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ORIGINAL ARTICLE

Frequency of Hyperuricemia in Tuberculosis patients during Intensive Phase of Therapy

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ABSTRACT

Objective: To determine the frequency and pattern of hyperuricemia, including symptomatic and asymptomatic presentations, among tuberculosis patients receiving pyrazinamide as part of first-line anti-tuberculous therapy.

Methods: A cross-sectional study was conducted at the department of pulmonology of a tertiary care hospital from September 2022 to February 2023, 155 patients diagnosed with pulmonary or extra-pulmonary tuberculosis and treated with a standard regimen containing pyrazinamide. Serum uric acid levels were measured at 4, 6, and 8 weeks. Hyperuricemia was defined as uric acid greater than 6.6 mg/dL. Patients were clinically evaluated for symptoms related to hyperuricemia. Demographic factors, weight, and TB type were analyzed for association with biochemical elevations.

Results: The mean age of patients was 28.9 ± 12.5 years, and females comprised 52.9% of the cohort. Hyperuricemia developed in 136 (87.7%) patients, of whom most were asymptomatic, while 20 (12.9%) experienced symptomatic hyperuricemia presenting with mild arthralgia not requiring treatment modification. Mean serum uric acid levels rose progressively from 3.3 mg/dl at week 4 to 5.5 mg/dl at week 6 and 7.8 mg/dl at week 8. Hyperuricemia occurred in 85% of pulmonary TB, 87.8% of extra-pulmonary TB, and nearly all retreatment cases. No significant variation in hyperuricemia was observed across age, gender, or weight groups, indicating a uniform pharmacological effect of pyrazinamide.

Conclusion: Hyperuricemia is highly prevalent among TB patients receiving pyrazinamide, although symptomatic cases remain limited. The consistent rise in serum uric acid across demographic and disease subgroups highlights the predictable nature of pyrazinamide-induced hyperuricemia, emphasizing the importance of biochemical monitoring, particularly in retreatment patients.

Keywords: Tuberculosis, Pyrazinamide, Hyperuricemia, Adverse drug reaction, Serum uric acid.

INTRODUCTION

Tuberculosis (TB) remains a major global health challenge, particularly in low- and middle-income countries where disease burden, delayed diagnosis, and therapeutic complexities significantly impact outcomes. According to the World Health Organization (WHO), TB remains among the leading infectious causes of morbidity and mortality, with over 10 million new cases annually.[1] Pakistan continues to rank among the high-burden TB countries, contributing significantly to global case numbers.[2]

The standard first-line regimen for drug-susceptible TB includes isoniazid, rifampicin, ethambutol, and pyrazinamide during the intensive phase. Pyrazinamide is a cornerstone drug owing to its sterilizing effect against dormant intracellular Mycobacterium tuberculosis, allowing the overall treatment duration to be shortened.[3] However, its use is also associated with recognizable adverse effects, including hepatotoxicity, arthralgia, and hyperuricemia.[4]

Pyrazinamide-induced hyperuricemia results from inhibition of renal tubular secretion of urate.[5] While often asymptomatic, elevated uric acid may occasionally lead to acute gouty arthritis or treatment interruptions.[6] The frequency of such elevations varies widely in the literature, with reported rates ranging from 50% to over 90%, depending on population characteristics, dosage, and genetic factors.[7–9] Data from South Asia, particularly Pakistan, remain limited, and existing local studies often include small sample sizes or lack serial biochemical monitoring.

Understanding the frequency and pattern of pyrazinamide-associated hyperuricemia is critical for clinical decision-making, particularly in settings with high TB prevalence. Elevated uric acid may confound patient symptoms (arthralgia), mimic immune reconstitution–related discomfort, or complicate management in individuals with pre-existing renal or metabolic diseases.10 Furthermore, the increasing emphasis on patient-centered TB care necessitates better delineation of drug-related adverse effects.

This study aimed to determine the frequency of hyperuricemia in TB patients receiving pyrazinamide, assess its progression over the initial 8 weeks of therapy, and evaluate differences by sex and TB category.

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METHODS

This cross-sectional, observational study conducted at the department of Pulmonology, Bacha Khan Medical College Mardan from September 2022 to February 2023, included 155 patients diagnosed with pulmonary or extra-pulmonary tuberculosis at a tertiary-care teaching hospital in Pakistan. All patients were initiated on the standard WHO-recommended four-drug first-line regimen containing pyrazinamide during the initial 2 months of intensive phase.

All newly diagnosed pulmonary or extra-pulmonary TB including retreatment TB cases receiving pyrazinamide with age of ≥12 years and normal baseline hepatic function and renal parameters were included in the study. While patients Pre-existing hyperuricemia or gout or Chronic kidney disease or those with incomplete biochemical data were excluded from study.

Demographic variables (age, sex, weight) and TB category (pulmonary, extra-pulmonary, retreatment) were recorded. Serum uric acid levels were measured at: Week 4, Week 6 and Week 8 respectively. Hyperuricemia was defined as serum uric acid >6.6 mg/dL based on laboratory reference ranges applicable to the study population. The primary outcome was frequency of hyperuricemia. Secondary outcomes included: Trends in uric acid levels over time, Stratification by sex, Stratification by TB type, Symptomatic vs asymptomatic hyperuricemia.

Data were analysed using SPSS version 17. Categorical variables were expressed as percentages, while continuous variables were summarized as means ± SD. Stratified comparisons were descriptive in nature. Graphs of uric acid trends were generated for visualization. Missing data were minimal and excluded pairwise.

Ethical approval was obtained from the institutional review board, and written informed consent was taken.

RESULTS

The study population consisted of 155 TB patients, predominantly young adults, with a mean age of 28.9 ± 12.5 years and a median age of 27 years. The age range extended from 13 to 70 years, indicating inclusion of both adolescent and older individuals, although nearly three-fourths of the cohort fell between 20 and 34 years. The gender distribution was near-balanced, with a slight

female predominance, as females comprised 52.9% (n=82) and males 47.1% (n=73). This adequate representation allowed meaningful comparisons of biochemical outcomes, including uric acid elevations, without major sampling bias.

Analysis of the data showed that mean serum uric acid levels increased consistently over time, rising from 3.3 mg/dL at 4 weeks to 5.5 mg/dL at 6 weeks and 7.8 mg/dL at 8 weeks, demonstrating a progressive elevation during the intensive treatment phase. Hyperuricemia developed in 136 of the 155 patients (87.7%) receiving pyrazinamide. A distinction between symptomatic and asymptomatic hyperuricemia was evident in the cohort. Of the 136 patients (87.7%) who developed hyperuricemia, the majority (n=116; 85.3%) remained entirely asymptomatic despite biochemical elevation, whereas 20 patients (14.7%) experienced symptomatic hyperuricemia, accounting for 12.9% of the total study population. Symptomatic cases primarily reported mild arthralgia, and none of them developed acute gout or required interruption or modification of anti-tuberculous therapy. This pattern indicates that while hyperuricemia was highly prevalent during pyrazinamide therapy, clinically significant manifestations were relatively infrequent and manageable.

Table 1: Frequency of Symptomatic and asymptomatic hyperuricemia. (n = 155)

Category	Count	Percentage
Total hyperuricemia cases	136	87.7%
No hyperuricemia	19	12.3%
Symptomatic hyperuricemia	20	12.9% of total patients / 14.7% of hyperuricemic patients
Asymptomatic hyperuricemia	116	74.8% of total patients / 85.3% of hyperuricemic patients

Stratification by TB type showed that the frequency of hyperuricemia was 85% in pulmonary TB and 87.8% in extra-pulmonary TB. Nearly all retreatment patients exhibited hyperuricemia, suggesting increased susceptibility or a potential cumulative effect of repeated pyrazinamide exposure. Despite the high biochemical incidence, no patient progressed to acute gout, and all symptomatic cases were managed conservatively.

Both age and gender demonstrated high levels of hyperuricemia across subgroups, indicating a uniform effect of pyrazinamide irrespective of demographic characteristics. Hyperuricemia was slightly more common in females (90.2%) compared to males (84.9%), but the difference was not clinically significant. Younger and older patients showed similar substantial rises in uric acid levels by week 8, suggesting that pyrazinamide's inhibition of renal tubular urate excretion affects all age groups similarly. Overall, the findings indicate that neither age nor gender meaningfully modifies the risk of hyperuricemia, and that its development appears to be a consistent pharmacological effect of pyrazinamide therapy.

DISCUSSION

This study demonstrates that hyperuricemia is exceedingly common among tuberculosis patients treated with pyrazinamide, with an incidence of 87.7%, consistent with international data reporting biochemical elevations in 70–90% of patients receiving pyrazinamide.[11–13] The mechanism is well-established: pyrazinamide and its metabolites inhibit renal tubular secretion of uric acid, resulting in predictable accumulation.[5,14] The progressive rise in uric acid observed in our cohort from 3.3 mg/dL at week 4 to 7.8 mg/dL at week 8 mirrors the pharmacokinetic pattern previously described.[14,15] This temporal trajectory is clinically relevant, as urate-related discomfort typically emerges during the intensive phase, and symptoms may be misinterpreted as drug intolerance or alternative pathology.

A key finding of this study is the distinction between symptomatic and asymptomatic hyperuricemia. Although 87.7% of patients developed biochemical hyperuricemia, only 12.9% of the total cohort (20 patients) experienced symptomatic elevations. The majority remained asymptomatic, corroborating earlier observations that most pyrazinamide-associated hyperuricemia does not progress to clinical gout or require treatment interruption.[6,16] These findings reinforce the principle that routine prophylactic therapy is not warranted and that symptomatic cases can be safely managed with hydration, NSAIDs, or simple observation. No patient in our study required pyrazinamide cessation, emphasizing the overall tolerability of this adverse effect.

Retreatment patients demonstrated a 100% frequency of hyperuricemia, consistent with reports from high-burden regions suggesting increased susceptibility with repeated pyrazinamide exposure or altered host metabolism.[17] This subgroup may represent a population at higher risk for drug-induced metabolic disturbances and warrants closer monitoring. However, even in this group, symptomatic cases were not disproportionately elevated.

Age, gender, and weight did not meaningfully modify the risk of hyperuricemia in this cohort. Although hyperuricemic patients were slightly older, on average the difference was not clinically significant, and both younger and older participants exhibited similar uric acid trajectories by week 8. This supports the notion that pyrazinamide exerts a uniform pharmacological effect on urate retention across age groups. Similarly, while females demonstrated slightly higher rates of hyperuricemia (90.2%) than males (84.9%), the clinical impact of this difference appears minimal. Previous literature has noted potential sex-related differences in urate metabolism,18 yet our findings suggest these variations do not translate into meaningful differences in symptomatic presentation during TB therapy. Weight also demonstrated no significant association, aligning with studies reporting that pyrazinamide dose per kg does not independently predict hyperuricemia severity.[19]

Comparisons with regional studies further contextualize our findings. Research from Pakistan and India has documented hyperuricemia frequencies ranging from 60% to 92% consistent with our biochemical incidence.20,21 However, many of these studies lack serial monitoring. By providing trend data across three time points, our study offers a clearer depiction of the cumulative urate-retentive effect of pyrazinamide and provides objective evidence for the steepest rise occurring between weeks 4 and 8.

The strengths of this study include its adequate sample size, serial measurement of uric acid, inclusion of both new and retreatment TB cases, and representation of a typical clinical population treated under routine programmatic conditions. These factors enhance the generalizability of the findings. However, certain limitations must be acknowledged: the single-center design limits external validity; dietary intake and hydration status were not assessed; genetic polymorphisms affecting urate transport (such as SLC22A12 and ABCG2 variants) were not evaluated[22]; and multivariable regression was not performed to identify independent predictors of symptomatic hyperuricemia.

Future research should focus on identifying clinical or genetic factors associated with symptomatic progression, assessing the utility of targeted monitoring in retreatment patients, and evaluating whether baseline metabolic or renal parameters can predict susceptibility. Comparative studies between pyrazinamide-containing and pyrazinamide-sparing regimens may also help clarify the specific contribution of this drug to adverse metabolic effects.

CONCLUSION

This study demonstrates that hyperuricemia is a common and predictable biochemical effect of pyrazinamide therapy, occurring in 87.7% of tuberculosis patients. Despite this high incidence, only 12.9% developed symptomatic hyperuricemia, and no patient required discontinuation of treatment. The progressive rise in uric acid across the intensive phase, uniform across age, gender, and weight groups, reflects the well-established pharmacological action of pyrazinamide on renal urate handling. Nearly all retreatment patients exhibited hyperuricemia, suggesting heightened

susceptibility in this subgroup. Overall, pyrazinamide-induced hyperuricemia in our cohort was largely benign and clinically manageable.

Recommendations: Routine prophylactic treatment for hyperuricemia is not required, given the predominance of asymptomatic cases. However, periodic monitoring of uric acid levels during the intensive phase particularly in retreatment patients may aid in early detection of symptomatic cases. Patients presenting with arthralgia should be clinically evaluated, with NSAIDs used when necessary. Future studies should explore predictors of symptomatic hyperuricemia, including genetic predisposition and metabolic factors, and assess whether selective monitoring strategies could improve patient comfort without compromising treatment efficacy.

Limitations: This was a single-center study, which may limit the generalizability of findings to broader populations. Dietary patterns, hydration status, and baseline renal function which can influence uric acid levels, were not evaluated. Similarly genetic polymorphisms affecting urate transport (such as SLC22A12 or ABCG2 variants) were not assessed. Additionally, the study did not perform multivariable regression analysis to determine independent predictors of symptomatic versus asymptomatic hyperuricemia.

Authors Contributions

Concept & Design of Study, Data Collection: S. Ali, F. Rabbi
Drafting: A. U. Rehman
Data Analysis: S. Ali
Critical Review: F. Rabbi
Final Approval of Version: All Mentioned Authors Approved the Final Version.

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