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Original Research Article

Frequency of Hyperuricemia in Tuberculosis Patients Treated with Pyrazinamide

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Abstract: *Tuberculosis (TB) remains a major public health concern, and pyrazinamide is a key component of first-line anti-tuberculosis therapy. However, pyrazinamide is well known to cause hyperuricemia, which may lead to treatment intolerance, arthralgia, and non-compliance. Understanding its frequency and associated risk factors is essential for improving patient management.* ***Objective:*** *To determine the frequency of pyrazinamide-induced hyperuricemia in patients with pulmonary and extrapulmonary tuberculosis in the Medicine Unit of Hayatabad Medical Complex, Peshawar.* ***Methods:*** *This descriptive cross-sectional study included 151 patients aged 18–65 years with confirmed pulmonary or extrapulmonary tuberculosis. All participants had normal baseline renal and liver function tests and serum uric acid levels below 6.5 mg/dL before treatment initiation. Hyperuricemia after four weeks of pyrazinamide-containing anti-TB therapy was defined as serum uric acid >7.0 mg/dL in males and >6.5 mg/dL in females. Data were analyzed using SPSS version 22, with significance set at $p < 0.05$.* ***Results:*** *The mean age of participants was 42.46 ± 13.11 years, including 85 (56.3%) males. Pulmonary TB was present in 119 (78.8%) patients. Hyperuricemia developed in 72 (47.7%) patients. Significant associations were observed between hyperuricemia and middle age ($p = 0.002$), male gender ($p < 0.001$), and prolonged duration of TB before treatment initiation ($p = 0.003$)—conclusion**:** Nearly half of the TB patients receiving pyrazinamide developed hyperuricemia. Male gender, middle age, and longer pre-treatment disease duration were significantly associated with risk factors. Routine monitoring of serum uric acid during therapy is recommended to prevent complications and improve treatment adherence.*

Keywords: Hyperuricemia, Pyrazinamide, Tuberculosis, Adverse Drug Reaction, Serum Uric Acid

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Introduction

Tuberculosis (TB) continues to pose a public health challenge affecting people worldwide. Standard management of TB relies on a multidrug regimen in which pyrazinamide, a nicotinamide derivative, plays a pivotal role due to its intracellular bactericidal activity during the intensive initial phase of therapy. Pyrazinamide exerts its effect by targeting *Mycobacterium TB* in acidic microenvironments within macrophages and inflamed tissues, thereby facilitating shorter treatment durations and a lower likelihood of disease relapse (1-4). Pyrazinamide is associated with metabolic adverse effects, such as hyperuricemia. Elevated serum uric acid levels can be accompanied by joint pain and manifest with symptoms resembling gout. Such complications can impact patient adherence to therapy among individuals with preexisting metabolic disorders. Some patients report arthralgia that does not correspond directly to serum uric acid concentrations, yet discomfort still necessitates management, often employing NSAIDs. Aspirin has demonstrated uricosuric properties, suggesting potential utility in both alleviating Pyrazinamide-related arthralgia and reducing hyperuricemia itself (3-6).

Regional studies have examined disease-specific factors influencing the development of hyperuricemia during Pyrazinamide treatment. These investigations have recognized male sex, along with indicators of disease severity, including pleural effusion and radiological evidence of tuberculosis, as predictors of elevated serum uric acid. These findings underscore the importance of patient considerations when monitoring for Pyrazinamide-related metabolic complications as they influence both therapeutic outcomes and need for interventions (7-11).

Despite the proven efficacy of Pyrazinamide in shortening TB treatment and reducing relapse rates. Metabolic side effects, particularly hyperuricemia, complicate its use. There is a lack of region-specific data, especially from high TB burden countries like Pakistan. Understanding the frequency of hyperuricemia during Pyrazinamide therapy is therefore critical for optimizing clinical management and improving adherence to TB treatment protocols.

Methodology

This descriptive cross-sectional study was conducted in the Medicine Department at Hayatabad Medical Complex, Peshawar, from 24 May 2024 to 24 November 2024. Ethical approval was taken from the hospital (HMC-QAD-F-00). The sample size was 151 patients. This calculation was based on the proportion of 11% hyperuricemia among tuberculosis patients treated with pyrazinamide (12). A 95% confidence level and an absolute precision of 5% were applied. Consecutive non-probability sampling was used to enroll patients.

Patients aged between 18 and 65 years of either gender, with a confirmed Diagnosis of tuberculosis, either pulmonary or extrapulmonary. Diagnosis was based on clinical history, examination, chest radiography, sputum acid-fast bacilli (AFB) analysis, pleural fluid examination using GeneXpert, and a serum uric acid level below 6.5 mg/dl before the initiation of anti-tuberculosis therapy, with no prior history of joint pain and normal hepatic and renal function profiles. Patients with hepatic or renal dysfunction, diabetes mellitus, gouty arthritis, or pre-existing cardiac illness, as well as those using medications known to elevate uric acid levels, such as certain diuretics (e.g., metolazone, chlorothiazide), anticancer drugs, or low-dose aspirin, were not included.

Consent was obtained from every patient. Patients were enrolled from the outpatient department, tuberculosis clinics, and medical wards. All enrolled patients had been receiving a standard anti-tuberculosis drug regimen that included pyrazinamide for 4 weeks at the time of assessment. Hyperuricemia was assessed in all patients, defined as a serum uric acid level exceeding 7.0 mg/dl in male patients and 6.5 mg/dl in female patients.

SPSS 22 was used for analysis. Age and duration of TB were calculated using the mean and standard deviation. Hyperuricemia, gender, and type

of TB were presented as frequency and percentages. The Chi-Square test was used to assess the association of hyperuricemia with gender, age, duration of TB, and type of TB. A P-value ≤ 0.05 was considered significant.

Table 1: Association of hyperuricemia with duration of tuberculosis (Months)

Hyperuricemia	N	Mean	Std. Deviation	P value
Yes	72	5.88	2.069	0.003
No	79	4.91	1.827	

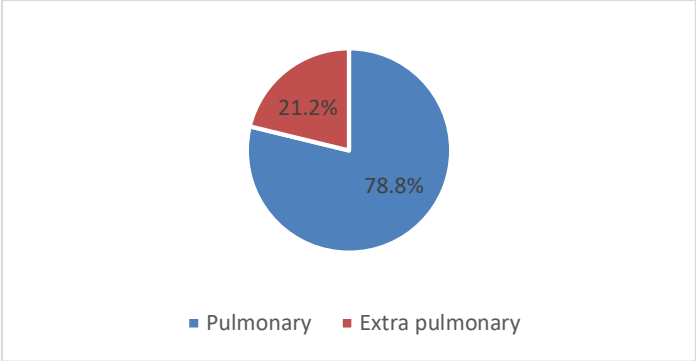

Figure 1: Type of tuberculosis

Table 2: Association of hyperuricemia with various parameters

Parameters		Hyperuricemia				P value
		Yes		No		
		n	%	n	%	
Age groups (Years)	18 to 35	12	16.7%	31	39.2%	0.002
	36 to 50	37	51.4%	22	27.8%	
	> 50	23	31.9%	26	32.9%	
Gender	Male	54	75.0%	31	39.2%	< 0.001
	Female	18	25.0%	48	60.8%	
Tuberculosis	Pulmonary	57	79.2%	62	78.5%	0.91
	Extra pulmonary	15	20.8%	17	21.5%	

Results

This study included 151 patients, with a mean age of 42.46 ± 13.105 years. The mean duration of tuberculosis illness was 5.37 ± 1.99 months. In terms of gender distribution, eighty-five (56.3%) were male, while 66 (43.7%) were female. A significant majority, 119 (78.8%), were diagnosed with pulmonary tuberculosis (Figure 1).

Analysis of hyperuricemia across age groups showed that it was higher in the 36–50-year age bracket (P = 0.002). Hyperuricemia was more common in male patients (P < 0.001) (Table II).

Hyperuricemia was diagnosed in 72 patients (47.7%). The mean duration of illness among those with hyperuricemia was 5.88 ± 2.06 months, significantly higher than the mean of 4.91 ± 1.82 months observed in the 79 patients without hyperuricemia (Table I).

Discussion

The present study examined the prevalence and correlates of hyperuricemia in a cohort of 151 patients with tuberculosis. The findings highlighted several important demographic and clinical patterns that both align with the existence.

Demographically, the study cohort had a mean age of 42.46 years, with a majority of male patients (56.3%). This profile is similar to the broader epidemiology of tuberculosis, which often shows a higher burden in adult males. The age distribution of this study lies between the younger mean age of 38.2 years reported by Sundas et al. and the older mean age of 56.8 years in the larger retrospective study by Shin et al (6,13). The gender distribution in the current study (56.3% male) is similar to the 60.9% reported by Sundas et al.. Still, it shows a higher proportion of females than the 25% noted in the smaller cohort studied by Putra et al. (5,6). This variation likely reflects differences in local TB epidemiology and healthcare-seeking behaviour between study settings. The finding that 78.8% of patients had pulmonary tuberculosis is in alignment with the high prevalence of pulmonary forms, 81.7% noted by Muhammad et al (14).

A key and novel metric reported in this study is the mean duration of tuberculosis illness, calculated at 5.37 months before treatment initiation. This variable is seldom documented in similar pharmacovigilance studies, which typically focus on treatment duration. Sundas et al. reported a mean treatment duration of 10.5 months, whereas other studies focused on the intensive two-month pyrazinamide phase (6, 14). This data point on illness duration provides crucial context, suggesting a period of active disease and potential metabolic stress before therapeutic intervention begins. Interestingly, a notable association was found between a longer pre-treatment illness duration and the development of hyperuricemia. This correlation suggests that the chronic inflammatory state and possibly the nutritional depletion associated with prolonged untreated TB may expose patients to metabolic disturbances like hyperuricemia upon the introduction of drugs such as pyrazinamide. This hypothesis merits further exploration.

The overall frequency of hyperuricemia in this study was 47.7%. This Figure is notably lower than the very high rates of 82.3% and 85.3% reported by Shin et al. and Muhammad et al., respectively (13, 14). It is closer to the 60% reported by Putra et al. (5). The current study defined hyperuricemia based on serum uric acid levels during treatment, but the timing of measurement relative to pyrazinamide administration is critical. Shin et al. demonstrated that hyperuricemia peaks around the second month of therapy and declines thereafter (13). Differences in the timing of laboratory assessment can therefore greatly influence reported prevalence.

The analysis revealed a highly significant association between male gender and hyperuricemia, with 75% of hyperuricemic patients being male. This strong male predominance is a consistent finding in the literature. Sundas et al. and Shin et al. both reported higher rates of hyperuricemia in males, with the former identifying male gender as a significant risk factor (6, 13). The pathophysiological basis for this association is well-documented and often attributed to the uricosuric effect of oestrogen in premenopausal women, leading to generally lower baseline serum urate levels than in men (16).

Regarding age, the current study found the highest proportion of hyperuricemic patients in the 36-50 years age bracket (51.4%). This aligns with the findings of Sundas et al., who identified the 36–45-year group as having the highest prevalence.[6] This pattern may relate to age-related changes in renal function, increasing prevalence of metabolic syndrome components, and lifestyle factors. The present study found no significant

association between TB type (pulmonary and extrapulmonary) and hyperuricemia, a result consistent with the non-significant finding reported in the comparative analysis by Shin et al. (13).

The novelty of the current study lies in examining the significant association between pre-treatment illness duration and hyperuricemia. This study proposes that a longer duration of active disease might be an independent risk factor for hyperuricemia.

Conclusion

In conclusion, this study found a higher frequency of hyperuricemia in TB patients (47.7%) and found significant associations of male gender, middle age group, and prolonged duration of TB with hyperuricemia.

Declarations

Data Availability statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned. (IRB-HMC-QAD-F-00)

Consent for publication

Approved

Funding

Not applicable

Conflict of interest

The authors declared no conflict of interest.

Author Contribution

AZ (Trainee Medical Officer)

Data Collection, Data entry, Data analysis, and Drafting an article, and Study Design,

SJ (Professor)

Conception, Manuscript review, Critical input, Conception of study, and Development of research methodology design

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the study's integrity.

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