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High Incidence of New-Onset Joint Pain in Patients on Fluoroquinolones as Antituberculous Treatment

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Keywords
Tuberculosis · Joint pain · Fluoroquinolones

Abstract
Background: Joint pain is frequently observed in patients on antituberculous treatment, and pyrazinamide is known to be associated with joint pain in patients receiving antituberculous treatment. Fluoroquinolone-associated joint pain and tendon injury have been reported in long-term corticosteroid and transplant recipients, but data are lacking in patients with tuberculosis. ***Objectives:*** The objective of this study was to examine the incidence of joint pain manifested during administration of antituberculous therapy and their association with fluoroquinolones. ***Methods:*** Patients diagnosed with tuberculosis attending the outpatient clinic over a period of 1 year were reviewed and divided into 3 groups: group A receiving pyrazinamide, group B receiving a fluoroquinolone, and group C receiving both pyrazinamide and a fluoroquinolone. Latency to onset of joint pain was noted in all 3 groups. Joint pain was initially managed with analgesics, and associated hyperuricemia was treated with allopurinol/febuxostat. Causative drugs were stopped in case of intolerable joint pain. ***Results:*** 260 patients (47% females, aged 38 ± 18 years; mean ± SD) were included [group A (n = 140), group B (n = 81), and group C (n = 39)]. Overall, 76/260 (29%) patients developed joint pain: group A – 24/140 patients (17%), group B – 32/81 patients (40%), and group C – 20/39 patients (51%). The median latency to the onset of joint pain was 83 days (interquartile range, IQR 40–167): 55 days (IQR 32–66) in group A, 138 days (IQR 74–278) in group B, and 88 days (IQR 34–183) in group C. Hyperuricemia was present in 12/24 (50%) patients in group A and 11/20 (55%) patients in group C. Pyrazinamide was stopped in 7/140 (5%) patients in group A, fluoroquinolones in 6/81 (7%) patients in group B, and both pyrazinamide and fluoroquinolones were stopped in 5/39 (13%) patients in group C because of intolerable joint pain. Major joints affected were knees and ankles. ***Conclusion:*** There is a high incidence of joint pain in patients receiving antituberculous treatment, which is higher when fluoroquinolones or the pyrazinamide-fluoroquinolone combination are administered as compared to pyrazinamide alone.

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Introduction

In clinical practice, it has been observed that joint pain or arthralgia is often experienced by patients receiving antituberculous treatment (ATT), with an incidence ranging from 4.7 to 14.4% [1, 2]. There is a paucity of data regarding the manifestation of joint pain in patients on ATT. Limited data are available referring to pyrazinamide (PZA) as a cause of joint pain, which is frequently attributed to an increase in serum uric acid levels [3–5]. Such joint pain is usually self-limiting, responds to analgesics, and is reversible after stopping the causative drug; sometimes, it may require the use of drugs such as allopurinol or febuxostat due to hyperuricemia [3].

It has been reported that patients receiving fluoroquinolones (FQs) as part of ATT may manifest joint pain/arthralgias. FQs are known to cause arthralgia, tendonitis, and even tendon rupture [6–9]. We observed some of these reactions in patients receiving FQs in the form of levofloxacin (Lfx) or moxifloxacin (Mfx). FQs are an integral part of drug-resistant (DR) tuberculosis (TB) treatment [10, 11]. Furthermore, later generations of FQs, namely Lfx and Mfx, have been reported to be correlated with improved outcomes in multidrug-resistant (MDR)-TB [12]. They may also be administered when patients develop side effects with first-line ATT drugs in drug-sensitive TB (DS-TB) and sometimes as augmented therapy in cases of disseminated disease. Joint pain manifesting during ATT can cause significant morbidity [13]. Typically, in clinical practice, such joint pain is treated with analgesics, allopurinol, or febuxostat in patients with elevated uric acid, or PZA and/or FQ treatment is discontinued. To our knowledge, there are no data available regarding the incidence of joint pain when FQs are administered as part of ATT. The objective of the current study was to examine the incidence of joint pain manifesting during ATT and to study their association with FQ treatment.

Patients and Methods

Patients who were diagnosed and treated for TB attending the outpatient clinic in a tertiary care center in Western India from July 2017 to June 2018 were reviewed. Patients who were diagnosed with TB before but were continuing anti-TB treatment during the study period were also reviewed. Overall, 368 patients diagnosed with TB who had attended the outpatient clinic were reviewed. These patients who were either already on ATT, were initiated on ATT, or were followed up after completion of ATT were included in the current study. The medical records were reviewed. A detailed history related to joint pain was asked at every follow-up visit at intervals of 4–6 weeks. Patients with preexisting joint pain prior to starting ATT ($n = 9$), patients with a follow-up <3 months ($n = 15$), and patients who came for specialist opinion and were referred back to their primary physician ($n = 84$) were excluded from the analysis. In total, 108 patients were excluded. Therefore, 260 patients remained in the analysis.

Table 1. Characteristics of the patients included in the study ($n = 260$)

Characteristics	Patients, *n* (%)
Female	47%
Mean age ± SD, years	38±18
Coexisting comorbidities	
Diabetes	34 (13%)
Hypertension	30 (12%)
Hypothyroidism	14 (5.4%)
Hepatitis C	1 (0.4%)
Chronic liver disease	2 (0.8%)
Hepatocellular carcinoma	1 (0.4%)
Hypersensitivity pneumonitis	1 (0.4%)
Sarcoidosis	2 (0.8%)
Primary Sjögren syndrome	1 (0.4%)
HIV	1 (0.4%)
Mean duration of treatment ± SD, days	389±230
Mean duration of follow up ± SD, days	396±357

First-line ATT was administered using standard medication (rifampicin, isoniazid, ethambutol, and PZA). Patients having DR-TB were administered second-line ATT as per Revised National Tuberculosis Control Program guidelines or individualized treatment regimen as described elsewhere [14–16]. FQs were administered to patients who developed side effects with first-line ATT and received FQs as replacement or as a part of the DR-TB regimen, or augmentation of first-line ATT in cases of disseminated disease.

Patients who developed joint pain were initially managed with analgesics, mainly paracetamol and, in some cases, ibuprofen. Serum uric acid levels were checked in patients who were receiving PZA. Hyperuricemia was defined as a serum uric acid concentration >6.5 mg/dL. Patients who had associated hyperuricemia were additionally treated with allopurinol or febuxostat. PZA was discontinued in patients having intolerable joint pain despite administration of analgesics or allopurinol/febuxostat. FQs were discontinued in patients having intolerable joint pain despite analgesics.

Patients were divided into 3 groups based on the administration of PZA and/or FQs (only PZA – group A, only FQ – group B, and both PZA plus FQs – group C). Patients who developed joint pain after stopping PZA and subsequent initiation of FQs were included in group B. Those patients who were administered both PZA and FQs and subsequently developed joint pain were included in group C.

The data are presented as means ± SD (range) and medians with interquartile ranges, as applicable. All patient records were anonymized and de-identified.

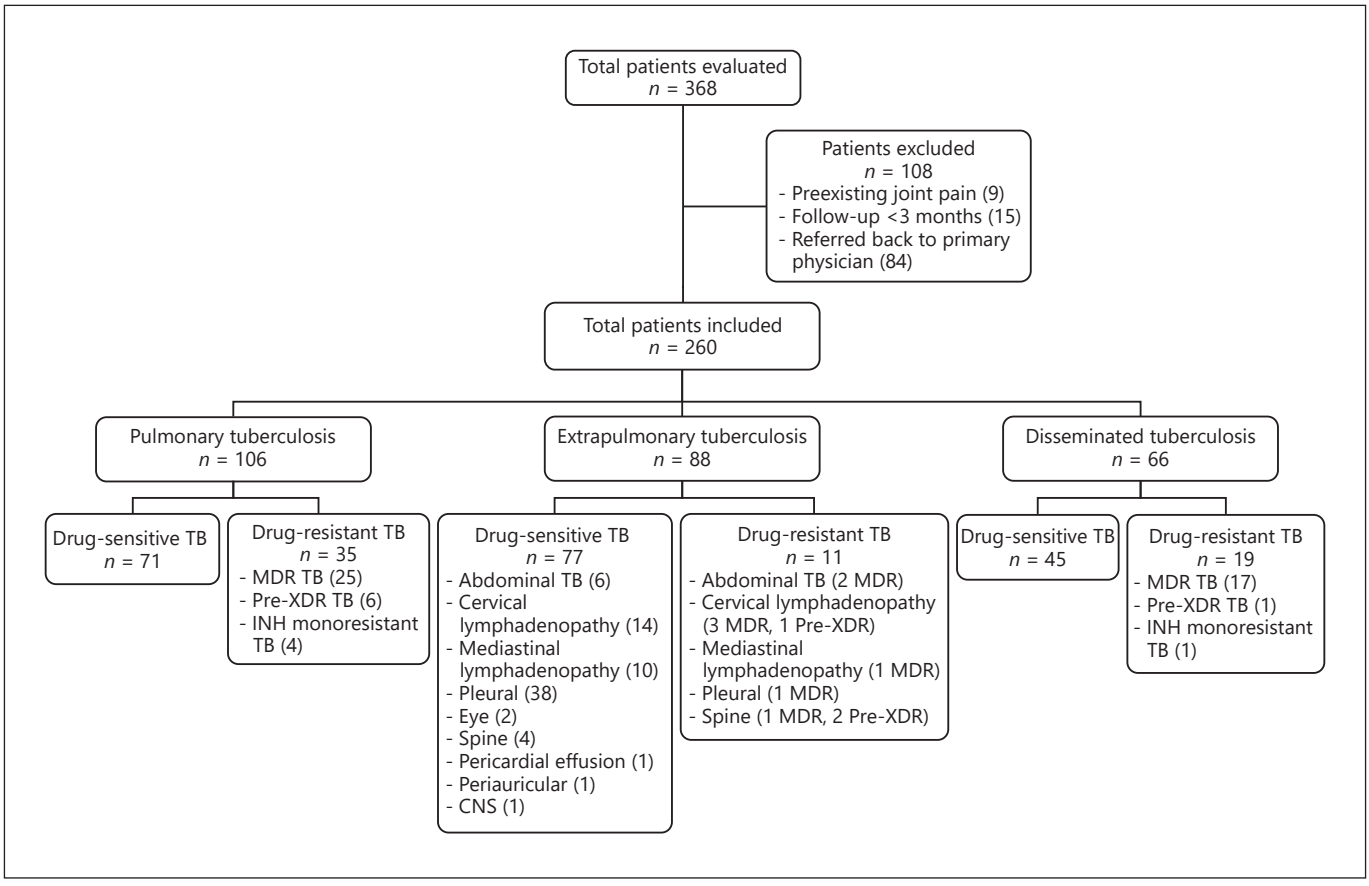

Fig. 1. Flowchart of the study selection process. INH, isoniazid; XDR, extensively drug-resistant tuberculosis.

Results

A total of 260 patients were included in the current study (47% females; mean age ± SD: 38 ± 18 years; Table 1). Two hundred patients (77%) received first-line ATT, and 60 patients (23%) had DR-TB. Of the 260 patients, 128 patients (49%) completed treatment (104 first-line ATT and 24 DR-TB), and 132 patients (51%) were still on treatment (96 first-line ATT and 36 DR-TB). Figure 1 shows the distribution of patients on the basis of site and type of tuberculosis. Amongst the 200 patients who received first-line ATT, 139 patients (71%) received only PZA along with other first-line ATT, and 60 patients (31%) received a FQ (Lfx 53 patients and Mfx 7 patients) with or without PZA. The indications for FQ administration include hepatitis on first-line ATT (34 patients), ethambutol-induced ocular toxicity (2 patients), isoniazid-induced psychosis (1 patient), and augmentation of first-line ATT in case of disseminated disease (23 patients). All patients with DR-TB were administered a FQ. Therefore,120/260 patients (46%) received a FQ (Lfx 74 patients and Mfx 46 patients).

Overall, 140/260 patients (54%) were in group A, 81/260 patients (31%) in group B, and 39/260 (15%) patients in group C. The mean duration of treatment was 389 ± 230 days (Table 2). PZA was administered for a mean of 99 ± 34 days in group A and 203 ± 136 days in group C. FQs were administered for a mean of 385 ± 312 days in group B and 305 ± 209 days in group C.

Overall, 76/260 (29%) patients developed joint pain: 24/140 patients (17%) in group A, 32/81 patients (40%) in group B, and 20/39 patients (51%) in group C (Table 1). The incidence of joint pain was 6.9 per 10 exposure years in group A, 6.2 per 10 exposure years in group B, and 4.3 per 10 exposure years in group C. Incidence ratio between group A and group B was 1.1 while it was 1.6 between group A and group C. The overall median latency to onset of joint pain was 83 days (IQR 40–167): 54 days (IQR 32–66) in group A, 138 days (IQR 74–278) in group B, and 88 days (IQR 34–183) in group

Table 2. Clinical details of patients with joint pain

Total patients (n = 260)	Group A (n = 140; 54%)	Group B (n = 81; 31%)	Group C (n = 39; 15%)
Females, %	49	47	44
Mean age ± SD, years	38±18	36±17	39±19
Mean duration of treatment ± SD (range), days	308±142 (99–887)	495±276 (119–1,461)	427±220 (113–768)
Total joint pain (n = 76; 29%), n	24 (17%)	32 (40%)	20 (51%)
Females, %	54	41	50
Mean age ± SD, years	31±11	40±17	39±19
Median latency until onset of joint pain, days	54	138	88
Interquartile range	32–66	74–278	34–183
Incidence rate, exposure per year	3.58	2.35	1.02
Associated hyperuricemia, n	12 (50%)	–	11 (55%)
Fluoroquinolone, levoflaxacin:moxifloxacin	–	21:11	14:6

Group A, only pyrazinamide; group B, only fluoroquinolones; group C, both pyrazinamide and fluoroquinolones.

Table 3. Joints in which arthralgia developed, according to treatment group (numbers refer to patients)

Groups	Knee joint	Ankle joint	Hip joint	Small joints	Shoulder joint	Back	Elbow joint
Group A	18	15	1	1	1	0	0
Group B	24	15	5	7	9	3	3
Group C	16	9	4	5	6	1	1
Total	59	40	11	14	17	5	5

Group A, only PZA; group B, only fluoroquinolones; group C, both PZA and fluoroquinolones.

C. The difference in the latency of joint pain in the 3 groups was statistically significant ($p < 0.0002$). Hyperuricemia was present in 12/24 (50%) patients in group A and 11/20 (55%) patients in group C. None of the patients in group B manifested hyperuricemia. The occurrence of joint pain was correlated with comorbidities like hypertension, diabetes, and hypothyroidism, but there was no statistically significant correlation ($p > 0.05$).

PZA was stopped in 7/140 (5%) patients in group A, FQs were stopped in 6/81 (7%) patients in group B, and both PZA and FQs were stopped in 5/39 patients in group C (13%) because of intolerable joint pain. The major joints affected were the knee (78%) and ankle joints (53%) in all of the groups (Table 3). Other joints involved were shoulder, elbow, hip, and small joints of the hands and feet. Pain was present only on movement. Tenderness or swelling were not observed. None of the patients were diagnosed with Achilles tendon rupture. None of the patients with spine TB (7 patients) developed joint pain. In 2 patients, Mfx was stopped temporarily for prolonged QTc interval. These patients were receiving high-dose Mfx at 600 mg per day. Mfx was subsequently re-introduced at 400 mg per day.

Discussion

The reported incidence of joint pain in patients receiving ATT ranges from 4.7 to 14.4% [1, 2]. The current study showed a relatively higher overall incidence of joint pain at 29% in patients receiving ATT (group A 17%, group B 40%, and group C 51%). To the best of our knowledge, there are no previously published data regarding joint pain related to FQs in patients receiving ATT. The findings of the present study reveal that there is a high incidence of joint pain in patients receiving ATT, and it is higher in those receiving FQs or PZA combined with FQs.

A recent study reported the occurrence of joint pain on average after the 4th month of starting ATT and did

not attribute the joint pain to any ATT medication in most of the patients [1]. In the current study, the median latency to the onset of joint pain was 83 days after initiation of ATT. Furthermore, the median latency to the onset of joint pain was significantly earlier in patients receiving only PZA (54 days) in comparison to those who received a FQ alone (138 days) or a FQ-PZA combination therapy (88 days). The onset of joint pain in patients receiving ATT in the present study was much earlier than previously reported [1]. In the study by Dela et al. [11], patients received FQs and PZA as part of MDR-TB regimen, but the authors did not look at the onset of joint pain separately for FQs and PZA. Hence, this may be a possible reason for the difference in the latency to onset of joint pains compared to our study.

PZA is reported to cause joint pain by inhibiting renal excretion of urate by inhibiting its renal tubular secretion, resulting in some degree of hyperuricemia [3]. In the current study, only 50% patients in group A who manifested joint pain had hyperuricemia and 55% patients in group C. This could be attributed to the uricosuric effect of rifampicin [17]. Joint pain was nondeforming and nonerosive, and this is consistent with earlier reports [4]. In the current study, only PZA-associated joint pain was observed in 17% of patients receiving only PZA (group A), which is similar to the findings by Inoue et al. [18] who reported an incidence of 17.6%.

The incidence of FQ-induced arthralgia in patients receiving FQs for a short duration ranges from 0.14 to 0.4% [19–21]. However, in patients receiving Lfx for more than 1 year for treatment of sinusitis, the reported incidence of arthralgia and/or myalgia was 25% [22]. In our study, 40% of patients who received FQs (group B) and 51% of patients who received both FQs and PZA (group C) manifested joint pain. Thus, the incidence of joint pain related to FQ administration in patients receiving ATT is high in comparison to earlier reports when administered for other indications. Furthermore, this incidence is higher in those receiving PZA and FQ combined. This high incidence of joint pain in our study is plausibly related to the longer duration of drug administration.

The exact mechanism of FQ-associated arthralgia is not clear. FQs exert toxic effects on tendons, cartilage, bone, and muscle [9]. In vitro studies have suggested that FQs may contribute to tendinopathies by inhibiting collagen maturation, reducing cell stability, and directly degrading matrix [23]. They also stimulate reactive oxygen species resulting in tendon toxicity along with changes in signaling protein function leading to alterations in cell regulation and repair [9]. These factors may also be speculated to cause arthralgia. An increased risk of FQ-induced tendinopathy including Achilles tendon rupture has been reported in patients on long-term corticosteroids and transplant recipients [7, 23]. Achilles tendinopathy has also been reported after ophthalmic Mfx [24]. None of the patients in the current study were transplant recipients or received corticosteroids.

The most commonly implicated FQs for arthropathy/tendinopathy include pefloxacin, ofloxacin, norfloxacin, ciprofloxacin, and Lfx [24]. To the best of our knowledge, there are limited data on arthralgias/tendinopathies with oral administration of Mfx and Lfx [22, 25–30]. In the current study, 47% of patients who were administered Lfx and 37% administered Mfx developed joint pain. This study demonstrates that Lfx and Mfx are associated with a high incidence of joint pain when administered as part of ATT. This is a very important clinical observation and impacts the management of patients receiving Lfx or Mfx. Furthermore, these medications may need to be stopped in patients with intolerable joint pain (29% in group A, 19% in group B, and 25% in group C). These findings also suggest that joint pain manifesting during ATT causes significant morbidity and may necessitate stopping the implicated medication. In our study patients, joint pain related to FQs was tolerable, and patients were encouraged and counseled to continue FQs as they are the core drugs of DR-TB and are associated with improved treatment outcomes. This information is very important clinically as clinicians need to be aware of the adverse effects of the medication and the causative drugs. In cases where joint pains are not tolerable, then a decision needs to be taken as to which medication needs to be stopped. Patients also need to be told about the potential side effects. Therefore, we believe that joint pain as a side effect of anti-TB medication is of important clinical relevance. Further studies are urgently required to quantify the joint pain and assess the associated long-term sequelae.

The limitations of the current study include its observational and retrospective nature; data were gathered from a clinical practice setting where patients were managed based on clinical decision making of the physicians. Being an observational and retrospective study, there can be both underestimation of joint pain as the records were reviewed, and overestimation of joint pain as patients were specifically asked about the presence or absence of joint pain. The systematic quantification of joint pain, the sequelae, time to recovery, detailed imaging, and possible drug interactions were not within the scope of the current study. Correlation of joint pain with age, smoking, weight, and type of work was also beyond the scope of the study.

Imaging was done in selected patients to rule out bone TB as suspected by the treating physician. In spite of these limitations, it should be highlighted that the data of the current study are from a real-world clinical practice setting and provide a clear indication that certain important ATT medications like PZA and FQs may need to be withdrawn because of side effects. Such debilitating adverse drug reactions cause significant morbidity in patients receiving ATT in addition to the morbidity of the existing TB disease. A large prospective study should be conducted including quantification of joint pain related to FQs with detailed imaging, time to recovery, and long-term sequelae. Studies assessing the possible risk factors and drug interactions of other anti-TB drugs should be conducted.

In summary, there is a high incidence of joint pain in patients receiving ATT. The occurrence of joint pain is higher when a FQ or a FQ-PZA combination is administered as ATT compared to PZA alone. The morbidity associated with the onset of joint pain during ATT may necessitate cessation of PZA and/or the FQ. This is the first large study to report on the incidence and implication of FQs in the development of new-onset joint pain in patients receiving ATT.

Statement of Ethics

The study was approved by the Ethics Committee of the Fortis Hiranandani Hospital, Navi Mumbai.

Disclosure Statement

All authors declare no competing interests

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Author Contributions

P.N.C. conceived the research idea. P.N.C., N.P.M., P.J.V., V.B.C., and T.T.L. collected data. P.N.C. and N.P.M. did literature search. P.N.C., N.P.M., J.D.L., and A.B.L.-T. did data analysis and wrote the manuscript. All authors contributed to data interpretation, critically reviewed the manuscript, and approved the final version of the manuscript for publication..

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