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Impact of Fluoroquinolones on Tendon Health: A Comprehensive Overview for the General Population and Athletes

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ABSTRACT

Introduction: Fluoroquinolones are a class of broad-spectrum antibiotics widely used to treat various bacterial infections. Despite their effectiveness, increasing evidence links fluoroquinolones to tendinopathy and tendon rupture, with cases occurring shortly after initiation or even months post-therapy. This review provides a comprehensive overview of the impact of fluoroquinolones on tendon health - highlighting the underlying pathomechanisms, clinical manifestations, and epidemiology of fluoroquinolone-associated tendinopathy.

Purpose of the work: The purpose of this study is to review the effects of fluoroquinolones on tendon health in the general population. Special attention is given to the athletes, who are particularly vulnerable to tendon injuries.

Materials and methods: A comprehensive analysis of research articles available on PubMed, Google Scholar, Web of Science, Embase, and Scopus was conducted using search terms related to: "fluoroquinolones," "tendinopathy," "tendon rupture," "athletes" and "connective tissue damage."

Results: Fluoroquinolones are linked to an increased risk of tendinopathy and tendon rupture, particularly among those with certain risk factors, including athletes. Understanding the mechanisms by which fluoroquinolones affect tendon tissue and recognizing early signs of tendon damage can help mitigate these risks. Prevention strategies, including cautious prescribing fluoroquinolones and targeted rehabilitation programmes, may reduce the adverse effects of fluoroquinolone usage, particularly in high-risk groups like athletes.

Keywords: fluoroquinolones; adverse effects; tendinitis; tendon rupture; tendinopathy

INTRODUCTION

Fluoroquinolones (FQs) are chemotherapeutic agents that, since their introduction in the 1990s, have become some of the most frequently prescribed antibiotics due to their exceptional pharmacokinetic (PK) and pharmacodynamic (PD) profiles, broad-spectrum antibacterial activity, and favorable tolerance [1]. Fluoroquinolones act by inhibiting bacterial nucleic acid synthesis through the disruption of the enzymes topoisomerase IV and DNA gyrase, and by inducing breakage of bacterial chromosomes. However, similar to other antibacterial agents, bacteria have developed resistance to quinolones due to their overuse [2]. Among the most commonly used fluoroquinolones are: ciprofloxacin, delafloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin [3].

Quinolones have been divided into generations based on their spectrum of antibacterial activity, pharmacokinetics, and clinical applications. Each generation has a distinct range of activity against different types of bacteria, with generations generally having broader spectra and improved efficacy against resistant strains. This broad group of antibiotics is divided into four generations: the first generation consists of quinolones, the second and third generations are fluoroquinolones, and the fourth generation includes naphthyridonequinolones [4].

First generation (quinolones)	Second generation (fluoroquinolones)	Third generation (fluoroquinolones)	Fourth generation (naphthyridonequinolones)
● Nalidixic acid	● Enoxacin ● Norfloxacin ● Ciprofloxacin ● Ofloxacin ● Lomefloxacin	● Sparfloxacin ● Grepafloxacin ● Clinafloxacin ● Gatifloxacin	● Moxifloxacin ● Gemifloxacin ● Trovafloxacin ● Garenoxacin

Table 1. Four generations of quinolone antibiotics - examples [2].

Among all antibiotics from this group ciprofloxacin is regarded as a critical drug for clinicians in the treatment of infections in elite athletes [8]. It has demonstrated particular

efficacy in managing the common issue of "traveler's diarrhea" in athletes competing internationally [5,6].

Our work aims to present the pathomechanism of tendon disorders in patients on fluoroquinolones, along with the clinical manifestations, epidemiological data, diagnostic and therapeutic approaches in this context.

ADVERSE EFFECTS

Compared to other classes of antimicrobials, FQs are associated with a higher incidence of adverse effects (AEs) involving the central nervous system (including headache, dizziness, confusion, seizures, depression, and insomnia) and gastrointestinal system (including nausea, vomiting, abdominal discomfort and pain, anorexia and, in some cases, diarrhea). They are also linked with potential cardiovascular disturbances (QTc prolongation and arrhythmias) and tendon disorders (tendinitis, tendon rupture, particularly involving the Achilles tendon), as well as joint disorders (arthralgia). Fluoroquinolones have a high affinity for connective tissues, especially in cartilage and bone. Animal studies have demonstrated that these antibiotics can cause damage to developing weight-bearing joints, making them contraindicated for use in children. [3,5]

Other, less common adverse effects include phototoxicity, acute kidney failure, aortic aneurysm (AA) and dissection (AD), allergic reactions, dysglycemia, CYP450 inhibition, hepatotoxicity, hematologic and immunologic effects, genotoxic effects, and retinal detachment [1,2,3].

The risk of acute tendinopathy or tendon rupture is 2 to 4 times higher with the use of fluoroquinolones [7,8]. Risk factors for the development of these adverse events include patients who are engaged in sporting activities or are very physically active [5,9,10], with diabetes mellitus [5,9,10], rheumatic disease [5,9,10], gout [10,11], hyperparathyroidism [5,9,10], advanced age [7], corticosteroid use [7], obesity [12], pre-existing conditions (e.g., autoimmune connective tissue diseases, renal failure [12]), and co-therapy with two drugs known to induce toxic tendinopathy [12].

PATHOMECHANISM OF FLUOROQUINOLONE-INDUCED TENDON INJURY

The primary function of tendons is to transmit mechanical forces from muscle to bone. These are poorly vascularized tissues that connect muscles to osseous structures [13,14]. Tendon strength against mechanical forces is predominantly provided by collagen, which constitutes the primary structural component of tendons [13,14,15]. Maintaining a balance

between collagen synthesis and degradation is crucial for proper tendon tissue remodeling and repair, particularly post-injury [13,14,15].

Collagen production in tendons is mediated by tenocytes, specialized cells located within the tendon extracellular matrix (ECM). This process culminates in the formation of collagen fibrils, fibers, and bundles [13,17]. The activities of tenocytes, including collagen synthesis and cellular proliferation, are counterbalanced by degenerative processes regulated by matrix metalloproteinases. These enzymes play an essential role in collagen degradation in response to tissue inflammation and injury [13,16]. Fluoroquinolones enhance matrix metalloproteinase activity, leading to an increased breakdown of the extracellular matrix [13].

A reduction in collagen production, as well as pathological changes such as increase in vascularity and alterations in ground substance, are observed in tendinopathy [11,18]. These changes result from modifications in cell function and ground substance composition [11,18,19]. At the biochemical level, these alterations include increased glycosaminoglycan (GAG) production [11,19]. Elevated GAG production results in enlarged water content within the tendon, potentially leading to increased tendon thickness [11].

Fluoroquinolones are believed to disrupt tendon function and elevate the risk of injury, particularly in weight-bearing joints subjected to mechanical stress. This is hypothesized to occur through multiple proposed mechanisms [13,20].

Fluoroquinolones have the potential to induce direct tissue damage, which may manifest as necrosis or apoptosis, depending on the exposure level [18]. Impaired integrin function and associated pathways, such as the MAP kinase pathway, have been linked to various deleterious outcomes, including cellular apoptosis and the generation of harmful free radicals [13,21,22]. Fluoroquinolones, recognized as chelators of cations, can deplete divalent ions such as magnesium, which are essential for proper integrin receptor signaling [13,20,21]. Additionally, FQ-induced tendon damage may be influenced by oxidative stress, mitochondrial toxicity [8,11] and epigenetic modifications [11,23]. Delayed or residual mitochondrial toxicity (e.g., mitochondrial dysfunction and depletion) may account for the occurrence of adverse effects on tendons [8,11].

SYMPTOMS OF FLUOROQUINOLONE-RELATED TENDINOPATHY AND TENDON RUPTURE

Acute pain is the most common symptom of fluoroquinolone-associated tendinopathy. Tendon pathology can result in pain during tendon loading [3,24]. Pain may be accompanied

by inflammatory symptoms such as: swelling, tenderness, erythema, or itching in tendon areas, and functional disability of tendons [5,25].

The Achilles tendon is most frequently affected by fluoroquinolone-induced tendinopathy, due to its weight-bearing role [5, 26]. The calcaneal (Achilles) tendon is involved in 90% of human cases, with nearly half of these cases presenting with bilateral involvement. Degenerative changes are predominantly localized within the tendon mid-substance rather than at the entheses. The rupture occurs in approximately 40% of cases, often within just two weeks of symptom onset [12]. Achilles tendon rupture prevails in half of the cases without warning [5, 9], though it may be preceded by pain [5].

Adverse effects have also been reported in various other tendons, including the peroneus brevis, patellar tendon, rectus femoris, supraspinatus, subscapularis, triceps brachii, adductor longus, finger and thumb flexor tendons, and tendons of the hip [5].

The mean time to symptom onset following FQ use has been reported as two weeks from the initial dose, though reports range from two hours to several months. Clinical imaging can provide deeper insights into the structural impact on tendons [11].

DIAGNOSTICS OF FLUOROQUINOLONE-ASSOCIATED TOXIC TENDINOPATHY AND TENDON RUPTURE

Fluoroquinolone-associated toxic tendinopathy results in both macroscopic and microscopic changes in the tendon. The development of these changes is typically not accompanied by inflammation or tendinitis but rather by microscopic changes associated with chronic degeneration, termed “tendinosis” [12].

Macroscopically affected tendons may appear rough, irregularly thickened, and discolored (typically tan or brown). Microscopically, degeneration is characterized by fibril disorganization, distortion, occasional apoptosis of tenoblasts and tenocytes, and changes in the extracellular matrix composition (detectable with special histologic stains), along with neovascularization [12,27]. In chronic cases, tendons may also exhibit fibrocartilaginous metaplasia and/or mineralization, particularly near entheses, where these lesions are referred to as “enthesopathy.” While these are common end-stage changes not specific to any particular etiology, spontaneous tendinosis observed in older individuals is generally modest—featuring tan or brown discoloration macroscopically, with minimal tendinosis and cartilage metaplasia microscopically—compared to the more severe tendon degeneration induced by toxicants [12].

Ultrasound and magnetic resonance imaging (MRI) are valuable tools for the clinical assessment of patients. Both modalities are sensitive and specific for aiding in the diagnosis of tendinopathy or rupture [5,28].

RISK FACTORS FOR THE DEVELOPMENT OF FLUOROQUINOLONE-RELATED TENDINOPATHY

Risk factors that exacerbate fluoroquinolone-related tendinopathy are presented in Table 2 [5,9].

Risk Factors That Exacerbate Fluoroquinolone-Related Tendinopathy
● sporting or very physically active patient [5,9,10] ● diabetes mellitus [5,9,10] ● rheumatic disease [5,9,10] ● gout [5,9] ● hyperparathyroidism [5,9,10] ● hypothyroidism [10] ● advanced age [7,10] ● systemic corticosteroid use [7,10] ● obesity [12] ● preexisting disease (e.g., autoimmune diseases of connective tissues, Crohn disease [10], ulcerative colitis [10], renal failure [12] ● cotherapy with two drugs that are known to induce toxic tendinopathy [12] ● magnesium deficiency [10] ● trauma (tendon or joint) [10] ● history of organ transplantation [10] ● hemodialysis [10]

Table 2. Risk Factors That Exacerbate Fluoroquinolone-Related Tendinopathy [5,9]

Recent case reports of fluoroquinolone-associated tendinopathy frequently involve athletes or individuals engaged in high levels of physical activity. The principal pathological stimulus for tendinopathy in these cases is the tendon response to loading during vigorous sport [1, 5, 29]. The extracellular matrix (ECM) of tendons can be adversely altered by matrix metalloproteinases, whose activity may be increased by intense physical exertion [13,30].

Additionally, metabolic factors, such as elevated levels of adiposity, are associated with an increased risk of tendinopathy [8,31].

Fluoroquinolones are known to enhance matrix metalloproteinase activity, while glucocorticoids have been shown to increase collagenase activity, both leading to greater degradation of the extracellular matrix. Conversely, platelet-derived growth factor (PDGF), delivered by neovessels, promotes the differentiation of tenoblasts into tenocytes, resulting in local overproduction of collagen. This unregulated collagen accumulation alters the ECM composition, favoring an increase in type III collagen and disrupting normal tendon structure and function [12].

EPIDEMIOLOGICAL DATA OF TENDON DISORDERS ASSOCIATED WITH FLUOROQUINOLONES

Tendon toxicity induced by fluoroquinolone antibiotics often develops as an acute event—sometimes within days or even following a single dose—with an estimated incidence of 0.14 to 0.4% [32,33,34] to as high as 2% [12]. The average age of individuals with fluoroquinolone (FQ)-associated tendinopathy is 64 years, with a male-to-female ratio of 2:1, and bilateral involvement in 27% of cases [32,26]. The estimated rate of Achilles tendon rupture associated with FQs is 2.7 per 10,000 patients for ofloxacin and 0.9 per 10,000 patients for ciprofloxacin [32,35].

Ciprofloxacin is identified as the most frequently implicated FQ, being responsible for 90% of tendon disorders associated with this drug class, with the risk of tendinopathy appearing independent of dosage [9,32]. In a cohort of 98 patients, pefloxacin was identified as the primary cause of fluoroquinolone-associated tendinopathy in 37% of cases, followed by ciprofloxacin, which accounted for 25.5% of cases [32,36]. Tendon disorders have also been linked to other fluoroquinolones, such as norfloxacin, ofloxacin, and levofloxacin [32,37,38].

In rodent models, fluoroquinolones featuring a methylpiperadinyl substituent at the seventh position of the chemical structure (e.g., ofloxacin, levofloxacin) have been associated with a higher incidence of tendon lesions. In contrast, fluoroquinolones with a piperadinyl substituent (e.g., norfloxacin, ciprofloxacin) have shown minimal to no toxicity. However, the exact contribution of these structural variations to tendon injury remains unclear [13].

IMPLICATIONS FOR ATHLETES AND PREVENTION STRATEGIES FOR FLUOROQUINOLONE-RELATED TENDON DISORDERS

The majority of patients (90%) with fluoroquinolone-associated tendinopathy are managed conservatively, with recovery typically taking a median of one month. However, long-term sequelae such as difficulty walking, decreased range of motion, and persistent pain can occur in up to 10% of patients. Prompt discontinuation of the fluoroquinolone, coupled with supportive measures such as analgesia and physiotherapy, is recommended for managing FQ-related tendinopathy [7].

Patients with fluoroquinolone-related tendinopathy are recommended to undergo a specialized rehabilitation approach. Rehabilitation should be conducted in two phases: the first phase involves bracing and support to allow the tendon to recover from the chemical injury caused by the fluoroquinolone, followed by a second phase of progressive loading [5,39].

In approximately 90% of active or athletic individuals with tendinopathy, eccentric exercise has been found to be effective, though its success is less expressed in more sedentary populations. While tendon loading through eccentric exercise may be suitable for treating tendinopathy in athletes, it may not be the most appropriate approach for managing fluoroquinolone-induced tendon conditions, especially in the early stages of symptom onset [5,40,41].

Vitamin E has shown potential in protecting human fibroblast cells from damage caused by ciprofloxacin, likely due to its ability to prevent free-radical damage in biological membranes. However, it remains uncertain whether this protective effect can be applied as a therapeutic strategy against the harmful effects of fluoroquinolones in patients [5,42].

Prevention of tendon Disorders Associated with Fluoroquinolone Use in the General Population and Athletes		
The category of preventive measures	**General Population [5, 43]**	**Athletes [10]**
Avoidance	Avoid the use of fluoroquinolones unless no alternative is available. Identify higher-risk individuals.	Avoid the use of fluoroquinolones unless no alternative is available.

Corticosteroid Use	Avoid concomitant corticosteroid administration.	Oral or injectable corticosteroids should not be used concomitantly with fluoroquinolones.
Physical Activity	Limit high-intensity physical activity during antibiotic courses.	Athletes, coaches, and training staff should understand the potential risk for developing this complication.
Symptom Management	Discontinue use of the fluoroquinolone if symptoms develop	Close monitoring of the athlete should be undertaken for 1 month after fluoroquinolone use.
Injury Prevention	Protect the symptomatic area to limit further injury.	-
Return to Activity	Initiate a graduated return to physical activities based on symptoms	-
Further Evaluation	Initiate further diagnostic evaluation and treatment as clinically indicated.	-

Table 3. Prevention of Tendon Disorders Associated with Fluoroquinolone Use in the General Population and Athletes [5,10,43].

When fluoroquinolones are required, patients should be informed about the potential adverse effects on the musculoskeletal system. This knowledge is essential for the early identification, prompt evaluation, and proper treatment of any symptoms that may occur [10].

CONCLUSION AND SUMMARY

Fluoroquinolones, introduced in the 1990s, are widely prescribed antibiotics due to their broad-spectrum activity [1]. Despite their efficacy, these antibiotics are associated with a range of adverse effects, particularly affecting the muscular, central nervous, gastrointestinal, and cardiovascular systems [3,5]. Among the more serious risks is tendon damage, especially tendinopathy and tendon rupture, with the Achilles tendon being most commonly affected. Athletes, older adults, and those on corticosteroids are at greater risk, with the likelihood of tendon injury being 2 to 4 times higher in fluoroquinolone users [7,8].

The mechanisms behind tendon injury are believed to involve disruptions in collagen synthesis, increased oxidative stress, and cytotoxic effects on tendon cells, which weaken tendon structure and function [13,20]. Prevention strategies, including cautious prescribing and rehabilitation programs, can help reduce these risks, particularly in high-risk groups such as athletes.

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