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ORIGINAL ARTICLE

IMPACT OF CHRONIC USE OF FLUOXETINE HYDROCHLORIDE ON THE CALCANEAL TENDON

João Pedro Barros Estanislau[1], Pedro Magalhães Telles[1], Wagner Costa Rossi Junior[1], Petrus Pires Marques[2], Flávia Da Ré Guerra[1]

[1] Department of Anatomy Institute of Biomedical Science Federal University of Alfenas, UNIFAL-MG, Alfenas, Brazil
[2] School of Medicine José do Rosário Vellano University-Unifenas, Alfenas, Brazil

Corresponding author's e-mail: flavia.guerra@unifal-mg.edu.br

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ABSTRACT

Introduction: Fluoxetine hydrochloride, in addition to its antidepressant effects in the treatment of psychiatric disorders, appears to influence the process of ligament repair. This study investigated its effects on the calcaneal tendon.

Aim: The aim of this study was to evaluate the influence of chronic use of fluoxetine hydrochloride on the morphology of healthy calcaneal tendons, their glycosaminoglycan distribution, and the organization of collagen fibers in rats from different groups using microscopic analysis.

Methods: 25 male rats of the Wistar rats were divided into two groups, the control and fluoxetine-treated groups, and after 60 days, they were euthanized and the tendons were processed for microscopic analysis.

Results: The tendons of rats treated with fluoxetine showed greater thickening and greater disorganization of fibers and cells, as well as less collagen deposition, compared to the control group.

Conclusion: Chronic use of fluoxetine hydrochloride had a significant impact on tendons, weakening their structures and predisposing them to future injuries.

KEYWORDS

Collagen, glycosaminoglycans, Achilles tendon, calcaneal tendon, ligament, extracellular matrix, fluoxetine

INTRODUCTION

Psychiatric disorders are becoming increasingly common worldwide. Depressive disorders are highly prevalent throughout life, with Major Depressive Disorder (MDD) being the 11th leading cause of mortality and disability worldwide, according to the World Health Organization, affecting approximately 7% of the adult population in the USA[1-3]. The treatment of these chronic conditions is based on the individual's symptomatic remission, mostly achieved through the use of psychotropic drugs, such as serotonin reuptake inhibitors (SSRIs), the first line of choice[3-6].

Randomized clinical trials have demonstrated the efficacy of SSRIs in treating depression with a 95% confidence interval[2,7]. However, some authors consider

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that an analysis of the drug class may not yield a precise conclusion about one of them. Fluoxetine hydrochloride is an example of this class of drug and acts by binding to 5HT transporters, preventing them from reuptaking serotonin in the synaptic cleft and potentiating the effect of this neurotransmitter on neuronal signaling. Serotonin plays an extremely important role in the central nervous system and modulates mood, pain perception, neuroendocrine function, and sleep-wake cycle[7,8].

In addition, the mechanism of action of fluoxetine hydrochloride has been studied in functions other than the classic antidepressant, such as the treatment of neuropathic pain with an analgesic effect[9,10] and interference in the inflammatory process of biological tissue repair under chronic use[8,11,12]. The drug is believed to be able to reduce the levels of pro-inflammatory cytokines[13,14], prostaglandin-E2[15,16] and regulates immunological synapses, suppressing the activation of T-cells by reducing the ability of dendritic cells to present.

Fluoxetine is the most prescribed antidepressant in Brazil and worldwide because of its tolerability and safety[17]. However, it is necessary to understand more about its possible interference in the other factors mentioned above, such as the inflammatory process in biological tissues.

Previous *in vivo* and *in vitro* studies in the literature have observed that exposure to fluoxetine hydrochloride has important anti-inflammatory effects, in addition to inhibiting the production of nitric oxide and prostaglandin E2 in connective tissues such as bones and cartilage[13-15].

This study therefore focuses on the calcaneal tendon ("Achilles tendon"). The calcaneal tendon is common to the superficial gastrocnemius and soleus muscles, which form the triceps suralis muscle of the leg. They are found in the posterior compartment and are responsible for the highest plantar flexion force of the foot[18]. Thus, due to the muscular strength of the aforementioned muscles in maintaining the orthostatic posture and gait cycle, taking into account the body weight and the bone attachment to the foot, the limb responsible for receiving all the weight and supporting it, the calcaneal tendon is the thickest and most resistant tendon in the human body.

This tendon, like others, is under constant stress from traction, leading to a greater inflammatory response and difficulties in cellular metabolism during tissue repair[18]. Other studies carried out in rodents under chronic use of fluoxetine hydrochloride have shown an influence of the drug on this repair mechanism[19-21].

Studies about the epidemiology of Achilles tendon ruptures shows an increase in its incidence, with European data indicating a variation from 11 to 37 cases per 100,000 people. In the United States, Achilles tendon rupture is the most common acute tendon injury, accounting for 38.2% of cases recorded in emergency departments between 2001 and 2020. The injury predominantly affects men compared to women, with incidence rates ranging from 1.7:1 to 30:1. Ruptures typically occur in young, active adults, with an average age between 38.7 and 44 years. Risk factors such as sex, age, and systemic conditions are considered non-modifiable, while dysmetabolic diseases (such as diabetes mellitus, hypercholesterolemia, thyroid disorders, and obesity), continuous use of medications, and involvement in sports are modifiable risk factors that impair tendon health[22-24].

There are no studies observing the effects of chronic fluoxetine hydrochloride use in healthy animals without psychiatric disorders or stress protocols. The widespread prescription of this drug has attracted the attention of the scientific community, as it is essential to understand the effects of prolonged exposure to the drug on different tissues. Therefore, the objective of the present study was to evaluate the effects of the drug on the tendon tissue of normal animals.

MATERIALS AND METHODS

Ethics committee

The study followed the ARRIVE guidelines and was approved by the Ethics Committee for the Use of Animals (CEUA-UNIFAL) of the Federal University of Alfenas, filed under number 26/2019, on July 11, 2019 *(Appendix 1)*.

Samples

Twenty four male Wistar rats *(Rattus norvegicus)* age of 60 days, weighing on average 180 grams, from the vivarium of the Federal University of Alfenas (UNIFAL-MG), were housed in boxes containing three animals each, treated with commercial feed and water *ad libitum*, and kept on a 12-hour light-dark cycle.

Experimental groups

Animals were divided into two experimental groups (n = 12 control; n = 12 fluoxetine-treated).

1) Group 1: Control group; without medication treated with sterile saline solution;
2) Group 2: Animals treated with fluoxetine hydrochloride.

Treatment

The treatment consisted of administering 10 mg/kg/day of fluoxetine hydrochloride (Prozac), diluted in sterile saline solution and administered by orogastric gavage. The dose was chosen based on previous studies as it was considered safe and representative for animal models[14,16,17,22,24,25].

The treatment lasted for 60 consecutive days and was carried out daily at the same time.

Euthanasia and collection of the calcaneal tendon

Three weeks after surgery and treatment, animals were euthanized with a lethal dose of anesthetic (4% isoflurane by inhalation) to collect the calcaneal tendon. Animals showing visible signs of distress, injury or abnormal behavior were excluded from the experimentations.

Morphological analysis

Processing for structural analysis under light and polarizing microscopy

After dissection, the Achilles tendons were fixed in a 4% formalin solution in Millonig buffer pH 7.4 for 18 h at room temperature. The pieces were then washed in buffer, dehydrated in alcohol baths, followed by transparency with xylene baths, and embedded in paraffin (Histosec). Sections of 7 µm were prepared.

For an overall view of the tissue, some sections were stained with hematoxylin and eosin (HE). Toluidine Blue staining was used for the detection of proteoglycans (0.025% in McIlvaine buffer, pH 4.0). The slides were left to stain for 10 min, quickly washed in water, and air-dried. They were then briefly immersed in xylene and mounted on Canada balsam. Observations and documentation were performed using an Olympus BX 60 microscope equipped with a photographic camera

For polarization microscopy serial longitudinal sections (7 µm thickness) were deparaffinized, stained with Picrosirius, and analyzed under polarization microscopy using an Olympus BX 60 microscope equipped with a polarizer and analyzer. The sections, considering the major axis of the tendon, were positioned at 45° between the crossed polarizer and the analyzer.

RESULTS

Tendons stained with hematoxylin-eosin were used to obtain information about the organization of the tissue, both the extracellular matrix, and the cells present in the different regions of the tendon. Toluidine Blue and Picrosirius red were used to assess glycosaminoglycan and collagen organization, respectively.

General evaluation of the tendon

In the general evaluation of the calcaneal tendon using HE staining under light microscopy, three different regions of the tendon were analyzed: the compression region, tension region, and epitendon.

The tendons of the animals in group 2, treated with fluoxetine, showed some differences compared to group 1, the control. In the tension region, there was a greater number and disorganization of cells compared to group 1; there was thickening of the epitendon in group 2, which was accompanied by a large presence of blood vessels *(Fig. 1)*, and the presence of more rounded nuclei was noted in a greater number of fibroblasts.

Evaluation of glycosaminoglycans

Toluidine Blue staining, visualized under light microscopy, in the tension and compression regions of the calcaneal tendons, showed a greater amount of glycosaminoglycans in group 2 than in group 1, as evidenced by the marked metachromasia *(Fig. 2)*.

Evaluation of collagen organization

Polarization microscopy showed greater collagen organization in group 1, the control group, compared to group 2, treated with fluoxetine. In addition, there was greater compaction of the fibers in the control group and less in group 2, which also showed less type I collagen than the first group *(Fig. 3)*.

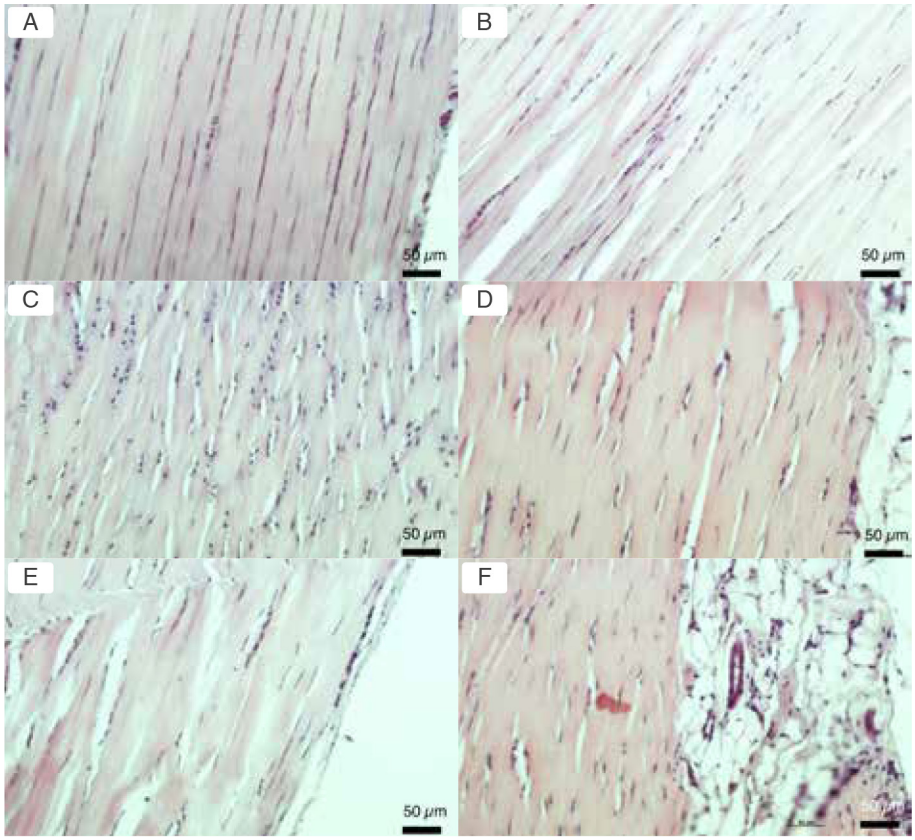


Figure 1. *Slides of calcaneal tendon stained with HE under light microscopy. Images A, C, and E (left column) are from the control group, with A: tension region; C: compression region and E: showing the epitendon. In B, D, and F (right column) are the images of the fluoxetine-treated group; B: tension region; D: compression region and F: epitendon.*

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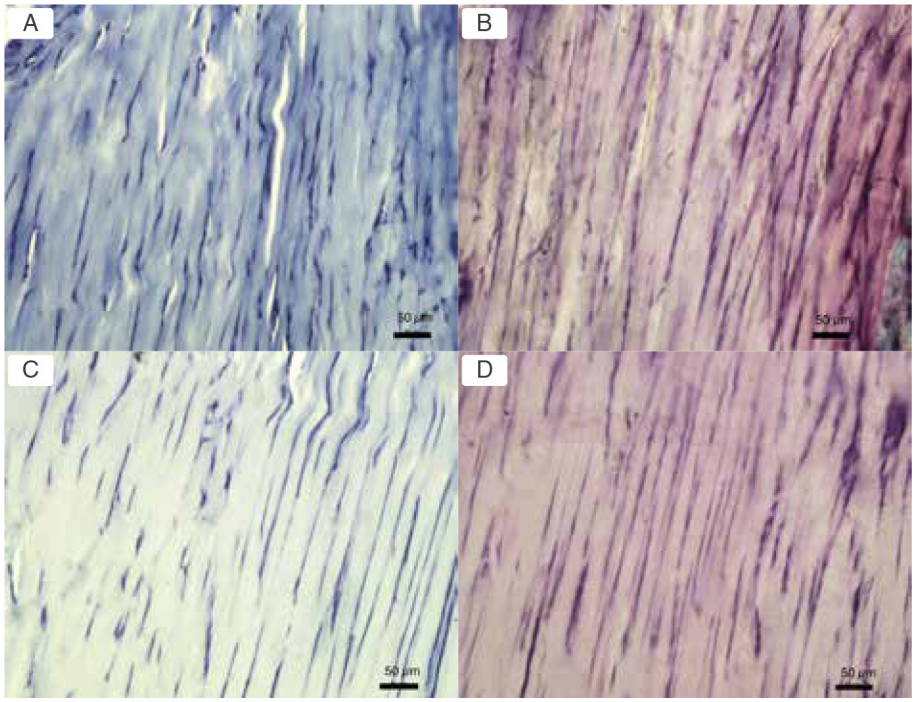


Figure 2. *Slides of calcaneal tendon stained with Toluidine Blue under light microscopy. Images A and C (left column) are of the control group, with A: tension region and C: compression region. In B and D (right column) are the images from the fluoxetine-treated group, B: tension region and D: compression region.*

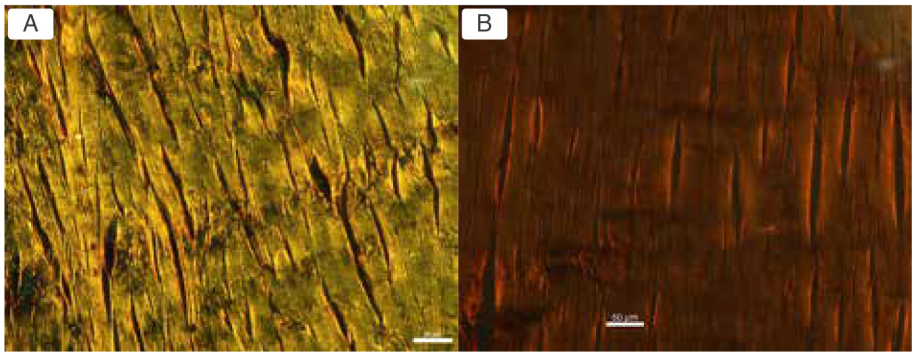


Figure 3. *Slides of the tension region of the calcaneal tendon stained with Picrosirius under polarizing microscopy. A: control group; B: fluoxetine-treated group.*

DISCUSSION

First, it is necessary to understand that tendons are dense and shaped formations of connective tissue. Connective tissue broadly establishes and maintains the shape of the human body, in association with bone and muscle tissue, and is composed of cells (fibroblasts are the most common), fibers (collagen, elastic, and reticular), and extracellular matrix (predominantly proteoglycans and glycosaminoglycans)[28]. In addition, tendons have a dense and shaped constitution, with whitish fibers due to the predominance of type I collagen and the cells, fibroblasts, are called tenocytes aligned in the specific direction of the traction they must support, by the contraction of the sarcomeres of the muscle ventricles to which they are associated, having a cord-like aspect[19,28,29].

In this study, we analyzed the effects of chronic treatment with fluoxetine on the morphology and composition of the calcaneal tendon in Wistar rats, which showed changes in tissue organization, glycosaminoglycan composition, and collagen fiber arrangement of the tendons treated with fluoxetine compared to the control, which may interfere with their resistance.

Fluoxetine hydrochloride, in a study using a different chronic treatment methodology, has been reported as a beneficial agent for remodelling the collagen fibers of tendons previously subjected to a stress and injury protocol, leading to an increase in the density of the extracellular matrix, greater thickness, and organization of collagen[30]. SSRIs, such as fluoxetine, maintain this neurotransmitter in the synaptic clefts to attenuate depressive effects. There are indications that inflammatory cytokines are related to depression and the renewal of injured tendons due to the inhibitory properties of pro-inflammatory cytokines such as interleukins (IL-6, IL-1β, and tumor necrosis factor alpha (TNF-α)[30]. However, these results differ from those found in a normal calcaneal tendon, where this positive action was not observed, and the impact of fluoxetine hydrochloride was shown to weaken healthy tissue.

In this regard, there are studies in the literature demonstrating the negative effects of psychological stress on rodent and human tissues that are undergoing a healing process, reducing their capacity for renewal, and the positive action of antidepressants, especially fluoxetine hydrochloride, occurs in these cases[31-33]. In this study, the rats were not subjected to a stress protocol, and chronic

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administration of fluoxetine showed no positive effects on the structure of healthy tendons, an important result suggestive of a side effect of the drug.

Histological evaluation using hematoxylin-eosin (HE) *(Fig. 1)* showed more obvious cell disorganization in the fluoxetine-treated group, especially in the tension region. This region corresponds to the middle portion of the tendon, and is most frequently involved in rupture and tendinopathies. Tendon strength is directly linked to the organization of its cells and collagen fibers[34], and the presence of more rounded nuclei found in these cells denotes greater activity in the manufacture of the extracellular matrix, which was not expected for the tension region. Thus, the chronic influence of the drug on the tissue suggests a change to a less resistant tendon.

The epitendon is a thin layer of connective tissue that covers the tendon, facilitates its nutrition, vascularization, and innervation, and acts as an interface between the tendon and adjacent tissues. It is composed of type III and I collagen fibers, the latter being responsible for the strength of the tissue. Its extracellular matrix, which is rich in proteoglycans, contributes to flexibility and elasticity. This region showed increased vascularization, which is indicative of greater metabolic activity, suggesting a tissue reaction to fluoxetine hydrochloride. This regenerative response causes thickening of the fibers[34]. In addition, the compression region, the portion closest to the insertion of the calcaneus bone, which is compressed against it during dorsiflexion of the foot, which therefore needs strong resistance to maintain walking, has thicker and more disorganized fibers. Thickening and disorganization mark a decrease in the tendon resistance.

Toluidine blue staining *(Fig. 2)* showed a greater amount of glycosaminoglycans in the compression region. The presence of this component in the compression region, together with the organization of collagen fibers, allows it to withstand constant compression with the calcaneus bone during joint movement, which is an important factor for its integrity. In addition, the amount of glycosaminoglycans was also higher in the tendon tension region of the fluoxetine-treated group, which was not expected for a normal tendon that has a predominance of cells and collagen in relation to the matrix. The increase in the component in the tension region shows intense remodeling of the tissue with the use of the drug[34].

Finally, in the polarization microscopy analysis *(Fig. 3)*, the orange color of the control group indicated great organization and compaction of the collagen and extracellular matrix, while the yellow-green color of the treated group indicated less organization and quantity of collagen in the tissue. Thus, in addition to the fibers having been altered in a more disorganized way, they have fewer type 1 collagen fibers, which is further evidence of a negative impact on the tendon in group 2 after chronic use of fluoxetine hydrochloride. Thus, fluoxetine hydrochloride proved to have an important influence on the normal tendon, stressing it and setting in motion a process of remodelling, which resulted in greater metabolic activity of the tenocytes, a decrease in collagen and its organization, an increase in glycosaminoglycans in the tension region, and a decrease in them in the compression region, characterizing the morphology of weakening of the calcaneal tendon, making it more susceptible to injury. This is particularly relevant given that fluoxetine is widely prescribed for the treatment of depression and other psychiatric disorders[7,8], and is used by patients with no history of tendon injury.

The scientific literature lacks similar studies carried out on healthy rats, though there are studies that have used injured tendons and have shown beneficial potential for tendon healing[20,30,31]. These differences may indicate a possible dual effect of fluoxetine hydrochloride, harming healthy tendons but helping compromised tendons.

This study revealed significant tissue changes resulting from chronic fluoxetine hydrochloride use. We consider it extremely important that future studies be conducted in greater depth, given that this is a widely prescribed drug today. Observing biomechanical changes in tissue resistance, as well as the drug's interaction with different components of the tissue's extracellular matrix, will further our understanding of the drug's interaction with tendons.

CONCLUSION

This study showed that chronic use of fluoxetine hydrochloride has a negative impact on the structure of the calcaneal tendon of rodents that have not been subjected to injury. Although previous studies have indicated that the drug can promote tissue remodelling of the tendon under injury conditions, our results show that in the absence of this factor, fluoxetine does not satisfactorily improve the organization or quantity of collagen fibers.

Chronic treatment with fluoxetine hydrochloride led to important changes in the tendon constitution. There was an increase in the cellular metabolism of tenocytes, with an increase in their proliferation, changes in the extracellular matrix of glycosaminoglycans, with an increase in them in the tension region and a decrease in them in the compression region, disorganization, and a reduction in the total density of type I collagen fibers. These structural changes compromise the biomechanical resistance of the tendon, making it more susceptible to injury and future ruptures.

In addition, the majority of patients who chronically take fluoxetine do not have previous tendon injuries, nor do they use the drug for this purpose. This study is therefore important as the results suggest a possible side effect of the medication, which should be investigated further. Therefore, it is essential to warn health professionals and patients about the potential risks of prolonged use of fluoxetine hydrochloride to maintain the integrity of normal tendons.

Limitations of the present study include the fact that only

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structural parameters were evaluated, without direct assessment of tendon biomechanical strength. Future studies should explore the long-term biomechanical consequences of chronic fluoxetine administration, including tensile strength and resistance to rupture, in order to correlate histological alterations with functional outcomes. In addition, further investigations at the molecular level could clarify how fluoxetine interacts with extracellular matrix proteins, such as collagen and metalloproteinases, and whether these effects are dose-dependent or reversible after drug discontinuation. Translational studies involving human tendon samples or clinical cohorts would also be valuable to confirm the relevance of these findings in clinical practice.

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