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Article

Hyperuricemia in Tuberculosis Patients Treated with Pyrazinamide

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ABSTRACT

Background: Pyrazinamide (PZA), a cornerstone of first-line anti-tuberculosis therapy, is associated with a high incidence of hyperuricemia, a potentially overlooked metabolic complication that may impact treatment adherence. Despite its frequent use, limited data exists on the demographic and clinical predictors of PZA-induced hyperuricemia in the local Pakistani population, creating a gap in risk-based monitoring strategies. **Objective**: This study aimed to determine the prevalence and associated factors of Pyrazinamide-induced hyperuricemia in patients with pulmonary tuberculosis, focusing on demographic variables (age, gender) and clinical indicators (pleural fluid analysis, ADA estimation, radiological findings). **Methods**: A descriptive cross-sectional study was conducted at the Pulmonology Department of Khyber Teaching Hospital, Peshawar, enrolling 46 patients aged 18–65 years diagnosed with pulmonary tuberculosis. Patients with renal, hepatic, or rheumatologic conditions were excluded. Serum uric acid (SUA) levels were recorded at 0, 2, 6, and 8 weeks of Pyrazinamide treatment. Pleural fluid, ADA levels, and imaging were assessed. Ethical approval was obtained, and all procedures adhered to the Declaration of Helsinki. Data were analyzed using SPSS v27; chi-square and paired t-tests assessed associations, with $p < 0.05$ considered significant. **Results**: The mean age was 38.2 ± 10.5 years; 60.9% were male. Statistically significant associations were found between hyperuricemia and age ($p = 0.001$), gender ($p = 0.049$), pleural fluid analysis ($p = 0.005$), ADA estimation ($p = 0.014$), and radiological/histopathological findings ($p = 0.034$). Treatment duration was not significantly associated ($p = 0.235$). **Conclusion**: Pyrazinamide-induced hyperuricemia is significantly associated with demographic and disease severity markers in TB patients. Routine uric acid monitoring, especially in middle-aged males and those with pleural or radiological involvement, may improve therapeutic safety and adherence.

Keywords: Tuberculosis, Pyrazinamide, Hyperuricemia, Serum Uric Acid, Pleural Effusion, ADA, Radiology

INTRODUCTION

Tuberculosis (TB) remains a significant public health concern worldwide, with an estimated one-third of the global population infected and millions affected by active disease each year. Pakistan is among the top five countries with the highest TB burden and ranks fourth globally in the prevalence of drug-resistant TB. The country's TB incidence is estimated at 231 cases per 100,000 population, with a prevalence of 350 cases per 100,000 individuals (1, 2). The standard treatment for TB includes a multi-drug regimen in which Pyrazinamide (PZA), a synthetic derivative of nicotinamide, plays a crucial role due to its intracellular bactericidal activity, particularly effective during the initial intensive phase of treatment. PZA targets Mycobacterium tuberculosis in acidic environments, such as macrophages and inflamed tissues, contributing to shorter therapy durations and reduced relapse rates (3, 4). However, despite its therapeutic benefits, PZA is commonly associated with adverse metabolic effects, particularly hyperuricemia. This condition, defined as a serum uric acid (SUA) level exceeding 7.0 mg/dL, results from the accumulation of pyrazinoic acid, a metabolite of PZA that inhibits renal uric acid excretion, leading to elevated serum urate levels (5, 6).

The frequency of hyperuricemia in patients treated with PZA varies across studies, with reported incidences ranging from 43% to 100% (5). While often asymptomatic, hyperuricemia can be accompanied by arthralgia and in some cases may resemble gouty symptoms. This complication can negatively affect treatment compliance, especially in populations with underlying metabolic risks or renal impairments. Moreover, some patients experience

arthralgia that may not directly correlate with SUA levels, yet still warrants management, often with non-steroidal anti-inflammatory drugs like aspirin (3). Aspirin has also been found to mitigate hyperuricemia itself through uricosuric effects, making it a potential adjunctive option for managing PZA-associated arthralgia (3). Despite these observations, clinical practice has yet to standardize SUA monitoring during TB therapy, particularly in settings where resource limitations restrict regular biochemical screening. The prevalence and impact of hyperuricemia in TB patients, especially in the Pakistani population, are underreported in the literature, with limited local data evaluating risk factors and clinical outcomes related to PZA-induced metabolic disturbances.

Prior studies from South Asia and the Middle East have explored demographic and disease-related contributors to hyperuricemia, highlighting associations with male gender, middle age, and markers of disease severity, including pleural effusion, elevated adenosine deaminase (ADA), and radiological confirmation of TB (7–10). However, findings remain inconsistent regarding the influence of treatment duration and comorbid conditions such as renal dysfunction, suggesting that multiple interacting factors may determine the risk of hyperuricemia in TB patients. Furthermore, while hyperuricemia has been studied in broader chronic disease contexts, there remains a lack of focused investigations in patients undergoing DOTS-based TB therapy in specialized tertiary care settings in Pakistan. This gap in evidence necessitates local studies to guide clinical decision-making, improve patient safety, and tailor monitoring strategies in TB treatment protocols.

This study was conducted to evaluate the frequency of hyperuricemia and its associated clinical and demographic risk factors in TB patients receiving Pyrazinamide at a specialized pulmonology unit. By analyzing variables such as age, gender, duration of treatment, pleural fluid findings, ADA levels, and radiological or histopathological confirmation of disease, the study aimed to provide a clearer understanding of which subgroups are at elevated risk. This research seeks to contribute to local data, address a significant gap in TB management practices, and ultimately inform clinicians on the need for routine SUA monitoring and early intervention. The central research question guiding this investigation was: What are the demographic and clinical factors associated with the development of hyperuricemia in tuberculosis patients treated with Pyrazinamide at Khyber Teaching Hospital, Peshawar?

MATERIALS AND METHODS

This descriptive cross-sectional study was conducted at the Pulmonology Department of MTI/Khyber Teaching Hospital, Peshawar, Khyber Pakhtunkhwa, Pakistan, over a period of approximately six months. The sample size was determined using a sample size calculator with a confidence level of 95%, a margin of error of 14.31%, and an anticipated population proportion of 43%, resulting in a final sample of 46 participants. Non-probability consecutive sampling was used to recruit patients from the pulmonology outpatient department and inpatient wards. Adults aged 18 to 65 years with a confirmed diagnosis of pulmonary tuberculosis who were initiating anti-tuberculosis treatment including Pyrazinamide were eligible for inclusion. Patients with a history of joint pain, pre-existing hyperuricemia, hepatic or renal dysfunction, diabetes mellitus, gouty arthritis, cardiac diseases, or those receiving medications known to elevate uric acid levels were excluded to avoid confounding. Informed written consent was obtained from all participants after providing detailed information about the study in clear and understandable language.

Each patient underwent baseline clinical and demographic evaluation. The primary outcome was the development of hyperuricemia, defined as a serum uric acid (SUA) level >7.0 mg/dL. Secondary outcomes included the presence of self-reported arthralgia and any association between hyperuricemia and variables such as age, gender, pleural fluid analysis, ADA estimation, and radiological or histopathological findings. Diagnostic workup for tuberculosis included chest radiography, sputum acid-fast bacilli (AFB) testing, pleural fluid D/R and Gen-Xpert, and in selected cases, PCR for Mycobacterium tuberculosis RNA. Serum uric acid levels were measured at four time points: at baseline (prior to treatment), and then at 2, 6, and 8 weeks following initiation of Pyrazinamide-containing therapy. Participants reporting arthralgia were treated with aspirin, and SUA was reassessed two weeks after intervention. Laboratory testing followed standard hospital protocols.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants, and patient confidentiality was maintained throughout the study using anonymized data codes and restricted access to identifiable information. Data were entered and analyzed using SPSS version 27. Descriptive statistics were used to summarize demographic and clinical characteristics. Paired Student's t-test was used to compare pre- and post-treatment serum uric acid levels. Associations between categorical variables and hyperuricemia were assessed using chi-square tests. A p-value of less than 0.05 was considered statistically significant. All analyses were conducted with two-tailed testing (7).

RESULTS

A total of 46 patients diagnosed with pulmonary tuberculosis and receiving Pyrazinamide-containing treatment were included in this study. The mean age of participants was 38.2 ± 10.5 years. The sample comprised 28 males (60.9%) and 18 females (39.1%). The mean duration of tuberculosis treatment among participants was 10.5 ± 5.2 months. Table 1 presents a summary of demographic and clinical variables along with their respective statistical associations with hyperuricemia.

A statistically significant association was observed between age and the development of hyperuricemia ($p = 0.001$), with the 36–45-year age group contributing the highest proportion (26.1%) of patients. Gender was also significantly associated with hyperuricemia ($p = 0.049$), with males representing the majority of affected individuals. However, duration of TB treatment showed no statistically significant association with hyperuricemia ($p = 0.235$), indicating that treatment duration did not independently influence the risk of elevated uric acid levels.

Among the diagnostic markers, pleural fluid analysis demonstrated a significant association with hyperuricemia ($p =$

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0.005). Patients who underwent pleural fluid testing were more likely to present with elevated serum uric acid, potentially indicating a relationship between pleural involvement and metabolic disturbances. Similarly, Adenosine Deaminase (ADA) estimation was significantly correlated with hyperuricemia (p = 0.014), supporting its role as a marker of disease activity and inflammatory response. Radiological and histopathological confirmation of tuberculosis was also significantly associated with the development of hyperuricemia (p = 0.034), suggesting that patients with radiologically or histologically confirmed TB were at higher risk for metabolic complications. These findings emphasize that age, male gender, and diagnostic indicators of disease severity are important predictors of Pyrazinamide-induced hyperuricemia. Table 1 provides a comprehensive overview of the variables evaluated in the study.

Table 1: Demographic and Clinical Variables in Relation to Hyperuricemia Among TB Patients Treated with Pyrazinamide (N = 46)

Parameter	Frequency (%)	Mean ± SD	p-value
Age (Years)	–	38.2 ± 10.5	–
18–25	8 (17.4%)		0.001
26–35	10 (21.7%)		
36–45	12 (26.1%)		
46–55	10 (21.7%)		
56–65	6 (13.0%)		
Gender	–		0.049
Male	28 (60.9%)		
Female	18 (39.1%)		
Duration of TB Treatment (Months)	–	10.5 ± 5.2	0.235
Pleural Fluid Analysis	–		0.005
Yes	18 (39.1%)		
No	28 (60.9%)		
ADA Estimation	–		0.014
Yes	23 (50.0%)		
No	23 (50.0%)		
Radiology and Histopathology	–		0.034
Yes	34 (73.9%)		
No	12 (26.1%)		

These results highlight statistically significant associations between key demographic and diagnostic variables and the presence of hyperuricemia, supporting the need for targeted biochemical monitoring in at-risk subgroups of TB patients receiving Pyrazinamide. No post hoc analysis was required as categorical variables were tested individually against hyperuricemia presence using chi-square tests.

DISCUSSION

The present study investigated the prevalence and determinants of hyperuricemia in tuberculosis (TB) patients treated with Pyrazinamide, with a specific focus on demographic and clinical variables. The findings reveal that age, male gender, pleural fluid analysis, ADA estimation, and radiological or histopathological confirmation of TB are significantly associated with the development of hyperuricemia during Pyrazinamide-containing therapy. These results underscore the clinical importance of monitoring serum uric acid (SUA) levels, particularly in high-risk subgroups, to mitigate potential treatment-related complications and optimize therapeutic outcomes.

The observed association between age and hyperuricemia is consistent with previous reports suggesting that middle-aged individuals are more prone to metabolic complications during anti-TB therapy. In the current study, the highest prevalence was noted among patients aged 36–45 years, aligning with findings by Kumar et al., who reported increased susceptibility in individuals aged 30–50 years (7). Aging is known to influence renal function and inflammatory responses, both of which may contribute to altered uric acid metabolism. Similarly, male predominance in hyperuricemia incidence, as observed in this study, is supported by studies conducted by Al-Harbi et al. and Liu et al., who highlighted that males typically exhibit higher baseline SUA levels and greater renal urate reabsorption capacity compared to females (9, 10). These gender-related differences in uric acid handling are likely mediated by hormonal and enzymatic variations, offering a plausible biological explanation for the disparity.

Interestingly, no significant association was found between the duration of TB treatment and the development of hyperuricemia. This contrasts with studies such as those by Fakhrzadeh et al. and Sama et al., which demonstrated that prolonged Pyrazinamide exposure led to cumulative uric acid retention and increased risk of symptomatic hyperuricemia (11, 12). The absence of this association in the present study may be attributed to a relatively uniform treatment duration across patients or to the exclusion of individuals with pre-existing renal or hepatic impairments, which could have minimized inter-individual metabolic variability. It is also possible that uric acid levels plateau early in treatment, limiting the incremental impact of extended therapy duration.

The study's findings regarding pleural fluid analysis and ADA estimation further reinforce the hypothesis that disease severity and systemic inflammation are key mediators of Pyrazinamide-induced metabolic effects. Patients with positive pleural fluid analysis or elevated ADA levels exhibited significantly higher rates

of hyperuricemia, echoing the results of studies by Chaudhary et al. and Zhao et al., where inflammatory markers were linked to impaired urate excretion (7, 14). ADA reflects T-cell-mediated immune responses, and its elevation in TB pleuritis may indicate active inflammation capable of altering renal tubular function. These biological mechanisms underscore the importance of assessing inflammatory status when initiating treatment with uricosuric agents such as Pyrazinamide.

Radiological and histopathological findings also showed a significant association with hyperuricemia in this study. This suggests that patients with more severe or advanced pulmonary TB may be more susceptible to treatment-related metabolic complications. Patel et al. and Singh et al. similarly reported that extensive radiological involvement in TB was linked to higher uric acid levels, possibly due to increased systemic inflammatory burden and oxidative stress (15, 16). These observations support the clinical relevance of integrating radiological staging with biochemical monitoring to anticipate and address drug-induced adverse effects.

The strengths of this study include its focused design, strict exclusion criteria to minimize confounding variables, and the use of serial SUA measurements to track metabolic trends throughout the intensive treatment phase. Additionally, the incorporation of diverse diagnostic modalities, including pleural fluid analysis, ADA estimation, and imaging, allowed for a comprehensive assessment of clinical severity in relation to metabolic derangements.

However, several limitations warrant consideration. The relatively small sample size (n = 46) limits the generalizability of findings and restricts subgroup analyses, particularly for gender- or age-specific comparisons. The non-probability sampling method may introduce selection bias, and the absence of a control group not receiving Pyrazinamide limits causal inference. Moreover, other biochemical markers of renal function or inflammation were not included, which may have provided further insight into the pathophysiological mechanisms underlying hyperuricemia.

Future studies should aim to validate these findings in larger, multicenter cohorts and explore longitudinal patterns of uric acid fluctuations beyond the intensive treatment phase. Investigations comparing different TB regimens, including those excluding Pyrazinamide, may also help clarify drug-specific metabolic risks. Furthermore, randomized trials evaluating the prophylactic or therapeutic use of agents like aspirin or allopurinol in preventing Pyrazinamide-induced hyperuricemia could contribute to more effective clinical management strategies.

This study highlights a significant association between Pyrazinamide-induced hyperuricemia and specific demographic and clinical characteristics, particularly middle age, male gender, and indicators of severe TB involvement. These findings underscore the need for proactive uric acid monitoring and risk stratification in TB management protocols. While the metabolic side effects of Pyrazinamide are often overlooked, this study demonstrates their potential clinical relevance and the importance of early detection to ensure uninterrupted and effective TB treatment.

CONCLUSION

This study demonstrates that Pyrazinamide-induced hyperuricemia is a clinically significant concern among tuberculosis patients, particularly in middle-aged males and those with radiological, histopathological, or pleural involvement. The findings align with the study's objective of evaluating factors associated with hyperuricemia in TB patients treated with Pyrazinamide and underscore the need for routine monitoring of serum uric acid levels during treatment. Early identification and management of hyperuricemia can help prevent treatment interruptions and improve patient adherence, thereby enhancing therapeutic outcomes. Clinically, these results support integrating metabolic surveillance into standard TB care protocols, especially in high-risk populations. Further research is warranted to explore long-term outcomes and evaluate potential prophylactic strategies for mitigating Pyrazinamide-related metabolic effects.

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