

Tendon Injury and Fluoroquinolone Use: A Systematic Review

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Abstract

Background Fluoroquinolone antibiotics are commonly used to treat infections and are prescribed by general practitioners, medical specialists and surgeons. Tendon injury has been associated with the use of these medications but the risk associated with newer fluoroquinolones has not been established.

Objectives The aim of this systematic review was to evaluate the evidence from observational studies to determine the strength of the association between fluoroquinolone

use and tendinopathy, and to identify risk factors for this complication.

Methods We searched MEDLINE, EMBASE and the Cochrane Collaboration from inception through May 2013 to identify observational studies focused on tendon injury and fluoroquinolones. Studies with original data were selected for inclusion following the PRISMA guidelines. Of the 560 abstracts screened, 16 relevant studies were independently rated by three authors (WW, AS, DC) using the Newcastle-Ottawa Quality Assessment Scale, and assigned a quality score out of 9. High-quality studies (i.e. scored 4.5 or higher) are summarized in detail in this article. Data were independently extracted by two authors (WW, AS).

Results Overall, 16 studies were included in our study. Eight were deemed to be of high quality and five specifically evaluated Achilles tendon rupture. In addition, three studies examined Achilles tendinitis, and three included tendon disorders (including any tendon rupture) as an outcome. Results from these studies suggest that individuals exposed to fluoroquinolones are at increased risk for Achilles tendon rupture, particularly within the first month following exposure to the drug (odds ratios ranged from 1.1 to 7.1). One study showed an increased risk of tendon rupture in those over 60 years of age. Five studies stated that individuals taking fluoroquinolones and oral corticosteroids are at increased risk for tendon injury compared with those taking fluoroquinolones alone. Four studies examined the differential effect of a limited number of fluoroquinolones. Ofloxacin had the highest risk of tendon injury in three of the studies.

Limitations Included studies are observational in nature and rely on self-report, which may lead to misclassification or underestimation of tendon injury.

Conclusions Observational studies showed an increased risk of tendon injury, including tendon rupture and

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tendinitis, with exposure to fluoroquinolone antibiotic therapy. Although this complication appears to be rare, concomitant corticosteroids increase the risk for tendon injury, which varies depending on the fluoroquinolone used.

1 Background

Fluoroquinolone-associated tendinopathy has been reported in the literature and the incidence is estimated to be 0.14–0.4 % [1]. The Achilles tendon is often affected; however, case reports of inflammation of other tendons related to fluoroquinolone use have been published [2–8]. The symptoms can range from mild pain around the affected tendon to complete rupture necessitating a surgical intervention. In 2008, mounting public pressure and increased evidence of fluoroquinolone-associated tendinopathy forced ‘black-box’ warnings and ‘Dear Doctor’ letters from manufacturers highlighting this potential complication [9].

Fluoroquinolone antibiotics were first available in the mid-1980s, with norfloxacin, ciprofloxacin and ofloxacin being the earliest introductions of their class [10]. Since then, fluoroquinolones have been used to treat a wide variety of infections, including urinary tract, respiratory tract, gastrointestinal, skin, bone and joint infections. As such, this class of medication is prescribed by a variety of medical specialties ranging from general practitioners to medical specialists and surgeons. The bactericidal activity of the earliest fluoroquinolones involved inhibition of DNA gyrase in gram-negative pathogens, whereas the more recent newer ‘respiratory’ agents (e.g. levofloxacin, moxifloxacin) were expanded to inhibit topoisomerase IV in gram-positive pathogens, and have activity against atypicals and anaerobes [10]. Canadian and American respiratory treatment guidelines for community-acquired pneumonia (CAP) recommend respiratory fluoroquinolones, such as levofloxacin and moxifloxacin, as first-line therapy for CAP and also for the treatment of chronic obstructive pulmonary disease (COPD) exacerbations [11, 12].

To our knowledge, there has been only one published systematic review of the literature evaluating fluoroquinolone-associated tendinopathy, which used data from 1966–2001 [13]. This review primarily included case reports ($n = 98$) which most commonly involved pefloxacin and ciprofloxacin. From the case reports, the authors concluded that the median duration of onset of tendon injury was 8 days and that 50 % experienced tendon rupture, particularly in individuals receiving oral corticosteroids. Risk of tendon injury was felt to be highest with pefloxacin compared with ciprofloxacin. In addition, older

individuals, those with renal impairment, or concomitant use of oral corticosteroids, are at increased risk of tendon injury related to fluoroquinolone use based on the previously published systematic review [13]. However, some unanswered questions remain. The newer respiratory fluoroquinolones (i.e. levofloxacin, moxifloxacin) were not well represented in the previous review, therefore the risk of tendon injury associated with these medications has not been systematically evaluated. In addition, the effect of specific risk factors on tendon injury, such as fluoroquinolone dose, duration of therapy, age and sex, remain uncertain.

Since the systematic review published in 2003 [13], additional observational studies have been published on this topic which may shed light on these unanswered questions. Fluoroquinolone prescribing has significantly increased over the years [14], therefore it is important to increase awareness and expand our knowledge about this association so patients can be monitored closely for this potential adverse event. In this article, we systematically reviewed the evidence from observational studies to determine the strength of the association between fluoroquinolone use and tendinopathy, and to identify risk factors for this complication.

2 Methods

Following PRISMA guidelines, we searched MEDLINE (1948 through to 17 May 2013), EMBASE (1947 through to 17 May 2013) and the Cochrane Collaboration (2005 through to 17 May 2013) for published articles on tendon injuries and quinolones (last searched 17 May 2013). The following search terms were used across all databases: ‘tendon’, ‘tendonitis’, ‘tendon injury’, ‘tendinopathy’, ‘quinolones’, ‘fluoroquinolones’, ‘ciprofloxacin’, ‘gatifloxacin’, ‘levofloxacin’, ‘moxifloxacin’, ‘norfloxacin’, ‘ofloxacin’, ‘enoxacin’ and ‘pefloxacin’ (the search strategy can be found in the electronic supplementary material). Inclusion criteria were observational research studies on human subjects published in the English language. We did not include randomized controlled trials as they have strict selection criteria and often exclude those at highest risk of adverse events. Furthermore, tendon injury in such trials can be very rare. Population-based observational studies reflect real-life clinical practice; therefore, review of observational studies is critical to evaluate the prevalence of adverse events. Review articles, pathophysiology studies, case reports and animal studies were excluded. We included articles where tendon injury was the primary outcome of the study. Article titles and abstracts were screened for inclusion by three authors (WW, AS, DC) independently. If there was uncertainty based on the

abstract, the full text was obtained and reviewed. Any disagreements were resolved by consensus. Articles were evaluated and data extracted by two authors (WW, AS) independently on the type of fluoroquinolone studied, fluoroquinolone dosage and duration, time to onset, incidence rate, risk ratio, the type of outcome identified and whether or not specific risk factors identified previously in the literature were evaluated, such as age, sex, corticosteroid use, prior history of fluoroquinolone-associated tendinopathy and renal disease. Disagreements were resolved by consensus.

2.1 Assessment of Risk of Bias

All studies included in the review were assessed for quality using the Newcastle-Ottawa Quality Assessment Scale for assessing the quality of non-randomized studies in meta-analyses and systematic reviews [15]. Two rating scales were used—one for cohort studies and one for case-control studies. The cohort evaluation tool involved rating the study on representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that the outcome of interest was not present at the start of the study, comparability of the cohorts on the basis of the design or analysis, assessment of the outcome, follow-up length and adequacy of follow-up. Case-control studies were evaluated based on the case definition, representativeness of cases, selection of controls, definition of controls, comparability of cases and controls, ascertainment of exposure, whether the same method was used for cases and controls, and the non-response rate. For studies using an alternative study design (e.g. case-series, correlational, cross-sectional), the evaluation form for case-control studies was utilized to assess the quality of the study [16]. All included articles were independently rated on each of the items by three authors (WW, AS, DC). Any instances of disagreement were resolved by consensus. Each study could receive a maximum rating of nine. High-quality studies were deemed to have a score of 4.5 or greater (the mid-point for the rating scale). Results for high-quality studies are presented in this review.

3 Results

The search identified 469 unique abstracts, from which 16 observational studies were identified (Table 1) for inclusion in our study. Figure 1 shows an overview of the study selection process. Five case-control studies and six cross-sectional/case-series studies [17–27] were identified as well as five cohort studies [28–32]. Two studies examined the post-transplant population (heart, lung) [23, 29] and four studies were surveillance pharmacovigilance studies of

self-reported adverse events associated with fluoroquinolone use [18, 22, 25, 27]. The remaining ten studies were population-based database studies using either prescription dispensing and consumption data, health administrative data or general practice data [17, 19–21, 24, 26, 28, 30–32]. The mean age of study subjects varied from 47 to 68 years. Of those studies that reported the follow-up time after exposure ($n = 10$), the range was from 1 to 18 months. Results from the quality assessment scale for the case-control, cross-sectional and cohort studies are presented in Table 2. All five case-control studies were of high quality [17, 19–21, 24]; however, only three of the five cohort studies [28, 30, 31] met the criteria for high quality. None of the cross-sectional/case-series studies met the criteria for high quality. Of the eight high-quality studies reported in this review, two studies did not specify the names of the fluoroquinolones studied [17, 30]. The remaining six studies included the following fluoroquinolones: ciprofloxacin (six studies), ofloxacin (five studies), norfloxacin (four studies), levofloxacin (three studies), tosufloxacin (one study), moxifloxacin (one study), prulifloxacin (one study), sitafloxacin (one study), garenoxacin (one study), sparfloxacin (one study), fleroxacin (one study) and gatifloxacin (one study). Although a meta-analysis was planned, due to the diversity of the patient populations, study outcomes and fluoroquinolones studied, it was not possible to conduct this analysis.

3.1 Incidence of Tendon Injury

Two studies reported on the incidence of tendon injury, which was found to be rare, ranging from 0.08 to 0.2 % [28, 31].

3.2 Type of Tendon Injury

3.2.1 Tendon Rupture

Four case-control studies and one cohort study assessed the risk of Achilles tendon rupture and one study examined any tendon rupture following fluoroquinolone exposure (Table 3). Four studies found a significantly increased risk of Achilles tendon rupture [20, 21, 24, 30], whereas one study reported an increased risk of any tendon, not limited to the Achilles tendon [odds ratio (OR) 2.0, 95 % CI 1.2–2.3] [17]. A sixth study [19] reported an increased risk (i.e. OR 1.2) but these results were not statistically significant, with a 95 % CI of 0.9–1.7. Of note, the study by van der Linden et al. [24] reported the risk of Achilles tendon rupture stratified by age (<60 vs. ≥60 years), whereas the other studies reported an OR for tendon rupture for the entire cohort without stratification by age.

Table 1 Description of the included studies

Studies (location)	Data	Population	Subjects	Female (%)	Age (y; mean)	FQ type	Timeframe ^a
Case-control/cross-sectional/case-series studies							
Wise et al. [17] (UK)	General Practice (1986–2009)	General	Achilles tendonitis: 28,907 cases Tendon rupture: 7,685 cases Crossover design, control period as 1 year ago	47 in Achilles tendonitis cases 32 in tendon rupture cases	Median: 47.7 in Achilles tendonitis cases, 55.8 in tendon rupture cases	Not specified	30 days
Lapi et al. [18] (Italy)	Surveillance pharmacovigilance (2005–2006)	Adverse events reports	272 ADR	55	61.0	Cipro, Levo, Moxi, Prul	NA
Seeger et al. [19] (US)	Admin (1997–2001)	General	947 cases and 18,940 controls	27 in cases, 51 in controls	91 % cases <60	Cipro, Levo, Oflox	6 months
Corrao et al. [20] (Italy)	Admin (2002–2003)	General	22,194 cases and 104,906 controls	64 in cases	55.9 in cases	Cipro, Levo	15, 30 and 90 days
van der Linden et al. [21] (UK)	General Practice (1988–1998)	General	1,367 cases and 50,000 controls	32 in cases, 52 in controls	48 in cases, 47 in controls	Cipro, Norf, Oflox	1, 6 and 18 months
Leone et al. [22] (Italy)	Surveillance pharmacovigilance (1999–2001)	Adverse events reports	425 ADR	55	47 % <60	Cipro, Levo, Moxi, Norf, Prul, Enox, Rufl, Peflox, Lome, Oflox	NA
Chhajed et al. [23] (Australia)	Transplant centre	Lung transplant	72 FQ users, 29 non-FQ users	50	47.6	Cipro	NA
van der Linden et al. [24] (UK)	General practice (1992–1998)	General	742 cases and 10,000 controls	61 in cases	56 in cases	Cipro, Norf, Oflox	30 and 90 days
van der Linden et al. [25] (Netherlands)	Surveillance pharmacovigilance (1988–1998)	Adverse events reports	42 tendon ADR	24	Median: 68	Cipro, Norf, Peflox, Oflox	NA
van der Linden et al. [26] (Netherlands)	Pharmaco drug (1991–1996)	General	251,000 FQ users	NS	NS	Cipro, Peflox, Oflox	NA
Pierfitte and Royer [27] (France)	Surveillance pharmacovigilance (1993)	General	421 tendon ADR	44	62	Cipro, Norf, Peflox, Oflox	NA
Cohort studies							
Hori et al. [28]	General practice (1996–2009)	General	17,147 FQ users, 38,517 cephalosporins users	NS	NS	Cipro, Levo, Tosu, Moxi, Prul, Sita, Gare, Spar, Fler, Gati, Oflox, Norf	30 days
Barge-Caballero et al. [29] (Spain)	Transplant centre (1995–2006)	Heart transplant	242 FQ users in 149 patients	21	58.8	Cipro, Levo, Norf	30 days
Sode et al. [30] (Denmark)	Admin (1991–1999)	Funen County	28,262 FQ users	62 in FQ users	55 in FQ users	Not specified	90 days

Table 1 continued

Studies (location)	Data	Population	Subjects	Female (%)	Age (y; mean)	FQ type	Timeframe ^a
van der Linden et al. [31] (Netherlands)	General practice (1995–1996)	General	1,841 FQ users, 9,406 non-FQ users	64 in FQ users, 71 in non-FQ users	53 in FQ users, 45 in non-FQ users	Cipro, Norf, Oflox	1 month
Wilton et al. [32] (UK)	Prescription and survey (1988–1991)	General	33,620 FQ users, 22,525 non-FQ users	68 in FQ users, 58 in non-FQ users	52 in FQ users, 37 in non-FQ users	Cipro, Norf, Oflox	6 weeks

Admin administrative, *ADR* adverse drug reaction, *Cipro* ciprofloxacin, *Enox* enoxacin, *Fler* fleroxacin, *FQ* fluoroquinolone, *Gare* garenoxacin, *Gati* gatifloxacin, *Levo* levofloxacin, *Lome* lomefloxacin, *Moxi* moxifloxacin, *NA* not applicable, *NS* not stated, *Norf* norfloxacin, *Oflox* ofloxacin, *Peflox* pefloxacin, *Prul* prulifloxacin, *Ruf* rifloxacin, *Sita* sitafloxacin, *Spar* sparfloracin, *Tosu* tosufloxacin.

^a Timeframe shows the exposure time before index date for case-control studies and follow-up time for cohort studies

3.2.2 Achilles Tendinitis

Achilles tendinitis was evaluated by one case-control study, one case-crossover study and one cohort study (Table 3). van der Linden et al. [31] examined 1,841 subjects exposed to fluoroquinolone and 9,406 controls, and compared the risk of developing Achilles tendinitis between the two groups. A non-significant increase in the rate of Achilles tendinitis was reported between the exposed group and reference group [relative risk (RR) 3.7; 95 % CI 0.93–15.14]. A later study by the same group found a statistically significant increased risk of Achilles tendinitis in those ≥ 60 years of age recently prescribed fluoroquinolones (OR 3.1; 95 % CI 2.0–4.8) [24]. Wise et al. [17] reported an increased risk of Achilles tendinitis in subjects exposed to fluoroquinolones (OR 4.4; 95 % CI 3.3–5.9).

3.2.3 Any Tendon Disorders

One study [20] included ‘tendon disorders’ as an outcome that included synovitis and tenosynovitis (tendon rupture was examined separately in this article). This study reported an increased risk of tendon disorders within 1 month following fluoroquinolone exposure but the risk was no longer statistically significant 1–3 months post-fluoroquinolone exposure (Table 3) [20]. A second study evaluated ‘tendon disorders’ that encompassed tendinitis, tendon rupture and peri-tendinitis. The study results were reported as a composite outcome rather than providing a risk estimate for the three tendon complications separately. There was a statistically significant increased risk of a tendon disorder in those who received a fluoroquinolone compared with individuals receiving cephalosporins (RR 6.29; 95 % CI 2.27–17.46) [28].

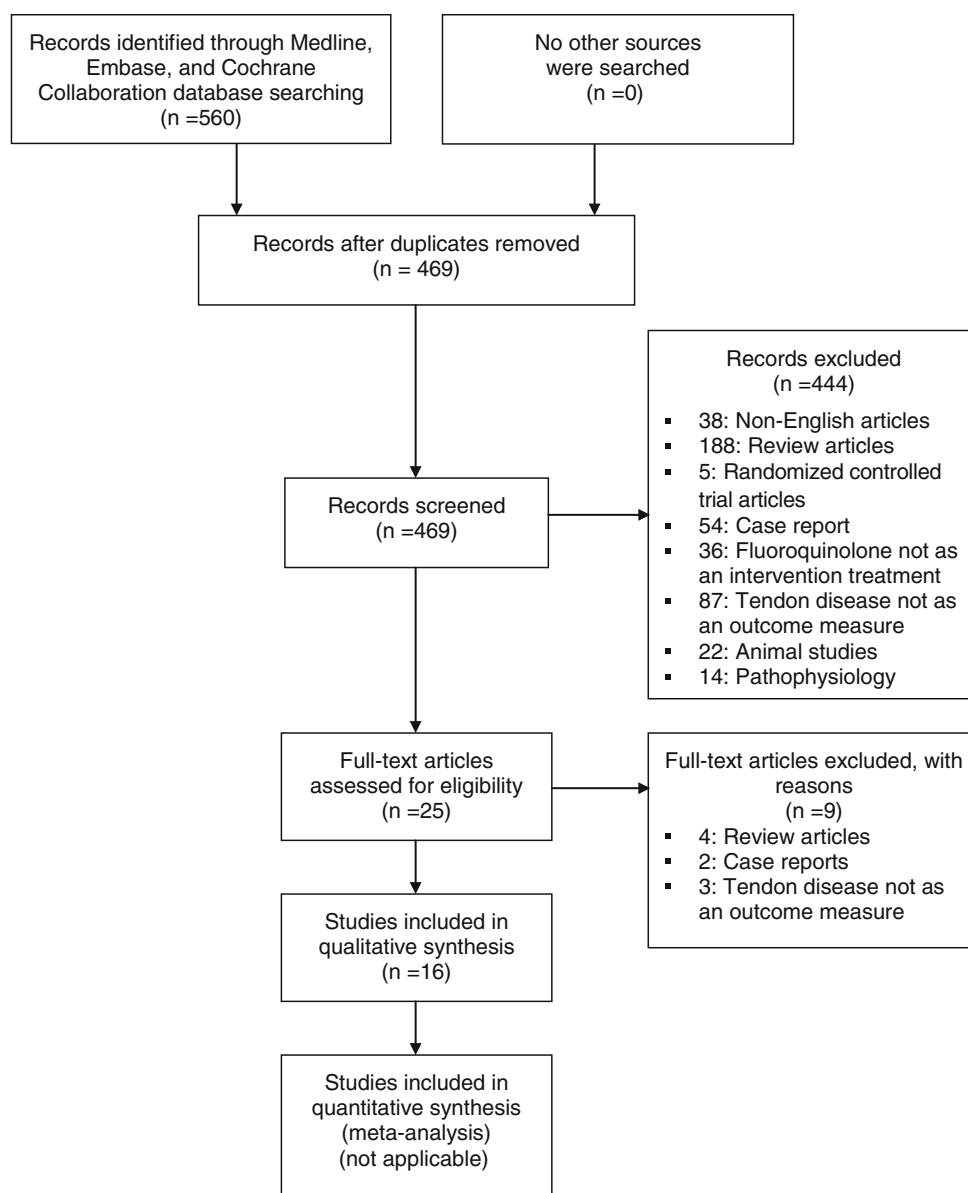
3.3 Timing of Tendon Injury

The time between the exposure and outcome varied between 15 days and 18 months in the five case-control studies. The three cohort studies followed individuals for either 30 or 90 days for the outcome [28, 30, 31]. The risk of Achilles tendon rupture seemed to be highest in the first month after exposure [17, 20, 21, 24] (Table 3). One study reported a continued statistically significant increased risk up to 6 months (OR 2.4; 95 % CI 1.5–3.7); however, results were not consistent across the studies [21].

3.4 Risk Factors for Tendon Injury

Risk factors for tendon injury are summarized in Table 4. Eight studies evaluated age as a risk factor for the tendon injury with inconsistent results. Three studies compared the

Fig. 1 PRISMA flowchart of the literature searches and selection process



risk of tendon disorders (Achilles tendon rupture in one study, composite outcome of tendon rupture, tendinitis or peri-tendinitis in the second study, and Achilles tendonitis in the third study) in those ≥ 60 years of age compared with those younger than 60 years of age. The risk of Achilles tendon rupture [20] and Achilles tendonitis [17] was significantly higher in those ≥ 60 years of age; however, the second study did not find a significant difference in tendon disorders in those ≥ 60 years of age compared with those younger than 60 years of age [28]. The remaining five studies did not specifically compare the risk in older versus younger populations but rather conducted a sub-group analysis based on age categories comparing the risk of tendon injury in exposed and unexposed individuals within a specific age group [17, 19, 21, 24, 30]. These subgroup

analyses did not yield statistically significant results in the risk of Achilles tendon rupture in the various age categories, with the exception of van der Linden et al. [21], who found that among those ≥ 80 years of age, the risk of tendon rupture was increased in those currently exposed to fluoroquinolone (OR 20.4; 95 % CI 4.6–90.1) as well as those recently exposed subjects (OR 7.4; 95 % CI 2.4–22.9). Individuals were considered currently exposed to fluoroquinolone if the index date fell within the prescription duration plus 30 days, and recently exposed to fluoroquinolone if the calculated prescription length was less than 180 days before the index date and the subject did not meet the definition of currently exposed. With respect to Achilles tendinitis and Achilles tendon disorders, van der Linden et al. [24] found a statistically significant

Table 2 Quality assessment of the included studies^a

Case control/cross-sectional/case-series studies ^b									
Studies	Case definition adequate	Representativeness of the cases	Selection of controls	Definition of controls	Comparability	Assessment of exposure	Same method of ascertainment	Non-response rate	Total quality score
Wise et al. [17]	Record linkage	Representative*	Community control*	No history of disease*	Yes**	Secure record*	Yes*	Yes*	8
Lapi et al. [18]	Independent validation*	Representative*	No description	No description of source	No	Interview not blinded	No	No	2
Seeger et al. [19]	Independent validation*	Representative*	Community control*	No history of disease*	Yes**	Secure record*	Yes*	Yes*	9
Corrao et al. [20]	Record linkage	Representative*	Community control*	No history of disease*	Yes**	Secure record*	Yes*	Yes*	8
van der Linden et al. [21]	Record linkage	Representative*	Community control*	No history of disease*	Yes**	Secure record*	Yes*	Yes*	8
Leone et al. [22]	Independent validation*	Representative*	No description	No description of source	No	Interview not blinded	No	No	2
Chhajed et al. [23]	Self-reports	Potential for selection bias	No description	No description of source	No	Written self-report	No	No designation	0
van der Linden et al. [24]	Record linkage	Representative*	Community control*	No history of disease*	Yes**	Secure record*	Yes*	Yes*	8
van der Linden et al. [25]	Self-reports	Potential for selection bias	No description	No description of source	No	Secure record*	No	No designation	1
van der Linden et al. [26]	Record linkage	Representative*	No description	No description of source	No	Secure record*	No	No designation	2
Pierfite and Royer [27]	Self-reports/record linkage	Potential for selection bias	No description	No description of source	No	No description	No	No designation	0
Cohort studies ^c									
Studies	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration	Comparability	Assessment of outcome	Follow-up long enough	Adequacy of follow-up	Total quality score
Hori et al. [28]	Somewhat representative*	Same community*	Secure record*	No	No	Record linkage*	Yes*	No	5
Barge-Caballero et al. [29]	Selected group	No non-exposed cohort	Secure record*	No	No	Independent assessment*	Yes*	No	3
Sode et al. [30]	Truly representative*	Same community*	Secure record*	No	Yes**	Record linkage*	Yes*	No	7
van der Linden et al. [31]	Truly representative*	Same community*	Secure record*	Yes*	Yes**	Record linkage*	Yes*	No	8
Wilton et al. [32]	Somewhat representative*	Same community*	Secure record*	No	No	Self-report	Yes*	No	4

^a Using the Newcastle-Ottawa Scale form. A study can be awarded a maximum of one star for each numbered item. A maximum of two stars can be given for comparability. The maximum quality score of all items could be nine. High-quality studies were deemed to have a score of 4.5 or greater

^b Using the Newcastle-Ottawa Scale form designed for case-control studies

^c Using Newcastle-Ottawa Scale form designed for cohort studies

Table 3 Tendon disease report: eight high-quality studies

Case-control studies									
Study	Exposure time before index date ^a	Type of tendon injury outcome		Achilles tendinitis			Any tendon disorders		
		Achilles tendon rupture ^b		Achilles tendinitis			Any tendon disorders		
		<i>n</i> (%) with FQ in case group	<i>n</i> (%) with FQ in control group	Adjusted OR (95 % CI)	<i>n</i> (%) with FQ in case group	<i>n</i> (%) with FQ in control group	Adjusted OR (95 % CI)	<i>n</i> (%) with FQ in case group	<i>n</i> (%) with FQ in control group
Wise et al. [17]	30 days	48 (0.6)	25 (0.3)	2.0 (1.2–3.3)	267 (0.9)	77 (0.3)	4.4 (3.3–5.9)		
Seeger et al. [19]	0–6 months	49 (5.2)	751 (4.0)	1.2 (0.9–1.7)					
Corrao et al. [20]	0–0.5 months	18 (0.08)	12 (0.01)	4.1 (1.8–9.6)				246 (1.14)	623 (0.61)
	0.5–1 months	4 (0.02)	10 (0.01)	1.9 (0.5–7.5)				144 (0.67)	489 (0.48)
	1–3 months	13 (0.06)	48 (0.05)	1.1 (0.5–2.2)				450 (2.06)	1,841 (1.77)
van der Linden et al. [21]	0–1 months	14 (1.06)	100 (0.20)	4.3 (2.4–7.8)					
	2–6 months	24 (1.73)	314 (0.64)	2.4 (1.5–3.7)					
	7–18 months	24 (1.73)	605 (1.22)	1.4 (0.9–2.1)					
van der Linden et al. [24] ^c	0–1 months	3 (17.6)	124 (3.1)	7.1 (1.7–29.1)	30 (9.9)	124 (3.1)	3.1 (2.0–4.8)		
	1–3 months	2 (11.8)	182 (4.6)	3.5 (0.7–17.3)	13 (4.3)	182 (4.6)	0.9 (0.5–1.6)		
	>3 months	4 (23.5)	839 (21.3)	1.4 (0.4–4.8)	56 (18.5)	839 (21.3)	0.8 (0.6–1.1)		
Cohort studies									
Study	No. of FQ exposure	No. of non-FQ exposure	Outcome measurement	Result					
Hori et al. [28]	17,147	Cephalosporins: 38,517	Tendon disorders	14 (0.082 %) in FQ group, 5 (0.013 %) in non-FQ group, RR = 6.29 (95 % CI 2.27–17.46)					
Sode et al. [30]	28,262	Background population	Achilles tendon rupture	Standardised incidence ratio: 3.1 (95 % CI 1.0–7.3)					
van der Linden et al. [31]	1,841	9,406	Achilles tendinitis	4 (0.2 %) in FQ group, 4 (0.1 %) in non-FQ group, adjusted RR = 3.7 (95 % CI 0.93–15.14)					

FQ fluoroquinolone, *n* number, OR odds ratio, RR relative risk

^a Index date refers to the diagnosis date of tendon disease (i.e. Achilles tendon rupture)

^b Wise et al. [17] reported tendon rupture as the outcome

^c van der Linden et al. [24] reported the results stratified by age. We reported the results of subjects who were aged 60 years or older

increase for those ≥ 60 years of age for both of these outcomes (Table 4). Corrao et al. [20] found no difference in the risk of tendon rupture (not specific to Achilles) or any tendon disorder between those below 60 years of age compared with those 60 years of age or older (p -value reported as >0.05).

van der Linden et al. [31] examined three fluoroquinolones—ofloxacin, ciprofloxacin and norfloxacin. A differential risk of tendon injury was found depending on the fluoroquinolone used. Ofloxacin appeared to have the highest risk of developing tendinitis [any area] (adjusted RR 4.9; 95 % CI 1.57–15.06) and Achilles tendinitis specifically (RR 10.1; 95 % CI 2.20–46.04), whereas the risk with ciprofloxacin or norfloxacin was not statistically significant compared with the non-fluoroquinolone reference group. Within this same paper, dosage and duration of fluoroquinolone was not evaluated due to the fact that essentially all courses were given for a similar duration and the majority of fluoroquinolone users took the same recommended daily dose. Seeger et al. [19] included ciprofloxacin, levofloxacin, ofloxacin and other non-specified fluoroquinolones and found no association between the type of fluoroquinolone used and the risk of Achilles tendon rupture. The cumulative fluoroquinolone dosage was calculated and the authors found a modestly higher risk (OR 1.5; 95 % CI 1.0–2.3) in the highest cumulative dose category (8000+ mg over 180 days), suggesting a dose-response relationship. van der Linden et al. [21] evaluated the association between tendon injury and both the type and dosage of fluoroquinolone used (ciprofloxacin, norfloxacin and ofloxacin were included in the study). The highest risk of Achilles tendon rupture was noted with ofloxacin (OR 28.4; 95 % CI 7.0–115.3) and this risk increased in those receiving a higher dosage as measured by the prescribed daily dosage equivalent. Finally, Hori et al. [28] found a differential risk of tendon disorders among fluoroquinolones compared with the reference population of subjects who received cephalosporins. Ofloxacin was associated with the highest risk (RR 80.2; 95 % CI 9.5–680.5) followed by moxifloxacin (RR 15.7; 95 % CI 3.1–81.0), tosufloxacin (RR 7.3; 95 % CI 1.4–37.5) and levofloxacin (RR 5.2; 95 % CI 1.7–15.5). An RR could not be estimated for the other fluoroquinolones examined in this study due to the fact that no outcomes were observed in those groups.

Corticosteroid use was evaluated as a risk factor for developing tendon injury in all five case-control studies, but was not specifically examined in the cohort or cross-sectional studies [17, 19–21, 24]. The route of administration of corticosteroids was specified as oral or systemic in two studies and not specified in three studies. All five studies reported an increased risk of Achilles tendon

rupture with an OR greater than 1 for those taking fluoroquinolone and corticosteroids; however, one of the studies reported results that were not statistically significant. Corrao et al. [20] showed that the OR was higher in those receiving fluoroquinolones and corticosteroids compared with those subjects receiving fluoroquinolones alone for Achilles tendon rupture and any tendon rupture. Similarly, van der Linden et al. [24] showed that for those aged 60 years or older, the OR for Achilles tendon disorders was 3.2 (95 % CI 2.1–4.9) in fluoroquinolone users compared with non-fluoroquinolone users, and that the OR increased to 6.2 (95 % CI 3.0–12.8) for those receiving fluoroquinolones and corticosteroids compared with non-fluoroquinolone users. van der Linden's second article published in 2003 [21] confirmed an increased risk for those over 60 years of age who were concomitantly treated with fluoroquinolones and corticosteroids. The risk of Achilles tendon rupture associated with current exposure to fluoroquinolones was increased (OR 5.3; 95 % CI 1.8–15.2) compared with non-fluoroquinolone users. This risk was significantly higher in those currently receiving or who recently took oral corticosteroids (OR 17.5; 95 % CI 5.0–60.9, and 18.4; 95 % CI 1.4–240.2, respectively) compared with non-fluoroquinolone users. Finally, Wise et al. [17] reported an increased risk in individuals with concomitant use of corticosteroids and fluoroquinolones compared with those taking fluoroquinolones without corticosteroids (OR 9.1; 95 % CI 4.6–18.0, and OR 3.2; 95 % CI 2.3–4.4, respectively), again supporting the claim that concomitant corticosteroids and fluoroquinolones increases the risk of adverse tendon events.

Obesity was found to be significantly associated with Achilles tendon rupture in one study [19] (OR 2.0; 95 % CI 1.2–3.1); however, a second study [17] found an increased risk of Achilles tendinitis in the non-obese population (OR 7.7; 95 % CI 4.3–13.7) compared with those who were obese (OR 2.4; 95 % CI 1.1–5.0). One study [19] found male sex to be a significant risk factor for tendon rupture (OR 3.0; 95 % CI 2.6–3.5). Two other studies [21, 24] reported the effect of fluoroquinolones on the occurrence of tendon rupture was not modified by sex, and a third study found a higher risk of Achilles tendinitis in women compared with men [17]. Corrao et al. [20] matched exposed and unexposed subjects on sex; therefore, the effect of sex on the outcome could not be evaluated. One study found the risk of Achilles tendinitis was significantly higher in those with diabetes who were taking fluoroquinolones (OR 7.0; 95 % CI 2.1–23.5) compared with non-diabetics (OR 4.1; 95 % CI 3.0–5.5) and in those with renal failure who were taking fluoroquinolones (OR 20.0; 95 % CI 2.7–149) compared with those without evidence of renal failure (OR 3.9; 95 % CI 2.9–5.2) [17].

Table 4 Risk factors related to tendon injury^a

Study	Risk factors			Concurrent corticosteroid use	
	Age (years)	FQ dosage	FQ type		
Achilles tendon rupture					
Seeger et al. [19]	18–59: 1.3 (0.9–1.8)	Cumulative dose <4,000 mg: 1.1 (0.5–2.2) 4,000–7,999 mg: 1.0 (0.6–1.8) 8,000+ mg: 1.5 (1.0–2.3) NR	Ofloxacin: 1.4 (0.6–3.6)	FQ only: 0.7 (0.2–1.9) ^b	
	≥60: 1.1 (0.5–2.3)		Levofloxacin: 0.6 (0.3–1.4) Ciprofloxacin: 1.4 (1.0–2.0) Others: 1.2 (1.0–1.4) NR	FQ + corticosteroid: 5.8 (0.9–38.6) ^b	
Corrao et al. [20]	Higher risk in ≥60 (<i>p</i> = 0.009)			FQ only: 3.0 (1.5–6.0) FQ + corticosteroid: 43.2 (5.5–341.1) FQ only: 5.3 (1.8–15.2) ^b FQ + corticosteroid: 17.5 (5.0–69.0) ^b	
van der Linden et al. [21]	Recent exposure: <60: 1.8 (1.0–3.5) 60–79: 2.0 (1.0–4.2) ≥80: 7.4 (2.4–22.9) Past use: <60: 0.6 (0.2–2.0) ≥60: 1.4 (0.4–4.8) Standardised incidence ratio: <60: 2.5 (0.5–7.4) ≥60: 4.0 (0.5–14.4)	Daily dose equivalents: 0.01–0.75: 1.7 (0.7–4.1) 0.76–1.25: 6.7 (3.8–11.7) >1.25: 12.5 (2.3–68.3) NR	Ofloxacin: 28.4 (7–115) Ciprofloxacin: 3.6 (1.4–9.1) Norfloxacin: 14.2 (1.6–128) NR	NR	
Sode et al. [30] ^c		NR	NR	NR	
Any tendon rupture					
Corrao et al. [20]	No difference (<i>p</i> = 0.7)	NR	NR	FQ only: 1.6 (1.3–2.0) FQ + corticosteroid: 3.1 (1.6–6.3)	
Achilles tendinitis					
Wise et al. [17]	<60: 1.6 (1.1–2.5) ≥60: 8.3 (5.4–12.8) <i>p</i> < 0.001 Current use: <60: 1.0 (0.5–1.8) ≥60: 3.1 (2.0–4.8) NR	NR	NR	FQ only: 3.2 (2.3–4.4) FQ + corticosteroid: 9.1 (4.6–18.0)	
van der Linden et al. [24]		NR	NR	NR	
van der Linden et al. [31] ^c		NR	Ofloxacin: 10.1 (2.2–46.0) Ciprofloxacin: 2.8 (0.3–25.2)	NR	
Achilles tendon disorders					
van der Linden et al. [24]	Current use: <60: 0.9 (0.5–1.6) ≥60: 3.2 (2.1–4.9)	NR	NR	FQ only: 3.2 (2.1–4.9) ^b FQ + corticosteroid: 6.2 (3.0–12.8) ^b	

Table 4 continued

Study	Risk factors		FQ dosage	FQ type	Concurrent corticosteroid use
	Age (years)				
Any tendon disorders					
Hori et al. [28] ^c	No significant difference ≥60 vs. <60: 0.83 (0.29–2.38)	NR	Levofloxacin: 5.2 (1.7–15.5) Tosufloxacin: 7.3 (1.4–37.5) Moxifloxacin: 15.7 (3.1–81.0) Ofloxacin: 80.2 (9.5–680.5)	NR	
Corrao et al. [20]	No difference (<i>p</i> = 0.7)	NR		NR	FQ only: 1.7 (1.5–1.9) FQ + corticosteroid: 1.8 (1.1–2.9)

FQ fluoroquinolone, NR not reported

^a We reported odds ratio (95 % CI) of comparison between exposure group and non-exposed unless otherwise indicated^b In those aged >60 years^c Numbers were reported as relative risk (95 % CI)

4 Discussion

The results of this review suggest that there is a significant association between fluoroquinolone use and tendon injury, in particular Achilles tendon rupture and tendinitis, which has been shown using different study designs and in different populations. Fluoroquinolone-associated tendinopathy is relatively uncommon, but when it occurs it tends to happen soon after exposure (within the first month). High-risk groups include those on concomitant corticosteroids and possibly the elderly population. Despite only a small number of relevant studies, tendon injury may be more common with specific fluoroquinolones, and higher dosages may be associated with higher risk. The current literature is problematic in that published studies examined different tendon outcomes and often relied on self-reporting, the specific fluoroquinolones included in the studies varied, newer fluoroquinolones were not extensively studied and the risk factors evaluated were inconsistent across the published studies, which limits the conclusions that can be drawn. Furthermore, there is a spectrum of disease in terms of tendon injury related to fluoroquinolone use. The majority of studies focused on Achilles tendon injury, although case reports of other tendons being affected by fluoroquinolones have been published [33, 34].

The pathophysiology of tendon injury following fluoroquinolone exposure is not completely understood and it is likely that the negative effect of fluoroquinolones on tendons is multifactorial. Animal models have shown that, following exposure to fluoroquinolones, there was an increase in matrix-degrading activity and a decrease in matrix synthesis and fibroblast cell proliferation, thereby weakening the tendon and increasing the risk of rupture [35]. Transmembrane proteins, called integrins, are involved in the structural stability of a cell and these proteins rely on magnesium as well as other cations. Fluoroquinolone antibiotics are known to chelate cations, thus potentially altering the stability of the cell structure weakening the tendon [36]. Exposure to fluoroquinolones stimulates oxygen radical production and induces matrix metalloproteinases, which are enzymes involved in tendon remodelling [37]. In addition to the potentially direct toxic effects of fluoroquinolones on tendons, increasing age and steroid use can weaken tendons further, which has been shown to increase the risk of tendon injury.

Despite its relatively low incidence, increasing vigilance and awareness of the association between fluoroquinolones and tendon injury is important for several reasons. The apparent disconnect between antibiotics used to treat an infection and seemingly unrelated inflammation of a tendon creates a situation whereby the physician who initially prescribed the drug may not be the same physician who is told about or who treats the complication. As such, it is

possible to miss the connection altogether, particularly if the patient and physician are not familiar with this adverse event. Although there is limited evidence to guide therapy of fluoroquinolone-induced tendinopathy, once symptoms of tendinitis occur the antibiotic should be discontinued and anti-inflammatory medications may be prescribed to control symptoms and possibly decrease the risk of a complete tendon rupture [38, 39]. Knowledge of this association is critical to ensure a timely diagnosis and management of this adverse event. Secondly, these medications are commonly prescribed and several treatment alternatives exist which could be considered for individuals at considerable risk for tendon injury. For example, the newer respiratory fluoroquinolones are recommended for management of CAP or treatment of COPD exacerbations. Individuals with COPD are often elderly and may be concomitantly treated with systemic corticosteroids. In these circumstances, alternative antibiotic therapy could be considered since both age and corticosteroid use significantly increases the risk of tendon injury, including rupture.

Strengths of our review include the systematic and comprehensive literature search, the fact that each study was evaluated for quality using a standard scale, and three reviewers independently evaluated the articles for inclusion. There are several limitations of the existing literature on fluoroquinolones and tendon injury. Due to the fact that tendon injury is a relatively rare adverse event related to fluoroquinolone use, and randomized controlled trials exclude those at highest risk of adverse events, we must utilize observational research which often includes self-report data. Self-report is typically an underestimate of the true prevalence of an adverse event since many individuals may not go to the effort of reporting the complication or, alternatively, they may not recognize the condition as an adverse event of a prescribed medication. The majority of observational studies identified in our search were either of low quality to be able to draw firm conclusions, or in a specific sub-population (e.g. transplant) and hence not generalizable. Of the high-quality studies examined, the newer respiratory fluoroquinolones such as moxifloxacin and levofloxacin were under-represented. These antibiotics are broadly used in the respiratory population and more information is needed to quantify the risk of tendon injury with these medications. The literature suggests that corticosteroid use and possibly age increase the risk of fluoroquinolone-associated tendon injury; however, other possible risk factors have not been adequately evaluated, e.g. the impact of renal failure, dose or duration of fluoroquinolone use and recent joint surgery, among others. Recent case reports have suggested that statins increase the risk of tendon rupture [40] and, given the prevalence with which this class of medication is used in the population, it

is possible that fluoroquinolone use in an individual taking statins may increase the risk of tendon injury above that of fluoroquinolone alone; however, this has never been formally evaluated.

5 Conclusion

Published observational studies show that there is an increased risk of Achilles tendon rupture and Achilles tendinitis (specifically in individuals ≥ 60 years of age) with exposure to fluoroquinolone antibiotic therapy. Those taking concomitant corticosteroids are at increased risk for this adverse event. Several unanswered questions remain with respect to the impact of fluoroquinolones on tendons other than the Achilles, which additional high-risk groups exist if any, and the impact of dosage and type of fluoroquinolone on the risk of tendon injury, which are all areas of future research.

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Author Contributions Dr. Stephenson had full access to all of the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, and had final responsibility for the decision to submit for publication. Study concept and design, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content was carried out by Drs Stephenson and Rochon, Mr. Wu and Mr. Cortes; acquisition of data was undertaken by Drs Stephenson, Wu and Cortes; statistical analysis was carried out by Drs Stephenson and Wu; funding was obtained by Dr Rochon; and study supervision was carried out by Dr Rochon.

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