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Impact of Age, Sex, Obesity, and Steroid Use on Quinolone-Associated Tendon Disorders

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Abstract

BACKGROUND—Quinolone antibiotics are associated with increased risk of tendinopathy. Identifying at-risk individuals has important clinical implications. We examined whether age, sex, glucocorticoid use, obesity, diabetes, and renal failure/dialysis predispose individuals to the adverse effects of quinolones.

METHODS—Among 6.4 million patients in The Health Improvement Network (THIN) database, 28,907 cases of Achilles tendonitis and 7,685 cases of tendon rupture were identified in a case-crossover study. For each participant, we ascertained whether there was a prescription of a quinolone and comparison antibiotic within 30 days prior to diagnosis of tendon disorder (case period) as well as prescription of the same medications within 30 days one year prior to disease diagnosis (control period).

RESULTS—Use of quinolones was strongly associated with an increased risk of Achilles tendonitis (OR=4.3, 95% CI: 3.2–5.7) and tendon rupture (OR=2.0, 95% CI: 1.2–3.3). No association was found between the use of other antibiotics and either outcome. The association with Achilles tendonitis was stronger among participants who were older than 60 years (OR 8.3 vs. 1.6), non-obese (OR 7.7 vs. 2.4), and who used oral glucocorticoids (GC; OR 9.1 vs. 3.2) and nonsignificantly stronger in women (OR 5.0 vs. 3.6), diabetics (OR 7.0 vs. 4.1), and renal failure/dialysis (OR 20.0 vs. 3.9). The effect for tendon rupture was stronger in women, with borderline-significance in glucocorticoid users and non-obese.

CONCLUSION—Quinolone-associated tendinopathy is more pronounced among elderly, non-obese persons, and individuals with concurrent use of glucocorticoids.

Keywords

quinolone; fluoroquinolone; tendon rupture; tendonitis

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Introduction

Fluoroquinolones are a class of antibiotics commonly used for treatment of respiratory and urinary tract infections. The use of fluoroquinolones in the United States and abroad has increased steadily since 1995 (1, 2), and became the most commonly prescribed antibiotic class for adults in the United States by 2002 (1). The large number of people at risk make it critical to understand potential side effects of these medications and what groups are particularly vulnerable.

In the early 1970's Bailey reported a young woman developed severe arthralgia after receiving nalidixic acid for three days(3). Since then, studies have shown that use of fluoroquinolones increases risk of tendonitis, especially Achilles tendonitis, and tendon rupture (4–11). Van der Linden and colleagues estimated that excess risk of Achilles tendonitis after use of fluoroquinolones to be 3.2 cases per 1000 patient years (9). In 1995 representatives of the U.S. Food and Drug Administration (FDA) stated that the agency would "update the labeling [package insert] for all marketed fluoroquinolones to include a warning about the possibility of tendon rupture" (12). More recently, a further muscle-related side-effect of fluoroquinolones was added to the boxed warning for the medications by the FDA, specifically related to increased weakness in myasthenia gravis (13).

The mechanism by which quinolones might cause these deleterious effects in tendons and cartilage remains somewhat unclear. Jorgensen et al. found necrosis and neovascularization without inflammation in ruptured Achilles tendons after quinolone use, and others have noted similar findings (14, 15). The pathological basis for tendinopathy by quinolone use is multifactorial, and is likely to include an ischemic component (16, 17), degradation of matrix (18), and toxic effects on the mitochondria and other cell components (19).

Given the wide use of fluoroquinolones in clinical care, identifying individuals who are more susceptible to the detrimental effects of quinolones has important clinical implications.. Using The Health Improvement Network (THIN) database that consists of 6.4 million patients from general practices across the United Kingdom, we conducted a case-crossover study to examine the association between quinolone use and risk of Achilles tendonitis and secondarily tendon rupture, and assessed whether such associations, if present, are modified by age, gender, obesity, concurrent glucocorticoid use, diabetes, or renal failure.

Methods

Source of Data

The study was based on information derived from The Health Improvement Network (THIN) database, which contains computerized medical information of approximately 6.4 million residents in the United Kingdom entered by general practitioners over a period from 1986 to 2009 (<http://www.epic-uk.org/>). Approximately 3.3 million of the participants are active. Because the National Health System (NHS) in the UK requires that all individuals be registered with a general practitioner regardless of health status, the cohort is representative of the general population of the UK. All information is recorded onsite at each practice with quality control to maintain high data completion rates. Specialist and hospital data sent to general practitioners is also included in the dataset provided that it is entered by the general practitioner. Data recorded in the THIN database include patient demographics, diagnoses, medications, laboratory results, socioeconomic status, subspecialty referrals, and vital status. Read codes from the THIN database are used to enter medical diagnoses, and a coded drug dictionary is used for the recording of prescriptions. The THIN database has been used by

many investigators for clinical research in a variety of fields and is described in greater detail elsewhere (20–22).

Study Subjects

We identified subjects who had a first time diagnosis with either Achilles tendonitis or tendon rupture at any site between January 1, 1986 and November 31, 2009. The onset of tendonitis can be gradual, developing over days to a few months, while the onset of tendon rupture is usually experienced as sudden. Achilles tendonitis was chosen because it has been identified in the past specifically as an association with quinolone use (18). Tendon rupture was chosen as a secondary outcome because it was felt that other forms of tendinopathy (e.g., tendonitis) were subject to greater misclassification bias. The most common sites of rupture and tendinopathy in past studies have been Achilles tendon, biceps, quadriceps, extensor pollicis longus, and rotator cuff (5, 23) so our two outcomes represent this range well. The date of diagnosis of Achilles tendonitis or tendon rupture was used as the index date. Subjects were excluded if his/her Achilles tendonitis or tendon rupture was diagnosed within the first two years of entry to the THIN database in order to avoid using diagnoses that might have been entered at the beginning of the subject's participation in the study but which actually represented events that occurred prior to study entry.

Exposure Assessment

For each subject, we defined a case period as the thirty days immediately prior to the diagnosis date, and a control period as the thirty days one year prior to the diagnosis date. We ascertained whether each subject had a prescription for oral or parenteral quinolone use during either or both of these periods. To assess potential confounding by indication, i.e., whether the tendinopathy is due to the condition for which quinolone was prescribed, we also obtained data on other antibiotics used for the same indications (trimethoprim, amoxicillin, nitrofurantoin). Since no study has shown that these antibiotics are associated with an increased risk of tendinopathy, we designated them to be comparator exposures.

Potential Effect Modifiers

The potential effect modifiers of interest consisted of age (< 60 years vs. ≥ 60 years), sex, body mass index (BMI) (< 30 kg/m² vs. ≥ 30 kg/m²), glucocorticoid use (concurrent use vs. no concurrent use), diabetes, concurrent renal failure or dialysis (combined due to low numbers). The age cutpoint was chosen based on clinical judgement and on the cutpoint used in past studies. The BMI cutpoint was chosen based on commonly used definitions of obesity.

Statistical Analysis

We examined the relation of quinolone and comparator antibiotic use to the risk Achilles tendonitis, respectively, using a conditional logistic regression model. To assess whether the effect of quinolones on the risk of Achilles tendonitis and tendon rupture varied by age, sex, BMI, glucocorticoid use, concurrent renal failure/dialysis, and diabetes, we repeated the analyses at each stratum of these variables. We tested potential effect modification by each of these variables by adding an interaction term (e.g., quinolone use*sex) into the conditional logistic regression model. We took the same approach to evaluating the association between quinolone or other antibiotic use and risk of tendon rupture, respectively. We estimated the rate difference of Achilles tendonitis and tendon rupture after initiation of fluoroquinolone use. Rate difference was calculated using the following formula: (IR*OR) – IR, where IR represents the baseline rate of Achilles tendonitis and tendon rupture, and OR represents the odds ratio as calculated by the case-crossover study. We also estimated the risk of each disease per 100,000 new fluoroquinolone prescriptions

over a 30-day period. All analyses were performed with SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).

The institutional review boards at Boston University and for the THIN project have approved the study. The funding sources had no direct role in the study.

Results

Between January 1986 and December 2009 we identified 28907 incident Achilles tendonitis cases and 7685 incident tendon rupture cases. Among subjects with Achilles tendonitis, 46.5% were women, 73.7% were younger than 60 years, slightly more than one third were obese (37.5%), 4.2% had diabetes, 1.4% had renal failure or were on dialysis, and 1.8% of them were concurrently treated with glucocorticoids in either case or control periods. Among subjects with tendon rupture, 31.9% were women, 57.7% were younger than 60 years, 29.8% were obese, 5.2% had diabetes, 2.2% had renal failure or were on dialysis, and 3.4% used glucocorticoids in either case or control periods (Table 2). As shown in Table 3, use of quinolones was associated with an increased risk of Achilles tendonitis (OR=4.3, 95% CI: 3.2–5.7). However, no such association was observed for the comparator antibiotic use. There was little co-use of quinolones with comparator antibiotics; thus, adjusting for comparator antibiotic use did not change the effect estimates materially (OR 4.4, 95% CI: 3.3–5.9). Similar findings were also observed for tendon rupture (Table 4). Glucocorticoid use without regard to quinolone use was associated with an increased risk of Achilles tendonitis with an odds ratio of 1.6 (95%CI 1.3–1.9).

The baseline rate of incident Achilles tendonitis and tendon rupture in the THIN cohort was 92 and 24 per 100,000 person-years, respectively. The rate difference was 302 and 24 per 100,000 person-years for Achilles tendonitis and tendon rupture, respectively. The risk of Achilles tendonitis within 30 days was 48 per 100,000 new fluoroquinolone prescriptions, while the corresponding risk of tendon rupture was 6 per 100,000.

The association of quinolone use with the risk of Achilles tendonitis varied according to potential effect modifiers (Table 5). The association was significantly stronger among subjects who were older than 60, non-obese, and concurrent glucocorticoids users compared with their counterparts. Although the effect of quinolones on the risk of Achilles tendonitis appeared to be greater in women than in men, the interaction term was not statistically significant. The effect of quinolones was greater in those with diabetes and renal failure/dialysis, but here again the interaction term did reach statistical significance.

The numbers for the secondary outcome of tendon rupture were small. The effect of quinolone use on tendon rupture was more pronounced among women than among men (OR 4.0 vs. 1.1; p for interaction=0.02), and was borderline statistically significant by obesity status (OR=2.6 among non-obese vs. OR=0.5 among obese; p for interaction=0.09), and concurrent glucocorticoid user (OR=3.7 for GC use vs. 1.3 for non-GC use; p for interaction=0.06). There was no statistically significant interaction by age category, diabetes, or renal failure/dialysis for tendon rupture.

Discussion

Using data collected from a large primary care population, we confirm previous findings that quinolone use increases the risk of Achilles tendonitis and tendon rupture. In addition, our study results indicate that the detrimental effects of quinolones are more pronounced among women, elderly, non-obese persons, and individuals with concurrent use of glucocorticoids.

Fluoroquinolones are a commonly used class of antibiotics to treat a wide variety of infections, ranging from pneumonia to urinary infections, and their use has increased over the past decades in most countries (2). Previous studies have demonstrated that quinolone use is associated with an increased risk of tendinitis, tendinopathy, and tendon rupture. Identifying subpopulations that are more susceptible to the effect of quinolones on tendons has important clinical implications.

Previous studies have examined several potential factors that may modify the effect of fluoroquinolones on the risk of tendonopathy. Van der Linden et al. found that the association between quinolones use and occurrence of Achilles tendon rupture was similar among men and women (10). However, in our study, the effect of quinolones on tendon rupture tends to be greater in women than in men. It is unclear why our findings are different from that reported by Van Der Linden. However, the two studies assessed different outcomes. In our study we examined both Achilles tendonitis and tendon rupture whereas van der Linden and colleagues assessed the association of quinolone use only with the risk of Achilles tendon rupture.

Previous studies also suggested that the effect of quinolone use on Achilles tendon rupture tended to be greater among older persons. For example, Van der Linden et al reported that the odds ratio for Achilles tendon rupture was 6.4 (95% CI 3.0–13.7) in persons aged 60–79 years, but increased to 20.4 (95% CI 4.6–90.1) in those 80 years (10). In a different study (9), the same authors found that for Achilles tendonitis, concurrent use of fluoroquinolones was associated with an adjusted relative risk of 1.0 (95% CI 0.5–1.8) for those under 60 years and 3.1 (95% CI 2.0–4.8) for those 60 years and older. Sode et al found that the corresponding relative risks for Achilles tendon rupture by age less than and greater than 60 were 2.5 (95% CI 0.5–7.4) and 4.0 (95% CI, 0.5–14.4) (8). Our findings are consistent with these previous findings and support the application of extra caution when considering quinolone use in persons older than 60 years.

Some studies have suggested that the detrimental effects of fluoroquinolones are more pronounced among people with renal failure (24, 25). Donck et al reported an increased risk of Achilles tendinopathy in renal transplant patients, but the numbers were small (11 events in 130 patients exposed to fluoroquinolones versus 5 events in 138 unexposed patients) (26). Our study suggested that the association between fluoroquinolone use and the risk of Achilles tendonitis tended to be stronger among subjects with renal failure or dialysis, albeit not statistically significant. This finding is consistent with that reported by Donck and colleagues, suggesting that use of fluoroquinolones among those with renal failure or on dialysis should be approached with caution.

A few studies also found that use of glucocorticoids in close temporal proximity to fluoroquinolones increases the risk for tendon rupture (5, 6, 9, 10). Van der Linden examined concurrent use of oral corticosteroids and quinolones among subjects aged over 60 years or older. Use of quinolones was associated with a 5-fold increased risk of Achilles tendon rupture (OR=5.3, 95% CI 1.8–15.2) among those not using corticosteroids and compared with an OR of 17.5 (95% CI 5.0–60.9) in those with concurrent exposure to corticosteroids (10). In the present study we found that quinolones were associated with 3.2 (95% CI = 2.3–4.4) odds of Achilles tendonitis in those unexposed to corticosteroids, compared with an odds ratio of 9.1 (95% CI = 4.6–18.0) for concurrent users of both quinolones and corticosteroids. Given the consonance of these findings, there appears to be an elevated risk for Achilles tendon maladies with concurrent use of these medications, and caution should be exercised when considering quinolones in those persons using corticosteroids.

Perhaps the most puzzling finding in our study is that non-obese individuals are at greater risk for the quinolone-mediated tendinopathy than are obese individuals. This approaches a paradoxical finding, since in the absence of quinolone use, obese persons are at higher risk for tendinopathy and tendon rupture, probably due to the greater mechanical forces exerted on body structures during activity (27). However, non-obese individuals may be more active while taking the medications, thus potentially increasing the risk for tendon injury. The direct effect of the quinolones on alteration of tendon structure through ischemic and toxic effects may provide the explanation for our findings. Although fluoroquinolones are recommended to be dosed by body weight in pediatric patients, they are normally used in fixed doses in adults without regard to weight. Only 11.1% of the Achilles tendonitis cohort and 1.7% of the tendon rupture cohort were younger than 18 years at case date, so our results primarily reflect the fixed dose use employed in adults. An obese person has a greater body volume and greater volume of tendon tissue through which to distribute the medication (28), resulting in a lower concentration of medication per unit tendon volume. Quinolones distribute into many tissue types (29), so we would expect that for this reason as well, there would be decreased concentration in all tissues including tendon in obese persons. This would result in a decreased direct effect of the quinolone on the tendon cells and structure, thus potentially decreasing the risk of rupture or tendinopathy in the obese person.

Our study has some limitations. The outcomes in our analysis are based on general practitioner diagnosis, which carries a risk of misclassification. In order to address this concern, we limited our analyses to Achilles tendonitis, which is more specifically identifiable by the general physician due to specific physical examination characteristics, and secondarily to tendon rupture, which is much less subject to misdiagnosis due to the severity and distinguishing clinical features. If misclassification does exist due to the above reasons, it would tend to bias the effect estimates towards the null. It would be of great interest to health care providers if one could assess the effect of each specific quinolone on the risk of Achilles tendonitis or tendon rupture. However, even with a database like THIN that consists of a relatively large number of incident cases of Achilles tendonitis and tendon rupture, the number of users of specific quinolones is small and we were not able to obtain robust effect estimates.

Several strengths of this study are worth noting. First, the number of incident cases in our study is larger than most previous studies, providing the opportunity to perform sub-group analysis to assess potential effect modification. To our knowledge, the present study is the first to examine these questions using a case-crossover study design which eliminates time-invariant confounding factors between individuals such as genetics and other inherent disease susceptibilities; this is a powerful approach that allowed us to identify interactions with confidence. The timing of onset of tendinopathy after fluoroquinolone use has been found to be on average 9–17 days after beginning of use, but has ranged from hours to many months, so we feel that the defined length of our exposure period (30 days plus prescription period) encompasses the major risk period. Finally, our parallel analysis using comparator medications reinforces that our findings are in fact due to the action of the quinolones and address the question of confounding by indication.

In summary, our study confirms that quinolone use increases the risk of Achilles tendonitis and tendon rupture. These detrimental effects of quinolones appear to occur more often among elderly, non-obese patients, and individuals with concurrent use of glucocorticoids, and may occur more often among women. These patient characteristics should be considered carefully by physicians when making decisions regarding antibiotic choice and greater caution may be needed in considering using quinolones in individuals with a higher risk profile.

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Table 1

Characteristics of subjects in the THIN database

Characteristic	Mean or percent
Sex (women, %)	51.6
Age (median (IQR))	36.3 (35.8)
BMI (median (IQR))	25.2 (6.6)
GC Use (yes, %)	10.1
Diabetes (%)	3.0
Renal Failure/dialysis (%)	2.9

Table 2

Characteristics of subjects with Achilles tendonitis or tendon rupture

Characteristic	Achilles Tendonitis	Tendon Rupture
Sex (women, %)	46.5	31.9
Age (median (IQR))	47.7 (24.7)	55.8 (27.3)
Age (<60 years, %)	73.7	57.7
BMI (median (IQR))	28.1 (7.6)	27.2 (6.3)
BMI (≥ 30 kg/m ² , %)	37.5	29.8
GC Use (yes, %)	1.8	3.4
Diabetes (%)	4.2	5.2
Renal Failure/dialysis (%)	1.4	2.2

Table 3

Association of antibiotic use and risk of Achilles tendonitis

Medication use	Case period	Control period	OR (95% CI)
Quinolone			
No	28640	28830	1.0 (reference)
Yes	267	77	4.3 (3.2–5.7)
Comparator Antibiotics			
No	28373	28197	1.0 (reference)
Yes	534	710	0.7 (0.6–0.8)

Table 4

Association of antibiotic use and risk of tendon rupture

Medication use	Case period	Control period	OR (95% CI)
Quinolone			
No	7637	7660	1.0 (reference)
Yes	48	25	2.0 (1.2–3.3)
Comparator Antibiotics			
No	7522	7512	1.0 (reference)
Yes	163	173	0.9 (0.7–1.2)

Table 5

Quinolone use and Achilles tendonitis by potential effect modifiers

Potential modifier	Quinolone use	Achilles tendonitis			p for interaction	Interaction index
		Case period	Control period	OR (95% CI)		
Men	Yes	115	38	3.6 (2.4–5.3)	0.24	1.4 (0.8–2.5)
	No	15,358	15,435			
Women	Yes	152	39	5.0 (3.4–7.6)	<0.001	5.1 (2.8–9.3)
	No	13,282	13,395			
<60 yrs	Yes	63	41	1.6 (1.1–2.5)	0.02	0.3 (0.1–0.8)
	No	21,241	21,263			
>=60 yrs	Yes	204	36	8.3 (5.4–12.8)	0.03	2.5 (1.1–5.5)
	No	7,399	7,567			
No obesity	Yes	108	21	7.7 (4.3–13.7)	0.39	1.7 (0.5–6.0)
	No	6,357	6,444			
Obesity	Yes	25	11	2.4 (1.1–5.0)	0.11	5.2 (0.7–39.5)
	No	3,854	3,868			
Glucocorticoid use	Yes	99	17	9.1 (4.6–18.0)	0.03	2.5 (1.1–5.5)
	No	726	808			
No glucocorticoid use	Yes	168	60	3.2 (2.3–4.4)	0.39	1.7 (0.5–6.0)
	No	27,914	28,022			
Diabetes	Yes	26	5	7.0 (2.1–23.5)	0.11	5.2 (0.7–39.5)
	No	1254	1275			
No Diabetes	Yes	241	72	4.1 (3.0–5.5)	0.11	5.2 (0.7–39.5)
	No	27386	27555			
Renal Failure/Dialysis	Yes	30	3	20.0 (2.7–149)	0.11	5.2 (0.7–39.5)
	No	470	497			
No Renal Failure/Dialysis	Yes	237	74	3.9 (2.9–5.2)	0.11	5.2 (0.7–39.5)
	No	28170	28333			