# HYPERURICEMIA & ARTHRALGIA DURING PYRAZINAMIDE THERAPY IN PATIENTS WITH PULMONARY TUBERCULOSIS.

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**ABSTRACT:**

**Objective:** To assess the effect of Pyrazinamide induced Hyperuricemia in patients with Pulmonary Tuberculosis.

**Design:** Prospective study case control study

**Place and duration:** Liaquat University Hospital Jamshoro, during the period of one year from January 2014 to December 2014.

**Material and Methods:** Patients were selected from chest out-patient department and chest ward. Pulmonary Tuberculosis was diagnosed on the basis of history, clinical examination, chest radiography, sputum examination for Acid Fast Bacilli, pleural fluid D/R, and PCR. Patients were admitted in pulmonology ward for eight weeks. All patients underwent combination therapy with Rifampicin, isoniazid, ethambutol and pyrazinamide for eight weeks. All patients were evaluated for arthralgia based on self-reported signs and symptoms.

The details of demographic data, clinical characteristic, chemotherapy, adverse reaction to drugs and follow-up assessment as well as regular sputum bacteriology and serum uric acid levels were monitored at 0, 2, 6 and 8$^{th}$ week. Pyrazinamide was discontinued after 8 weeks of therapy.

**Result:** The serum uric acid estimation was done in a total of 46 patients, who have received Pyrazinamide for duration of 8 weeks. Our results indicated that 43% of patients showed hyperuricemia and 21.7% showed Arthralgia.

The mean uric acid level was significantly higher at 2, (6.8mg/ml), 6 (7.2mg/dl), and 7$^{th}$ week (7.4mg//dl) as compared to zero week (5.1mg/dl). An overall 75%, 71% and 69% total increase was observed respectively over time.

**Conclusion:** This study concluded that anti-tuberculosis drug therapy with Pyrazinamide affect the uric acid levels, resulting in significant hyperuricemia with some arthralgia. This change was found to be spontaneously reversible or with Aspirin therapy.

**Key Words:** Tuberculosis; Uric acid; Pyrazinamide; Hyperuricemia; Arthralgia

This article may be cited as: Inayat N, Shah RH, Lakhair MA, Sahito R. Hyperuricemia & Arthralgia During Pyrazinamide Therapy In Patients With Pulmonary Tuberculosis.. Pak J Chest Med 2016; 22(4): 154-8

## INTRODUCTION

Tuberculosis (TB) is an infectious disease that can spread from person-to-person. The disease is caused by bacterium known as Mycobacterium tuberculosis. It is the second leading cause of death by infectious cause after HIV and AIDS.[1] Tuberculosis is a curable infectious disease[2] that impacts more than 2 billion people (about 1/3$^{rd}$ of world's population).[3] According to the world health organization (WHO) 9.6 million individuals became ill with tuberculosis & 1.5 million died in the year 2014.[4] Tuberculosis is one of the major health problem and Pakistanis currently ranked 5$^{th}$ amongst countries with highest burden of tuberculosis[5] with 4$^{th}$ highest burden of drug resistance, whereas globally approximately 420,000 new TB cases of drug resistant tuberculosis emerges every year. An estimated population of

Pakistan is currently around 184 million with annual incidence of TB being 231/100,000 and prevalence of 350 cases per 100,000 populations.[6,7] Pyrazinamide (PZA) is a drug used to treat tuberculosis. PZA is bactericidal and has a potent sterilizing effect principally in the acid medium within macrophages and at sides of acute inflammation.[8] PZA is only used in combination with other drugs such as Isoniazid and Rifampicin in the treatment of Mycobacterium Tuberculosis.[9-10] PZA is used in the 1st two months of treatment to reduce the duration of treatment required .[11] PZA is a pro drug that needs to be converted into its active form Pyrazinoic acid by bacterial enzyme (Pyrazinamidase is / nicotinamidase).[12,13] Pyrazinoic acid, a major metabolite of PZA can inhibit the renal tubular secretion of uric acid, resulting in increased urate production and subsequent Hyperuricemia.[14,15] Hyperuricemia with or without arthralgia is the main adverse effect of PZA.[16] Hyperuricemia is normally defined as serum uric acid (SUA) level greater than 7.0 mg/dl, the approximate level at which urate is super saturated in plasma.[17] This study aims to explore and observe adverse reaction of PZA during intensive phase of DOTS therapy and to determine the usefulness of aspirin in management of hyperuricemia and subsequent arthralgia.

## MATERIAL AND METHODS

This prospective& case control study was conducted at Pulmonology department, Liaquat University Hospital, Jamshoro (Sindh) Pakistan during the period of January 2014 to December 2014.

## SELECTION OF PATIENTS

A total of 46 patients were selected from Chest outpatient department (OPD) and pulmonology ward after confirming pulmonary tuberculosis based on history, clinical examination, chest radiography, sputum examination for acid fast bacilli, pleural fluid D/R Gen-x-pert, and polymerase chain reaction for mycobacterium tuberculosis RNA from CSF and in plural effusion.

Informed consent was taken from the patient. All patients underwent combination therapy with Rifampicin, Isoniazid, Ethambutol and Pyrazinamide for 8 weeks and were evaluated for self-reported arthralgia.

## INCLUSION CRITERIA

Patients aged between 18 – 65 years of age, with no history of joint pain, normal liver, renal function tests and serum uric acid level less than 6.5mg/dl were selected.

## EXCLUSION CRITERIA

Patients with hepatic or renal dysfunction, diabetes mellitus, Gouty arthritis, cardiac disease or use of drugs that cause hyperuricemia were excluded from the study.

The details of demographic data, clinical characteristic, radiography and related investigations were obtained using a questionnaire. Serum uric acid levels in patients receiving PZA were monitored at 0, 2, 6, 8 week patients and asked for any symptoms of arthralgia with the help of questioner. A total of three whole blood samples were obtained from these patients before, during and after combination therapy. Additionally patients complaining of pain were administered aspirin and another blood sample was collected two weeks post-aspirin administration from treated patients. Uric acid was quantified in serum samples of all patients.

## RESULT

A total of 46 patients were included in our study with 26 males and 20 females, between the age of 18 to 65 years and weight ranges from 30 to 60 kg. An estimated 90% of our patient population had pulmonary tuberculosis with only a small minority with extra-pulmonary tuberculosis. In case of extra-pulmonary tuberculosis, we mainly observe TB meningitis (6%) and pleural effusion (4%). The serum uric acid in all patients (n-46), prior to initiation of combination therapy at '0' week ranged from 2.6mg/dl to 5.4mg/dl. An increase in serum uric acid level was observed in 43% (20/46) of patients at the end of intensive phase therapy.

The result show significant increase in uric acid level from 0 to week 2, 6, 8,but a sharp increase in the levels of serum uric was observed weeks 2 and 6 where the levels increased from 2.6 mg/dl to 7.2 mg/dl. The levels remained stable between week 6 and 8 where a very small change (7.2 mg/dl -7.4 mg/dl) was observed (Table 1.)

## DISCUSSION

Tuberculosis is a communicable disease therefore therapy is targeted to completely eradicate bacteria from the body. In case of combination Tb therapy PZA plays a role of bactericidal and sterilizing drug. The inclusion of PZA in intensive phase, significantly improve sputum conversion rate, as a result inclusion of PZA is critical. However, PZA and ethambutol have been reported to induce hyperuricemia.[18] Patient's tolerance of anti-tuberculosis drug is extremely important for the treatment outcomes and as a consequence for tuberculosis control in general [19].The trend we observed between increasing serum uric acid levels and the number of weeks on combina-

Table: 1 Time course of uric acid concentration

| Time | Week | Uric acid concentration mg/dl |
|---|---|---|
| Pre-Treatment | 0 | 2.6mg/dl to 5.4mg/dl |
| Post-Treatment | 2 | 5.8 mg/dl ± 0.4 |
| Post-Treatment | 6 | 7.2 mg/dl ± 0.6 |
| Post-Treatment | 8 | 7.4 mg/dl ± 0.4 |

Among patients with hyperuricemia, a total of 10 patients complained of arthralgia, the joints that were mainly involved in arthralgia were found to be knees, shoulder and ankle (Table 2.). A total of 6 (60%) of 46 patients complained of knee pain followed by shoulder pain (20%) and ankle pain (20%)

Serum uric acid levels returned to normal (6.0mg/dl) in patient (n=6) who were treated with combination therapy for 8 weeks, discontinued for short while (2 weeks) followed by aspirin therapy for 02 weeks (Table 3).

Table: 2 Location of Affected Joints

| Location of affected joints | Number of cases % |
|---|---|
| Knee | 6 (60 %) |
| Shoulder | 2 (20 %) |
| Ankle | 2 (20 %) |

Table: 3 Serum uric acid levels in 6 patients before and after discontinuation of therapy

| Time | Uric acid concentration | |
|---|---|---|
| | Mean ± | Range |
| Pre -Treatment | 4.6 ± 0.6 | 2.6 -5.4mg/dl |
| Post -Treatment | 7.2 ± 0.6 | 2.6 -8.2mg/dl |
| After discontinuation of treatment for 02 weeks | 4.6 ± 0.2 | 4.0 -4.8mg/dl |

tion therapy in table-1(43%) is consistent with the studies performed by Sharma and colleague,[20] and Horsfall PALL et al[25] where incidence of Hyperuricemia was 43.4%, and 46% respectively in patients treated with combination therapy or Pyrazinamide alone. A total of 10/46 (21.7) participants developed joint pain subsequent to hyperuricemia. The results are comparable to study conducted in Nigeria,[21] where 20% of participants reported joint pain following hyperuricemia. Moreover, joints involved were also found to be comparable to the Nigerian study where joints mostly affected were the knee, shoulder and ankle. Aspirin is known to prevent Hyperuricemia and arthralgia caused by pyrazinamide [22-24] given this fact; we included a short-term aspirin therapy in our patients who were being treated with combination anti-tuberculosis therapy. Results of our study demonstrated a significant positive effect of aspirin on serum uric acid levels where the levels reverted to normal with relief in arthralgia. As a result, withdrawal of pyrazinamide was not necessary. Based on the observations made in this study we recommend a short course of Aspirin during intensive phase of treatment to prevent and treat hyperuricemia and arthralgia.

## CONCLUSION

This study concluded that the combination therapy remained a useful treatment in the management of TB. Hyperuricemia can be managed by observation, and does not require withdrawal of PZA. However the side effect caused by PZA in particular can be managed by short-term aspirin therapy.

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