflammation detected in the group receiving fluoroquinolones in the histological evaluation may be associated with these changes in cytokines and growth factors. The paradoxical effect observed in this study, where surgically repaired tendon healing is positively affected by fluoroquinolones despite their toxic effects on healthy tendons, can also be explained by similar mechanisms.

It has been suggested that fluoroquinolones may exhibit tendinopathy side effects through nitric oxide (NO).[5] Nitric oxide is a free oxygen radical released from cells such as macrophages, vascular endothelial cells, hepatocytes, and chondrocytes. It has been shown to play a role in inflammatory reactions characterized by edema.[5] It has been suggested that fluoroquinolone-related tendinopathy is characterized by increased vascular permeability and edema, and this effect can be reversed by potent NO inhibitors,

indicating that increased NO may play a role in the mechanism of tendinopathy.[5] However, NO also contributes positively to the healing of tendons with compromised integrity. This paradoxical effect, as found in our study, where fluoroquinolones exhibit toxic effects on healthy tendons while enhancing tendon healing biomechanically and histologically, is consistent.[23-25]

Another important mechanism involved in tendon healing, which is affected by fluoroquinolones, is the balance between metalloproteinase enzymes and tissue inhibitors of matrix metalloproteinase (MMP) molecules. Matrix metalloproteinases exert a delicate effect on the ruptured tendon and subsequent repair.[26] One of the tendinopathy-inducing effects of fluoroquinolones is their impact on metalloproteinases. The effects of fluoroquinolones on MMPs vary. It has been reported that while fluoroquinolones increase MMP-1 and MMP-3 levels, they decrease the basal level and secretion of MMP-13.[9,10] Matrix metalloproteinase 13 is involved in the early stages of tendon healing, while MMP-3 is influential during the degradation and remodeling phase of healing.[27] Matrix metalloproteinases may induce degradation close to the sutures, making the tendon tissue around the suture weak in early stages.[28] Bedi et al.[29] showed that doxycycline-mediated inhibition of MMP-13 contributes positively to histological, biomechanical, and collagen organization aspects of repaired rotator cuff tendon healing. Considering that fluoroquinolones reduce MMP-13 levels, a similar mechanism may explain their positive impact on the early stages of tendon healing.

In this study, the possibility exists that simultaneously cutting two tendons in rats and subsequently not applying any functional restriction may have affected tendon healing. It is not possible to evaluate the impact of these effects on the study results. However, all Achilles tendons in the study healed under the same conditions. Notably, in the biomechanical evaluation of the repair site in rats not treated with fluoroquinolone, the resistance to tensile forces was found to be consistent with previous studies in the literature.[30,31]

Histological evaluation showed that fluoroquinolones caused intense inflammation in the healing area in the first week but allowed for a more organized healing scar by the third week. Although the biomechanical dsifference decreased with the control group at the third week, it was consistent with the histological image. Histological findings indicate an early and rapid healing process characterized by inflammation, increased angiogenesis, likely mediated through NO, and MMP regulation. Since fluoroquinolone treatment was discontinued after the first week, any adverse effects that could be observed in the second and third stages of tendon healing were not histologically apparent. Healing in the fluoroquinolone-treated group could have continued to progress advantageously.

There are some limitations to this study. The initial ciprofloxacin levels in the blood could not be measured. However, there were no other variables that could explain the differences observed in the results. Second, during this study conducted on rat tendons, there was no immobilization or controlled rehabilitation applied after surgery. In this case, the effect of loads on tendons during healing could not be ruled out. However, when treatment was applied in the same way in all groups, it was considered that the effects on the results could be disregarded. Third, the ratios of changing cytokines and growth factors during tendon healing and how they were affected by ciprofloxacin was not measured. A study that can evaluate these cytokines and growth factors may provide a broader perspective. Lastly, this study could be planned with a follow-up of over six weeks to evaluate the effects of quinolones on tendon healing in the later stages of healing.

In conclusion, this study demonstrated that ciprofloxacin, one of the basic fluoroquinolones, did not exhibit the expected adverse effects on surgically repaired tendon healing in the early stages but likely contributed to healing in the short term by providing a rapid start to healing in the inflammatory phase. If supported by clinical studies, the use of this widely practiced antibiotic group in infections that may develop after tendon injuries may be safe, contrary to popular belief. Further investigations are necessary to define the mechanisms by which fluoroquinolones improve surgically repaired tendon healing.

Ethics Committee Approval: The study protocol was approved by the Gazi University Experimental Animals Ethics Committee (date: 28.11.2005, no: 00.00/99-17097). The study was conducted in accordance with the principles of the Declaration of Helsinki.

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

Author Contributions: Conceptualization, design: T.D., E.S.; Supervision, critical review: T.D., E.S., A.M.O.; Data collection and processing: T.D., E.E., T.B., G.T.K.; Analysis: T.D., E.S., A.M.O., E.E., T.B., G.T.K.; Literature reviev: T.D., A.M.O., T.B.; Writing the article: T.D.; Materials: T.D., G.T.K., A.M.O.

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