Musculoskeletal Medicine

Musculoskeletal Complications of Fluoroquinolones: Guidelines and Precautions for Usage in the Athletic Population

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Fluoroquinolone antibiotics are associated with a wide spectrum of musculoskeletal complications that involve not only tendon but also cartilage, bone, and muscle. Insights into the pathoetiology of fluoroquinolone toxicity on musculoskeletal tissues have been evolving over recent years. Although the pathoetiology is certainly multifactorial, alterations in cell signaling proteins and direct toxic effects on musculoskeletal tissues have been strongly implicated. Increasing age and concomitant systemic corticosteroid use appear to significantly increase the risk of adverse events. The purpose of this article is to review the musculoskeletal complications associated with use of fluoroquinolone antibiotics by adults; identify risk factors associated with fluoroquinolone toxicity; explore the possible pathoetiology of fluoroquinolone toxicity on tendon, cartilage, bone, and muscle; and offer recommendations regarding evaluation and treatment of fluoroquinolone-associated musculoskeletal complications. In addition, this review will provide recommendations regarding fluoroquinolone use in athletes and return to play after fluoroquinolone exposure.

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INTRODUCTION

Fluoroquinolone antibiotics are commonly used to treat a variety of infections, including urinary tract, respiratory tract, gastrointestinal tract, skin, bone, and joint infections [1,2]. First introduced in the 1980s to treat gram-negative bacterial infections [3], the popularity of fluoroquinolone antibiotics has increased because of their broad antimicrobial spectrum, multiple approved indications, and favorable pharmacokinetics [4,5]. In fact, between 1995 and 2002, fluoroquinolone prescribing tripled, making fluoroquinolones the class of antibiotics most commonly prescribed to adults in the United States [6]. Despite their popularity, a number of adverse effects have been attributed to fluoroquinolones, including adverse effects on musculoskeletal tissues. Fluoroquinolone-associated tendinopathy, which was first reported in the literature in 1983 [7], is a widely recognized complication of fluoroquinolone use that eventually led the U.S. Food and Drug Administration to add a black box warning label to all fluoroquinolones in 2008, citing increased risk of tendinitis and tendon rupture [8]. Fluoroquinolones exert a toxic effect not only on tendons but also on cartilage, bone, and muscle (Table 1). Knowledge of the full spectrum of the negative effects of fluoroquinolone antibiotics on the musculoskeletal system is currently evolving, and much of the mechanistic nature of the toxicity has not yet been fully elucidated.

The purpose of this article is to review the musculoskeletal complications associated with fluoroquinolone antibiotics in adults; identify risk factors associated with fluoroquinolone toxicity; explore the possible pathoetiology of fluoroquinolone toxicity on tendon, cartilage, bone, and muscle; and offer recommendations regarding evaluation and treatment of fluoroquinolone-associated musculoskeletal complications. In addition, this review will provide recommendations regarding fluoroquinolone use in athletes and return to play after fluoroquinolone exposure. The use of fluoroquinolone antibiotics in children continues to be highly debated in the literature and is beyond the scope of this review.

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Table 1. *Clinical musculoskeletal conditions associated with fluoroquinolones*

Area Affected	Conditions
Tendon	Tendinitis, tendinosis, tendon rupture
Cartilage/bone	Arthralgia, impaired fracture healing, cartilage lesions
Muscle	Myalgia, rhabdomyolysis

Tendon: Basic Science

Fluoroquinolone antibiotics (Table 2) are a synthetic derivative of the parent compound nalidixic acid and exert their bactericidal effects via inhibition of bacterial deoxyribonucleic acid (DNA) gyrase and topoisomerase IV [1,9,10]. The quinolone nucleus consists of a bi-cyclic ring structure with 8 positions whose constituent groups determine drug potency, pharmacokinetics, and activity against gram-positive organisms, as well as influence adverse effect profiles and drug interactions [5]. Fluoroquinolone antibiotics possess a fluorine atom at position 6, which explains in part the name of this class of antibiotics [5].

While the association between fluoroquinolones and tendon disorders has become increasingly more recognized and more widely studied, the exact pathoetiology has remained elusive. On histologic examination, findings in fluoroquinolone-associated tendon disorders are similar to those seen in overuse injuries in athletes (ie, abnormal fiber structure, hypercellularity, fibrotic areas, increased extracellular matrix [glycosaminoglycans], and neovascularization) [11]; however, the fluoroquinolone-associated changes are thought to occur much more rapidly than those seen in non–fluoroquinolone-related tendinopathy. Results of studies have been conflicting regarding the presence of inflammatory mediators [12]. Sonographic analysis of fluoroquinolone-associated tendon disorders demonstrate typical findings of tendinopathy (ie, thickening and hypoechogenicity) [13]. The processes that lead to these changes appear to be multifactorial.

Williams et al [14] were the first to show that fluoroquinolones (ciprofloxacin) have a direct effect on fibroblast metabolism. Canine Achilles tendon, paratenon, and shoulder capsule specimens were exposed to ciprofloxacin at various concentrations (physiological and supraphysiological). Increased matrix-degrading activity, decreased matrix synthesis, and decreased cell proliferation were seen in all 3 populations of fibroblasts at physiological drug concentrations. The researchers suggested that an acute increase in matrix-degrading activity with a concomitant decrease in cell proliferation and collagen synthesis could lead to tendon rupture, with a disproportionate effect on tendons that have a limited capacity for repair or that have been previously structurally compromised.

Fluoroquinolones are known to chelate divalent and trivalent cations (Ca^{2+}, Mg^{2+}, Zn^{2+}, and Al^{3+}). Magnesium and other cations are known to participate in the regulation of integrins. Integrins are transmembrane proteins that are involved in the structural stability of the cell (eg, attaching cells to the extracellular matrix as well as other cells) and also function in bidirectional signaling across the plasma membrane [15,16]. They are thought to play an important role in maintaining the integrity of various musculoskeletal tissues. Shakibaei et al [17] demonstrated a reduction in collagen type I, elastin, fibronectin, and β1 integrin in the Achilles tendons of juvenile dogs after treatment with ciprofloxacin. This study showed similar biochemical changes in tendon samples from dogs fed a magnesium-deficient diet for 6 weeks, which strengthens the hypothesis that fluoroquinolone toxicity could be related to chelation of magnesium. Sendzik et al [18] found that both ciprofloxacin and levofloxacin negatively affected the Map-kinase signaling pathway (which is important for cell differentiation and survival), likely via the fluoroquinolone's effect on integrin function secondary to complexing of divalent cations. Sendzik et al [18] also found that fluoroquinolones increased activated caspase-3, a marker of apoptosis, with confirmatory apoptotic changes on electron microscopy. The induction of apoptosis was thought to be a result of changes in the cell-signaling pathways induced by the fluoroquinolones.

Matrix metalloproteinases (MMPs) are a group of enzymes that participate in tendon remodeling [12]. Differences exist in MMP expression between normal and degenerative human tendons, which suggests that MMPs may play a role in tendinopathy development [19]. MMP-3 expression and activity is increased in tendons exposed to high mechanical demands (eg, Achilles, supraspinatus) possibly related to the remodeling that is necessary after repetitive microtrauma [12]. Corps et al [12] demonstrated that ciprofloxacin increased MMP-3 expression (both messenger ribonucleic acid [mRNA] and protein) and increased MMP-1 mRNA in human tendon-derived fibroblasts. Both levofloxacin and cip-

Table 2. *U.S. Food and Drug Administration approved fluoroquinolones*

Generic	Trade Name
First generation	
Nalidixic acid*	NegGram* (Sanofi-Aventis, Bridgewater, NJ)
Second generation	
Ciprofloxacin	Cipro (Bayer Pharmaceuticals, Germany)
Norfloxacin	Noroxin (Merck, Whitehouse Station, NJ)
Ofloxacin	Floxin (Ortho-McNeil, Titusville, NJ)
Third generation	
Levofloxacin	Levaquin (Ortho-McNeil, Titusville, NJ)
Moxifloxacin	Avelox (Bayer Pharmaceuticals, Germany)
Fourth generation	
Gemifloxacin	Factive (Cornerstone Therapeutics, Cary, NC)

*Nonfluorinated (ie, quinolone).

rofloxacin were found to increase MMP-1 and MMP-13 in cultured human tenocytes [18]. Interestingly, these same 2 MMPs are thought to be involved in tissue degeneration in rheumatoid arthritis [20].

Reactive oxygen species (ROS) are involved in a multitude of cellular processes. They are known to have a direct toxic effect on cells and cellular components, are important messenger molecules in the induction of several genes, and act as second messengers in inflammatory processes [21]. They appear to exert a biphasic effect on cells, with lower doses increasing proliferation and higher doses leading to cell death by apoptosis or necrosis [1]. Results of studies also have shown a causal relationship between intracellular ROS and induction of MMPs [21]. Pouzaud et al [21] investigated the involvement of oxidative stress in fluoroquinolone-associated tendon toxicity by using a spontaneously immortalized rabbit tendon cell line. The researchers were able to demonstrate moderate cytotoxicity 24 hours after fluoroquinolone exposure and more severe toxicity 72 hours after exposure with 4 different fluoroquinolones (pefloxacin, ofloxacin, levofloxacin, and ciprofloxacin). All fluoroquinolones were found to stimulate ROS production, which implicates oxidative stress in tendon toxicity. The researchers believed that ROS likely contributed to tendon toxicity both through direct toxic effects mediated by ROS themselves and indirect effects through the induction of MMPs.

Further evidence supporting the role of oxidative stress in fluoroquinolone-associated tendon disorders comes from studies that show protective effects of antioxidants [21-24]. Vitamin E protects human fibroblast cells [1], rat cartilage [25], astrocytes [24], and hepatic and cerebral tissue [23] from fluoroquinolone toxicity. More recently, the antioxidant ubiquinone (coenzyme Q10) demonstrated protective effects on human Achilles tendon cells exposed to ciprofloxacin and moxifloxacin [22]. A mitochondrial-targeted form of ubiquinone (MitoQ) demonstrated a larger protective effect than did untargeted ubiquinone. Oxidative stress frequently occurs in the mitochondria [22], and fluoroquinolone-induced oxidative damage to mitochondria in tenocytes and chondrocytes has been reported [26].

In summary, fluoroquinolones appear to exert their negative effects on tendons through a variety of mechanisms. Contributions from direct toxic effects are likely, possibly through induction of ROS and increased matrix breakdown through stimulation of MMPs. Changes in signaling protein function (likely related to the chelation of divalent cations, specifically Mg^{2+}), with subsequent alteration of cell regulation and repair, also have been implicated. Results of studies indicate that these effects may occur rapidly after fluoroquinolone exposure, which is consistent with the epidemiologic data. These mechanisms appear to lead to a mismatch in cell breakdown and repair that can lead to the clinical symptoms of tendonitis and/or tendon rupture. Preliminary data suggest that antioxidant strategies such as vitamin E or coenzyme Q10 supplementation may be beneficial, but further research is warranted.

Tendon: Clinical Manifestations

The first cases of fluoroquinolone-associated tendinopathy were reported in 1983 and involved 2 male patients who had undergone renal transplantation and were treated with norfloxacin [7]. Achilles tendinopathy developed in one patient, whereas the second patient presented with bilateral upper extremity third finger flexor tendinopathy, along with right ankle and hip pain. Fluoroquinolone-associated tendon rupture was initially reported in 1991 [27]. Subsequent to these initial reports, multiple cases of fluoroquinolone-associated tendinopathy have been published. Among reported cases, the Achilles tendon is most commonly involved [3,4,7,11,13,27-58]. However, multiple other tendons and tendon groups have been involved, including the common extensor tendon origin of the lateral elbow [59], subscapularis [55], biceps brachii [41], brachioradialis [40], adductor longus [60], plantar foot tendons [61], rectus femoris [62], flexor hallucis longus [63], supraspinatus, extensor pollicis longus, quadriceps, and patellar [3], and the tendons of the extraocular muscles [64]. Fluoroquinolone-associated tendinopathy symptoms have occurred as early as 2 hours after the initial fluoroquinolone exposure and as late as 6 months after the medication was discontinued [46].

The first epidemiologic study to demonstrate an increased risk for tendon disorders associated with fluoroquinolones was performed by van der Linden et al [65] in 1999. Through use of a primary care database from the Netherlands and a retrospective cohort design, tendinitis and/or tendon rupture was compared among users of fluoroquinolones and 4 other antibiotics that have no known association with tendon disorders. The risk window included the treatment duration plus 1 month. Twenty-two cases were identified via a 2-step process of case finding and case validation (none were ruptures). Potential cases were identified by searching both diagnostic codes and key words in the medical record (eg, tendinitis, tendon disorder, and tendon rupture). Charts were then reviewed by 2 general practitioners who were blinded to any patient exposure to the antibiotics of interest. Patients were excluded if they had a history of tendon disorder before antibiotic exposure, if another cause of tendinitis was likely (eg, trauma), or if the diagnosis was not that of tendon disorder (eg, bursitis). The mean age of fluoroquinolone users was 53 years, whereas the mean age of the reference group was 45 years. The adjusted relative risk of tendinitis to fluoroquinolones was 3.7 (95% confidence interval [CI], 0.9-15.1) for Achilles tendinitis and 1.3 (95% CI, 0.4-4.7) for other types of tendinitis. The risk difference between fluoroquinolones and the reference antibiotics was 4 cases per 100,000 days. Concomitant corticosteroid use was

low (4.6% for the fluoroquinolone group and 4.2% for the reference group) and not related to the presence of tendon disorder in this study.

In 2001, van der Linden et al [4] published a case series of 42 patients from the Netherlands in whom fluoroquinolone-associated tendon disorders had developed; 76% experienced tendinitis and 24% had a tendon rupture. The median patient age was 68 years (range, 18-91 years), with 71% of fluoroquinolone-associated tendinopathies occurring in patients older than 60 years. Men outnumbered women 3 to 1. Ninety percent of cases involved the Achilles tendon, and in more than half the tendons were affected bilaterally. Other affected tendons included the patellar tendon, common flexor, and extensor tendon origins at the elbow and the rotator cuff. The most commonly reported symptom was pain. Although most patients reported recovery within 2 months of discontinuing the fluoroquinolone antibiotic, 26% still reported pain and disability at follow-up (the time frame was not specified). Symptoms typically occurred within 1 week of exposure to fluoroquinolones (median, 6 days; range, 1-510 days). The vast majority (93%) reported symptoms within 1 month. The average fluoroquinolone-exposure duration was 2 weeks (range, 2-81 days). In 50% of the patients actively involved in sporting activities, the tendon disorder occurred during participation in sports. Twenty-four percent of patients were concomitantly taking oral corticosteroids. The frequency of tendon disorder among fluoroquinolone users was 4 per 100,000 prescriptions. The researchers believed that this figure represented substantial underreporting in light of data from the French spontaneous reporting system that estimated a frequency of 20 cases per 100,000 prescriptions [66] and previous prescription-event monitoring that showed a frequency rate of 2.4 per 10,000 patients for tendinitis and 1.2 per 10,000 patients for tendon rupture [67].

The same group published a case-control study in 2002 [53] that used a large United Kingdom general practice database to study the association of fluoroquinolones and Achilles tendon disorders. All patients 18 years and older who had received fluoroquinolones were identified, and those with a history of Achilles tendon disorder, cancer, AIDS, illicit drug use, or alcohol misuse were excluded. Tendon disorders associated with direct trauma also were excluded. A random sample of 10,000 patients who had not been exposed to fluoroquinolone antibiotics served as a control group. The researchers divided fluoroquinolone exposure into current use (within 30 days), recent use (30-90 days), past use (more than 90 days), and no use. The cohort consisted of 46,776 patients exposed to fluoroquinolones between July 1992 and June 1998. The adjusted relative risk of Achilles tendon disorders with current fluoroquinolone use was 1.9 (95% CI, 1.3-2.6), whereas the relative risk for subjects with recent and past use was similar to the control group. The relative risk with current use was 3.2 (95% CI, 2.1-4.9) for patients 60 years and older, and it was 0.9 (95% CI, 0.5-1.6) for persons younger than 60 years. Concurrent use of corticosteroids in persons older than 60 years increased the risk to 6.2 (95% CI, 3.0-12.8).

Another population-based case-control study from the United Kingdom that examined the specific association between fluoroquinolones and Achilles tendon rupture identified 1367 cases of Achilles tendon rupture and randomly selected 50,000 control subjects from the database [68]. Exposure was defined as current (within 30 days), recent (30-180 days), and past (6-18 months). More than 69% of total cases of Achilles tendon rupture were men with a mean age of 48 years. The adjusted odds ratio for Achilles tendon rupture with current fluoroquinolone use was 4.3 (95% CI, 2.4-7.8). Recent use increased the risk to 2.4 (95% CI, 1.5-3.7), and past exposure increased it to 1.4 (95% CI, 0.9-2.1). Although gender differences were not observed, patient age proved to be significant. No cases of Achilles tendon rupture occurred in patients younger than 60 years who were currently exposed to fluoroquinolones, but an adjusted odds ratio of 6.4 (95% CI, 3.0-13.7) for patients aged 60-79 years with current exposure and an adjusted odds ratio of 20.4 (95% CI, 4.6-90.1) in patients aged 80 years and older with current fluoroquinolone exposure was seen. When patients older than 60 years were further analyzed, the risk of Achilles tendon rupture was found to be dose dependent but was not affected by duration of treatment. Concomitant use of oral corticosteroids significantly increased the risk of tendon rupture. The odds ratio of Achilles tendon disorder in those not using corticosteroids was 5.3 (95% CI, 1.8-15.2), whereas current corticosteroid use increased the odds ratio to 17.5 (95% CI, 5-60.9), and recent corticosteroid use raised it to 18.4 (95% CI, 1.4-240.2).

A large population-based case-control study published by Corrao et al [37] from Lombardia, Italy, in 2006 investigated the association between fluoroquinolones and the risk of tendon disorder. Through the use of the national health services databases from the years 2002 and 2003, 22,194 cases and 104,906 control subjects were selected. Inclusion criteria included patients 18 years or older whose hospital discharge diagnosis was tendon disorder, including synovitis and tenosynovitis, and nontraumatic rupture of the tendon. The researchers did not specify whether "hospitalization" indicated that the patient was hospitalized for the condition or if it referred to the diagnosis of tendon disorder by a physician. If it referred to the former, then this study may have a selection bias toward patients with more severe tendon disorders. Exclusion criteria included a concomitant diagnosis of cancer, diabetes mellitus, thyroid disease, renal failure, AIDS, gout, rheumatoid arthritis, polymyalgia rheumatica, traumatic tendon injury, history of tendon disorders, or other disease of the musculoskeletal system or connective tissue. Up to 5 matched control subjects were randomly selected from the regional archive for each case. Exposure to

fluoroquinolones was categorized into current use (exposure within 15 days of hospitalization for tendon disorder), recent use (15-30 days), past use (30-90 days), and nonuse (>90 days or no exposure in 1 year preceding hospitalization). Of the case patients, 14,993 were hospitalized for tendinitis and 7201 for nontraumatic tendon rupture, 840 cases of which involved the Achilles tendon. More than 63% were women, and the mean age was 55.9 years. Current use of fluoroquinolones was found to increase the risk of tendon disorder (odds ratio 1.7 [95% CI, 1.4-2]), tendon rupture (odds ratio 1.3 [95% CI, 1.0-1.8]), and, specifically, Achilles tendon rupture (odds ratio 4.1 [95% CI, 1.8-9.6]). Concomitant use of fluoroquinolones and corticosteroids further increased the risk of both tendon rupture (odds ratio 3.1 [95% CI, 1.5-6.3]) and rupture of the Achilles tendon (odds ratio 43.2 [95% CI, 5.5-341.1]). The odds ratio for rupture of the Achilles tendon was significantly higher in patients older than 60 years, whereas the increased risk of tendinitis and tendon rupture in general was similar across all ages. Regarding rupture of the Achilles tendon, the authors estimated that 1 case would occur per every 5958 patients treated with fluoroquinolones (95% CI, 2148-23,085). When stratified by age, 1 Achilles tendon rupture per 1638 fluoroquinolone-treated patients older than 60 years could be expected (95% CI, 351-8843), and with concomitant corticosteroid use, 1 in 979 patients would be expected to have Achilles tendon rupture (95% CI, 122-9172).

A Danish population-based cohort study that investigated the use of fluoroquinolones and risk of Achilles tendon rupture was recently published by Sode et al [34]. They studied 28,262 first-time users of fluoroquinolones during the period 1991-1999. All cases of Achilles tendon rupture were identified, and the incidence rates among users and nonusers of fluoroquinolones were calculated. The risk of Achilles tendon rupture within 90 days of exposure to fluoroquinolones compared with the general population was 3.1 times higher (95% CI, 1.0-7.3). This risk of Achilles tendon rupture was 2.5 (95% CI, 0.5-7.4) times higher in patients younger than 60 years and 4 times higher (95% CI, 0.5-14.4) in persons older than 60 years. The absolute increase in risk was 12 cases of Achilles tendon rupture per 100,000 persons within 90 days of treatment with a fluoroquinolone (95% CI, 0.0-35.6). The researchers concluded that, although the relative risk of Achilles tendon rupture was increased 3-fold, the absolute risk was low.

The current literature shows a strong association between fluoroquinolone exposure and subsequent development of tendon disorders, including rupture. It appears that increasing age and concomitant corticosteroid exposure further increase this risk. Gender has not been reliably identified as a risk factor. Other conditions (Table 3) have been reported commonly in patients with fluoroquinolone-associated tendon disorders [4,46,68,69], but specific risk associated with these factors has not been formally studied.

Table 3. *Potential risk factors*

Increasing age
Systemic corticosteroid use
Participation in a sport
Magnesium deficiency
Trauma (tendon or joint)
History of organ transplantation
End-stage kidney disease
Hemodialysis
Osteoarthritis
Rheumatoid arthritis
Psoriatic arthritis
Systemic lupus erythematosus
Ankylosing spondylitis
Reiter syndrome
Polymyalgia rheumatica
Ulcerative colitis
Crohn disease
Diabetes mellitus
Hyperparathyroidism
Hypothyroidism

Cartilage/Bone: Basic Science

Concerns regarding the chondrotoxic nature of fluoroquinolones began with studies that showed irreversible cartilage damage in growing animals [70,71], which led to the ongoing debate in the pediatric literature regarding the use of fluoroquinolones in the pediatric population. However, a recent study that used a lamb model failed to show significant effects on proximal tibial growth velocity after exposure to gatifloxacin or ciprofloxacin, and no chondrotoxic changes were found on subsequent histologic evaluation [72].

Several researchers who have examined the effects of fluoroquinolones on adult human cartilage in vitro have demonstrated inhibition of cell proliferation of chondrocytes [70], along with development of necrotic chondrocytes with abundant accumulation of glycogen and hypervacuolization [71,73]. Several possible mechanisms have been suggested for the toxic effects of fluoroquinolones on cartilage, including a deficiency of functionally available magnesium, inhibition of mitochondrial dehydrogenase and proteoglycan synthesis, altered DNA metabolism (through inhibition of DNA polymerase), tissue accumulation of fluoride, and increased ROS production in chondrocytes [71]. Results of studies have shown that magnesium-deficient diets are capable of producing cartilage changes similar to that caused by fluoroquinolone exposure in both canines and rats [74], and dietary magnesium supplementation was able to reduce the histologic changes in rats exposed to fluoroquinolones [75]. As in tendons, these changes were probably secondary to altered cell-matrix interaction through magnesium's effect on integrin functions, as well as possible increased production of ROS associated with magnesium deficiency, as seen in fluoroquinolone-treated rabbits [74].

To further examine the relationship between magnesium and fluoroquinolone-associated cartilage disorders, horse

and canine chondrocytes were exposed to ciprofloxacin and enrofloxacin in the absence and presence of varying doses of magnesium [75]. As expected, the total number of chondrocytes decreased in the fluoroquinolone-treated groups, with a dose-dependent decrement in the loss of chondrocytes in the magnesium-supplemented groups. Furthermore, magnesium supplementation had positive effects on cell adhesion and morphology. Cell proliferation likewise decreased in the fluoroquinolone-exposed groups and was not responsive to magnesium supplementation, which brings into question other pathoetiologies regarding decreased cell proliferation in fluoroquinolone-exposed chondrocytes. The researchers postulated that ROS or other divalent cations, such as calcium, magnesium, and zinc, whose role in fluoroquinolone toxicity have not been investigated, may have been responsible for the decrease in cell proliferation.

Pfister et al [25] studied the effects of oral vitamin E (tocopherol) and magnesium supplementation on ciprofloxacin-associated chondrotoxicity. Juvenile rats were divided into 4 groups: those fed a normal diet, a vitamin E–enriched diet, a magnesium-enriched diet, or a diet enriched with both vitamin E and magnesium. These diets were initiated 10 days before the rats were given ciprofloxacin. Two days after fluoroquinolone exposure, cartilage samples from the knee joints were histologically examined, and cartilage and plasma concentrations of magnesium, calcium, and vitamin E were measured. Fluoroquinolone-associated cartilage changes were observed in all groups, but the supplemented groups showed significantly less change, with the magnesium and vitamin E combination group demonstrating the least change. Both plasma and cartilage concentrations of magnesium and tocopherol were significantly higher in the supplemented groups than in the animals that received the normal diet, which supports the potential role of magnesium deficiency in the pathogenesis of fluoroquinolone-associated chondrotoxicity.

The inhibitory effect of fluoroquinolones on osteoblastic cells in vitro was investigated by Holtom et al [2] from the University of Southern California. MC3T3-E1 murine calvaria-derived osteoblastic cells were exposed to ciprofloxacin, levofloxacin, and trovafloxacin, and osteoblast cell growth and extracellular matrix mineralization were then measured. All 3 fluoroquinolones inhibited cell growth and mineralization in a dose-dependent manner. Readily achievable serum levels of trovafloxacin were found to inhibit osteoblast proliferation and mineralization. Ciprofloxacin toxicity occurred at concentrations slightly higher than those typically seen with therapeutic dosing, whereas levofloxacin toxicity required concentrations that were moderately higher than therapeutic levels. However, theoretically, local fluoroquinolone administration could cause local tissue (eg, bone) concentrations that are higher than those achieved with systemic administration, which may effect bone healing. Therefore the researchers concluded that caution should be exercised when considering the local use of fluoroquinolone antibiotics in a region where bone healing is taking place.

Mayo Clinic researchers studied the effect of ciprofloxacin on experimental fracture healing in rats [76]. The study was designed to simulate the effect of systemic exposure to ciprofloxacin (such as treatment of a urinary tract infection) in the setting of a healing fracture. The treatment group received ciprofloxacin for 3 weeks, beginning 7 days after production of closed, nondisplaced, bilateral femoral fractures. Concentrations of ciprofloxacin were similar to standard therapeutic concentrations. Radiographic healing was decreased compared with control subjects that had no fluoroquinolone exposure at 4 weeks. Torsional strength and stiffness were decreased by 16% and 49%, respectively. Fracture callus in the treatment group showed abnormal cartilage morphology and endochondral bone formation as well as a significant decrease in chondrocyte number compared with control subjects. The researchers concluded that ciprofloxacin's negative effect on chondrocytes led to inefficient conversion of cartilage to bone and the subsequent decreased mechanical properties of the fractured callus in rats.

The same group investigated the effects of other fluoroquinolone antibiotics on bone healing [77]. The same study design as previously described was used to investigate the effect of systemic exposure to levofloxacin and trovafloxacin on experimental fracture healing in a rat model. The results were similar to those seen in the previous study. The researchers concluded that inhibition of early fracture healing is likely a fluoroquinolone class effect. As a result of these findings, the researchers recommended not using fluoroquinolone antibiotics in patients with fractures or in the perioperative period after a joint replacement unless no alternative antibiotic is available.

Cartilage/Bone: Clinical Manifestations

Whereas arthralgia is thought to occur in approximately 1% of patients who take fluoroquinolones, a retrospective review of patients who take fluoroquinolones for sinusitis found the incidence of arthralgia and/or myalgia to be 25%, which is more than twice the incidence of any other adverse effect [78]. Determining the prevalence of clinically significant arthralgia after fluoroquinolone use has been difficult because of a lack of formal case definitions, lumping of diagnoses, and the presence of confounding factors. Nonetheless, an association between fluoroquinolones and arthralgias has been postulated.

At the present time, no formal studies investigating arthropathy and fluoroquinolones in adults have been published. Although a full discussion of this subject in the pediatric population is beyond the scope of this review, it is worth noting that multiple studies have examined the association between fluoroquinolones and arthropathy in children by imaging their joints with magnetic resonance imag-

ing (MRI) [79-83]. MRI findings are somewhat difficult to interpret given the presence of possible confounding factors, but joint effusion and cartilage abnormalities have been reported [83,84]. Although some follow-up studies failed to show persistent MRI changes [81,83], one case report cited persistent abnormalities on a bone scan after clinical and MRI resolution [84]. The extent of fluoroquinolone-associated arthralgia and its relationship with underlying structural changes remains indeterminate.

Based on the basic science research that demonstrates an increased delayed union and nonunion rate of fractures in rats exposed to fluoroquinolones [76,77], and given that fracture callus is a rapidly growing cartilaginous complex that undergoes intramembranous and endochondral ossification (similar to maturing cartilage) [77], it is reasonable to suspect that fluoroquinolones may negatively affect fracture healing in humans. Experimental data that support this observation in animal models was previously discussed [2,76,77], but formal investigation in humans is currently lacking.

Muscle: Basic Science

Although the etiology of fluoroquinolone-associated muscle disorders has yet to be fully elucidated, evidence supports a relationship with both latent myopathic disorders and the fluorine atom in fluoroquinolones. Despite no history of myopathy, an electromyogram (EMG) performed on a 54-year-old woman with apparent ofloxacin-induced rhabdomyolysis demonstrated evidence of myopathy [85]. The patient's myalgias and muscle weakness resolved upon discontinuation of ofloxacin. It is unknown whether the myopathic findings on EMG were related to the acute rhabdomyolysis or an underlying myopathy. In another case, a 33-year-old man thought to have norfloxacin-induced rhabdomyolysis was found to be susceptible to malignant hyperthermia by in vitro contracture tests [86], which raises the question of a possible link between the 2 conditions. His clinical complaints of myalgia and weakness and laboratory abnormalities resolved 6 months after discontinuing the norfloxacin. The researchers hypothesized that a similar muscle deficit may have accounted for the patient's susceptibility to malignant hyperthermia and rhabdomyolysis induced by fluoroquinolones. Both malignant hyperthermia and fluoroquinolone-associated muscle disorders are thought to be triggered by a fluorine-containing compound [86]. To further investigate this possible connection, the same French investigators studied muscle function in 3 patients who presented with myalgia, tendinopathy, and arthralgia associated with fluoroquinolone exposure [87]. These results were compared with 3 patients exposed to fluoroquinolones who had no adverse events and 9 subjects with no known muscle disease who had not taken fluoroquinolones. Muscle contraction and metabolism were investigated through the use of histology, in vitro contracture tests, and 31P magnetic resonance spectroscopy (31P MRS). The 3 patients with fluoroquinolone-associated myalgia and weakness displayed similar metabolic abnormalities, whereas the 3 subjects exposed to fluoroquinolones with no adverse effects displayed normal metabolic profiles. These findings led the researchers to conclude that the adverse effects recorded in the 3 patients were related to a pre-existing muscular anomaly revealed by fluoroquinolone treatment. Further support for the hypothesis that fluorine may be the trigger for fluoroquinolone-associated myopathy comes from the fact that no adverse muscular events have been reported with unfluorinated quinolones. In addition, steroid myopathy is thought to occur more frequently with fluorinated steroids (ie, dexamethasone and triamcinolone) than with nonfluorinated steroids (ie, prednisone or hydrocortisone) [88-90]. The researchers recommended that any patient experiencing myalgias associated with fluoroquinolone exposure should undergo noninvasive muscle metabolic testing with 31P MRS along with a subsequent muscle biopsy for histoenzymology and contracture tests if a metabolic disorder is found.

Muscle: Clinical Manifestations

A variety of muscle syndromes have been reported in association with fluoroquinolone use, ranging from mild myalgias to life-threatening rhabdomyolysis [78,85-87,91-95]. In fact, some investigators have proposed that myalgias may be the most common adverse effect of fluoroquinolone use [78]. Symptoms, which typically consist of diffuse muscle pain with or without weakness [86,87,91] and perhaps a predilection for proximal muscle groups [85,92], appear to manifest within 1 week after initiation of fluoroquinolone treatment [94] and often resolve within 1-4 weeks after discontinuation of the medication [78,86,91,92], although symptoms that persisted up to 6 months have been reported [86]. Statins may potentiate fluoroquinolone-associated myopathy [91,92]. Furthermore, an association may exist between an underlying myopathic process and the development of myalgias and/or rhabdomyolysis after fluoroquinolone exposure, as previously discussed.

Evaluation and Treatment

Although no randomized placebo-controlled human trials have been conducted to guide clinicians, the following evaluation and treatment recommendations have been developed on the basis of the available basic science literature and epidemiologic data previously discussed. Proper management (Table 4) of fluoroquinolone-associated musculoskeletal complications starts with an understanding of persons who are at increased risk and by using an alternative antibiotic when possible to treat infections in at-risk individuals. When fluoroquinolone use is necessary, patients should be

Table 4. *Management*

Identify higher-risk individuals
Avoid concomitant corticosteroid administration
Limit high-intensity physical activity during antibiotic course
Discontinue use of the fluoroquinolone if symptoms develop
Protect the symptomatic area to limit further injury
Initiate a graduated return to physical activities based on symptoms
Initiate further diagnostic evaluation and treatment as clinically indicated

made aware of the possible musculoskeletal symptoms associated with fluoroquinolone use to promote early recognition and proper evaluation and treatment should they occur. The published literature suggests that most cases will resolve after discontinuation of the medication within a few days to weeks, which makes extensive evaluation unnecessary in many cases.

A thorough musculoskeletal history, including current activity level, should precede any prescription of fluoroquinolone. Patients should be advised to limit high-intensity physical activity during fluoroquinolone treatment, especially if they currently have a tendon, joint or muscle disorder or have a history of such a disorder. If symptoms develop, the offending medication should be discontinued as soon as possible, with alternative treatment provided per the clinical scenario.

Fluoroquinolone-associated tendon disorders most often present acutely, with pain being the most common symptom. Single or multiple tendons may be affected. Prompt protection of the symptomatic area should ensue to limit risk of more significant injury, such as progression to tendon rupture. Although the appropriate duration of protection remains unknown, significant structural changes have been shown to persist in animal studies for as long as 20 weeks after fluoroquinolone exposure [17], and clinical symptoms have been reported to manifest as late as 6 months after exposure [46]. Certainly, caution should be exercised while the patient is still symptomatic. A gradual return to activities should be initiated based on the resolution of the patient's symptoms.

When a more significant injury is clinically suspected, imaging modalities such as MRI or diagnostic ultrasound can be helpful in evaluating the tendon and grading the severity of injury. Screening asymptomatic individuals exposed to fluoroquinolones with musculoskeletal ultrasound has not been found to identify those at risk of developing a tendon disorder [96], although further investigations with larger sample sizes are required. If a more significant tendon injury is identified (eg, tendon rupture), then treatment should proceed as clinically indicated and include surgical consultation when appropriate.

As previously mentioned, little is known regarding the clinical presentation and outcomes of fluoroquinolone-associated cartilage and bone disorders. The clinician should be aware of the possibility of arthralgia and arthropathy associated with fluoroquinolones, as well as delays in fracture healing and increased nonunion rates. More severe symptoms may necessitate discontinuation of the fluoroquinolone. Severe or persistent symptoms may warrant further evaluation with radiography, computed tomography, or MRI. As with tendon disorders, it would seem reasonable to protect the symptomatic area, with a gradual reintroduction of weight-bearing activities as tolerated after symptom resolution.

Although rare, rhabdomyolysis and its associated complications need to be considered in patients who present with fluoroquinolone-associated muscle disorders, given the possibility of significant morbidity and mortality associated with rhabdomyolysis. When symptoms are mild, without associated weakness, simple discontinuation of the fluoroquinolone and watchful waiting seem appropriate. When symptoms are more severe, persistent, or are accompanied by weakness, muscular tenderness to palpation or red-to-brown discoloration of urine, or when other concerning features of significant muscle injury are present, then laboratory evaluation should be conducted, including complete blood cell count, creatine kinase, electrolytes, measures of kidney and liver function, and urinalysis to assess for myoglobinuria, with referral and treatment as clinically indicated.

Because an underlying myopathy may be related to the development of fluoroquinolone-associated myalgia and rhabdomyolysis, patients with significant symptoms and/or confirmed rhabdomyolysis associated with fluoroquinolone antibiotic use may warrant further investigation for a latent myopathy. In addition, consideration of malignant hyperthermia susceptibility testing in those rare cases of rhabdomyolysis may be reasonable given the potentially dire consequences of the disorder. Some authors have suggested using systemic corticosteroids to treat fluoroquinolone-induced myalgias [94], but, given the association between corticosteroid use and tendon complication, this would not seem advisable.

Similar pathoetiologic mechanisms may be responsible for fluoroquinolone-associated changes across all tissue types, although this supposition is not fully supported by the literature. Existing data regarding these mechanisms suggest that treatment with antioxidants (eg, vitamin E and coenzyme Q10) and/or magnesium may prevent or reduce these toxic effects. However, further research is necessary before making formal recommendations regarding antioxidant and/or magnesium supplementation. The clinician should be aware of persons at increased risk of magnesium deficiency (eg, patients with diabetes, renal tubular disorders, alcoholism, and malabsorption) [97] and consider further evaluation as appropriate. If magnesium supplementation is considered, one must remember the pharmacokinetic interactions between quinolones and magnesium (as well as other cations) and consider either temporal separation in dosing or use of dif-

ferent routes of administration to avoid decreased efficacy of the antibiotic [25]. Although purported in the lay media [98], currently no evidence supports treatment of persistent symptoms with infusions of antioxidants such as glutathione.

Fluoroquinolones and the Athlete: Proposed Guidelines for Use

Despite the acknowledgment of increased risk of fluoroquinolone-associated tendon disorder in persons participating in sporting activities, limited clinical recommendations can be found in the literature to guide sports medicine physicians, athletes, or coaches on appropriate precautions and return to play after fluoroquinolone exposure. The only guidelines found come from Lavallee [99] in a 2003 issue of *USA Weightlifting* magazine. Given more recent insights into the pathoetiology and clinical history of fluoroquinolone-associated musculoskeletal complications, the following guidelines are proposed:

1. Athletes should avoid all use of fluoroquinolone antibiotics unless no alternative is available.
2. Should a fluoroquinolone antibiotic be prescribed, the athlete, and ideally the coaching and athletic training staff, should be made aware of the increased risk for the development of musculoskeletal complications. Health Insurance Portability and Accountability Act guidelines should always be followed when discussing the athlete's health with coaching and athletic training staff.
3. Oral or injectable corticosteroids should not be administered concomitantly with fluoroquinolones.
4. Consideration should be given to supplementation with magnesium and/or antioxidants during the fluoroquinolone treatment course if no contraindications are present.
5. Training alterations should begin at the time of the first dose, including a reduction in high-intensity and ballistic activities and total training volume. The reductions should remain throughout the duration of the antibiotic course. If the athlete has no symptoms after completing the full course of the antibiotic, then a graduated return to full activity under direct medical supervision should be initiated, with close monitoring for the development of musculoskeletal symptoms.
6. All athletic activity should cease at the onset of symptoms, with graduated return to activities when the person is asymptomatic. The fluoroquinolone should be discontinued if possible, and alternative antibiotic treatment should be prescribed if clinically indicated.
7. Close monitoring should continue for 1 month from completion of the antibiotic course. The athlete should understand that symptoms have been reported as late as 6 months after fluoroquinolone exposure, and prompt medical evaluation should be sought if symptoms develop. During this period, special consideration should be given to adequate recovery between bouts of high-intensity activity or competitions.

CONCLUSIONS

In conclusion, fluoroquinolone antibiotics are associated with a wide array of musculoskeletal complications involving tendon, cartilage, bone, and muscle that are likely underrecognized and underreported. The pathoetiology of these complications continues to be investigated but appears to be related to alterations in cell-signaling proteins, as well as direct toxic effects. Certain groups are at increased risk, and appropriate precautions should be taken in these individuals. Further research is needed to identify patients at risk for more serious complications and to evaluate possible preventative and therapeutic interventions. Until more is known, caution should be exercised in the prescription of fluoroquinolone antibiotics when other classes of antibiotic are available. Patients should always be counseled regarding the risk associated with fluoroquinolones, even when they are prescribed according to standard recommendations.

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