Original Article

Hyperuricemia after taking TB Drugs

Hyperuricemia in Patients Taking Anti-Tuberculosis Drugs Including Pyrazinamide for both Category-1 and Category-2 Tuberculosis, in Population of KPK-Pakistan

Jamaluddin[1], Nizamuddin[2], Abid Shah[2] and Waheed Iqbal[2]

ABSTRACT

Objective: To document hyperuricemia in patients taking Anti-Tuberculosis Therapy (ATT) including Pyrazinamide (PZA) in both CAT-1 and CAT-2 Patients.

Study Design: An open labeled & single centered longitudinal study.

Place and Duration of Study: This study was conducted at the Khyber Medical College (KMC) & Khyber Teaching Hospital, Peshawar from December 2016 to May 2017.

Materials and Methods: Sixty patients with pulmonary tuberculosis were enrolled. Patients were assigned into 2-groups (30 patients in each group), including group-A as CAT-1 patients, who were taking ATT for the first time and group-B as CAT-2, who presented with recurrent tuberculosis and were put on ATT for the second time. Standard ATT was given to group-A and Streptomycin was added to standard ATT in group-B for the first 02-months and uric acid (UA) level was done before the initiation of therapy, at the end of two-month intensive regimen and 02-months after the stopping Pyrazinamide. The primary target was to find out hyperuricemia in both groups.

Results: In CAT-1 patients, uric acid was increased to 6.44 ± 0.91 after two months aggressive regimen, and with discontinuation of pyrazinamide in CAT-1 patients for two month the uric acid falls again to 4.71 ± 0.83. Similarly, in CAT-2 patients, uric acid was increased to 6.64 ± 0.91 with two months therapy which downgrade to 5 ± 1.15 after two months of stopping pyrazinamide. There is significantly increase in uric acid level with two months of ATT in both groups (p-value=0.01). There is 100% recovery in female patient in Cat-1 as compared to Cat-2 female patients (91.6%), similarly 94.77% males improved in Cat-1 as compared to Cat-2 males whose recovery is 86.67%.

Conclusion: ATT including PZA can cause significant hyperuricemia, in both CAT-1 and CAT-2 patients. This raised in uric acid level is reversible with discontinuation of PZA, but may persist in some of CAT-2 patients.

Key Words: Hyperuricemia, Anti tuberculosis drugs, Pyrazinamide, CAT-1 and CAT-2**.**

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INTRODUCTION

Tuberculosis is infectious disease, which is caused by Mycobacterium Tuberculosis. It is very common in the developing countries including Pakistan, but it is also increasing in the developed countries due to HIV-AIDS. Globally, 10.4 million new cases were reported in 2016. About 10% are them are co-infected by HIV infection. It is the ninth common cause of death worldwide and the first amongst the infectious disease. Pakistan is at number five amongst 22 countries with high incidence of tuberculosis. Annually, about 480,000 people are infected and around 70,000 people die due tuberculosis[1,2].

[1.] Department of Medicine / Pharmacy[2], Khyber Medical College and Teaching Hospital Peshawar.

Correspondence: Mr. Waheed Iqbal, Pharmacist, Department of Pharmacy, Khyber Teaching Hospital Peshawar.
Contact No: 0334-9190299
Email: waheediqbal22@gamil.com

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The number of new cases and recurrent cases is alarming and may be more, as most of the cases are not reported. It is a treatable disease and timely diagnosis followed by complete course of ATT can prevent mortality of the patient and spread of infection in the community. Anti tuberculosis drugs are given for six months including 2-months as intensive phase and 4-months as maintenance phase. In the intensive phase, we are using four drugs for CAT-1 patients, including Isoniazid, Rifampicin, Ethambutol and Pyrazinamide. Streptomycin is added to all these drugs for the first two months in case of CAT-2 patients. Most of the treatment failure occurs due to poor compliance with the therapy. Poor compliance is due to longer duration of treatment and multiple adverse effects caused by all ATT[3]. Hyperuricemia is one of the most important adverse effects, which occurs with Pyrazinamide (PZA) and to some extent with ethambutol. Streptomycin can impair renal function and can further increase it in case of CAT-2 patients. Pyrazinamide is a bacteriostatic drug, which may be bactericidal at high concentration. It is one of the most important amongst the first line ATT drugs, which is recommended in the intensive

phase for both CAT-1 and CAT-2 patients. It is converted in the body into its active metabolite, pyrazinoic acid. Hyperuricemia occurs due to impaired excretion of uric acid in the proximal tubules of the kidney due PZA metabolite, pyrazinoic acid.

In the human body, uric acid is produced by purine metabolism. Most of the mammals metabolise it to allantoin and allontoic acid with the help of uricase, which is easily water-soluble and easily excreted in urine. In contrast to most other mammals, humans don't have sufficient enzyme level of uricase, due to which there is rapid accumulation of uric acid in the serum. It precipitates in the form of urate crystal, leading to the clinical manifestation of gout and urolithiasis. Very high-level uric acid can lead to acute kidney injury in the form of acute renal failure. In human body, approximately 70% of uric acid is excreted via kidneys, while the rest passes into the gastrointestinal tract, where it is oxidized to allantoin, allantoic acid and urea. Uricase and other enzymes, which are present in the normal intestinal flora, do this[4].

Hyperuricemia is usually defined as a serum uric acid (SUA) level greater than 7.0 mg/dl in male and SUA level greater than 6.5mg/dl in females. It is a very important metabolic condition, which "may be caused by increased urate production (over producers) or decreased renal urate excretion (under excreters)"[5]. Usually, it is caused by under excretion. In most of the patients, it is usually asymptomatic, but elevated levels of uric acid can cause crystal deposition in many organs of the body including skin, joints and kidney. This can lead to gout, skin tophi, kidney urate stones and urolithiasis[6].

In case of tuberculosis, asymptomatic hyperuricemia occur in the first two months of intensive therapy. PZA is considered to be the most notorious in all ATT for this adverse effect in all adult and children[7,8]. Most of the ATT causing some degree of renal stress and affect the renal excretion of many metabolic waste products including urate. This can increase the effects of PZA and thus accumulation of uric acid occurs more quickly in case of giving all anti tuberculosis drugs. Streptomycin, which is given in case of CAT-2 tuberculosis can also impair the renal function and thus can further increase the urate level[9].

There are a number of documented studies, conducted at both national and international level to document this association. In this study, we have focused to compare the level of hyperuricemia in both CAT-1 and CAT-2 patients, taking ATT including PZA. We have conducted this study to evaluate this association in the population of Khyber Pukhtoonkhwa.

MATERIALS AND METHODS

This single center & longitudinal study was conducted in the KMC & Teaching Hospital, Peshawars starting from December 2016 to May 2017. The sample size was calculated with the help of WHO-online calculator. Ethical committee approval was taken in advance and after informed consent, 60 patients having pulmonary tuberculosis were enrolled. All these patients were divided into 2 groups, labeled as group-A as CAT-1 cases, who, group-B as recurrent CAT-2 cases. All the demographic and clinical information like age, sex, ethnicity and treatment strategy were obtained from the patients. All patients in CAT-1 were put on four drugs including Isoniazid, Rifampicin, Ethambutol and Pyrazinamide, while streptomycin was added to these drugs in case of CAT-2 cases. Serum uric acid level was recorded initially, at the end of two month of therapy and after two month of the discontinuation of pyrazinamide.

Statistical Analysis; SPSS version 16.0 was used for analysis of all the data including frequencies, percentages. Independent sample T-test was applied to determine the difference between the means of two groups with 95% of confidence level, and significant p-value of ≤ 0.05. The Graph was constructed using Microsoft Excel 2013. All the findings were presented in graphs and tables.

RESULTS

The study consists of 60 patients, which were classified into two groups of 30 in each individual. CAT-1 were treatment naïve patient while in CAT-2 those patients were included who were put on ATT for the 2nd time. In CAT-1, 19 (63.3%) were males while 11 (36.7%) were females, the UA at start of anti-tubercular therapy, at two months and after two months of stopping ATT was 4.67 ± 0.72, 6.44 ± 0.91 and 4.71 ± 0.83 respectively. All the values are summarized in table 1.

Similarly, in CAT-2 patients, male vs female ratio was 19 (56.7%) and 13 (43.3%) respectively. Uric acid was 4.67 ± 0.74 at start of therapy and was upsurges to 6.64 ± 0.91 with two months therapy which downgrade to 5 ± 1.15 after two months of stopping pyrazinamide. All the data is summarized in table 2.

Table No. 1: CAT-1 patients

		Frequency	Mean	SD
Age		30	48.53	9.96
Gender	Males	19(63.3%)	-	-
	Females	11(36.7%)	-	
Uric Acid at start		30	4.67	0.72
Uric Acid at 2 months		30	6.44	0.91
Uric Acid after 2 months of stopping therapy		30	4.71	0.83

Table No. 2: CAT-2 patients

Variables		Frequency	Mean	SD
Age		30	48.43	11.57
Gender	Males	17(56.7%)	-	-
	Females	13(43.3%)	-	
Uric Acid at start		30	4.67	0.74
Uric Acid at 2 months		30	6.64	0.19
Uric Acid after 2 months of stopping therapy		30	5.0	1.15

Table No. 3: Improvement of males and females between two groups after stopping therapy

Females			
Variables	Uric Acid (2.4-6)	Uric Acid above 6	Improve-ment
ATT 1st time	11	0	100 %
ATT 2nd time	12	1	91.6 %
Total	23	1	
Males			
Variables	Uric Acid (3.4-7)	Uric Acid above 7	Improvement
ATT 1st time	19	1	94.77 %
ATT 2nd time	15	2	86.67 %
Total	33	3	

Table No. 4: Differences between means of uric acid between two groups

		Mean	SD	T	P. value	95% CI
UA-1	ATT 1st time	4.6700	.72595	-.035	0.972	-0.38-0.37
	ATT 2nd time	4.6767	.74124			
UA-2	ATT 1st time	6.4467	.91264	-.759	0.451	-0.70-0.31
	ATT 2nd time	6.6400	1.05458			
UA-3	ATT 1st time	4.7167	.83173	-1.091	0.280	-0.80-0.23
	ATT 2nd time	5.0000	1.15460			

Table No. 5: Test for association

	Mean	SD	p-value
Uric Acid at start	4.67	0.72	0.01
Uric Acid After 2 months	6.54	0.98	

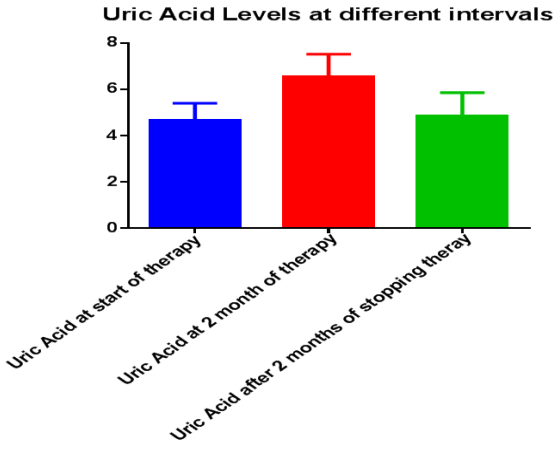

Figure No. 1: Uric Acid levels at different intervals

Although there no significant differences between the UA levels at different intervals of both groups (summarized in table 4.0) but there is significant increase of UA levels (4.67 ± 0.72) at start of the therapy and after two months of the therapy (UA levels = 6.4 ± 0.91 in Cat-1 and UA levels = 6.6 ± 1.05) with p-value 0.01 as shown in table 5.

After stopping of ATT therapy, there is 100% recovery of females patient in CAT-1 as compared to CAT-2 females patients (91.6%), similarly 94.77% males improved in CAT-1 as compared to CAT-2 males whose recovery is 86.67% as shown in table 3.

The overall UA levels are graphically shown in figure 1.0 while the comparison of upsurges in UA level between males and females is graphically in figure 2.0.

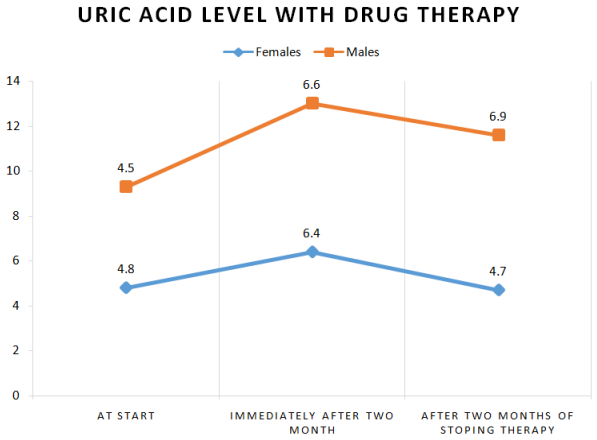

Figure No. 2: Uric Acid levels between males and females in both groups

DISCUSSION

Tuberculosis is a dreadful chronic infectious disease, targeting mostly the poor and under privileged communities in the world. But at the same time, it is a potentially curable disease with a very good outcome, if timely diagnosed and treated. Anti-tuberculosis medication is recommended for six months including first 2-months as intensive phase and last 4-months as maintenance phase. In the intensive phase, along with other ATT, pyrazinamide is given. Its metabolites can cause decrease excretion of uric acid by the kidney and thus can lead to hyperuricemia.

In our study, we have two groups as CAT-1 and CAT-2. In CAT-1, the UA was 4.67 ± 0.72, 6.44 ± 0.91 and 4.71 ± 0.83 at the start, at two months and after two months of stopping ATT respectively. Similarly, in CAT-2 patients, UA was 4.67 ± 0.74 at start of therapy and was upsurges to 6.64 ± 0.91 with two months therapy which downgrade to 5 ± 1.15 after two months of stopping pyrazinamide. In our study, after stopping of ATT therapy, there was 100% recovery of female patient in CAT-1 as compared to CAT-2 female patients (91.6%). Similarly 94.77% male improved in CAT-1 as compared to CAT-2 male whose recovery was 86.67%.

The findings of our study are also closed to the findings of another study conducted by Mahantesh A et al, at Bangalore. It was observed " that mean serum uric acid at 0th week was 5.1 mg/dl, which increased to 6.8 mg/dl and 6.6 mg/dl at 2nd and 8th week, respectively". Among all these patients, "48.72% patients showed 25-

50% increase in the uric acid level, while 41.02% patients showed an increase in serum uric acid level beyond normal range (>7 mg/dl)". Similarly, there were non-significant increased in UA levels in 41.02% patients from 2nd and 8th week[10].

The finding of our study are also close to the finding of another study, conducted by Louthrenoo W et al, "showing a little higher results at second week, with a significant increase in uric acid level (9.78 ± 3.21 mg/dL, P < 0.001)". In all theses patients, these changes persisted for the whole second month, but returned to the baseline value at the end of fourth month. Over all, only 13 patients (81.25%) had developed hyperuricemia[11].

The findings of our study are also close to the finding of another study, conducted by Pokam BD et al, showing that "hyperuricemia was observed in 56/96 (58.3%) of the studied group as compared with four of 32 (12.5%) in the control group ($p < 0.001$)". It was also observed in this study that treatment duration was significantly associated with hyperuricemia ($p = 0.0016$), while gender has a very little effects ($p = 0.1275$)[12].

These finding of our study are closed to the finding of another study, conducted by Inayat N et al, showing that the serum uric acid in all patients (n-46) was increased progressively and significant surge was observed in 43% (20/46) of patients at the end of 2-months intensive therapy. In this study, there was progressive 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 in weeks 2 and 6, where the levels increased from 2.6 mg/dl to 7.2 mg/dl. This level remained stable between week 6 and 8, where a very small change (7.2 mg/dl -7.4 mg/dl) was observed. Although in our study, there is no such significant differences between the UA levels at different intervals of both groups but there is significant increase of UA levels (4.67 ± 0.72) at start of the therapy and after two months of the therapy (UA levels = 6.4 ± 0.91 in Cat-1 and UA levels = 6.6 ± 1.05) with p-value 0.01[13].

Based on the result observed in this study show that significant hyperuricemia can occurs during intensive phase of anti tuberculosis treatment, especially in CAT-2 patients. However these are usually mild and self-limiting and do not need to stop the ATT. But severe symptomatic hyperuricemia may need a treat while keeping the ATT continuous.

CONCLUSION

The serum uric acid increases with anti-tuberculosis therapy, especially in CAT-2 patients. Though, it usually improved spontaneously without any intervention, but its level need to be closely monitored in tuberculosis patients and should be treated accordingly if symptoms appear.

Author's Contribution:

Concept & Design of Study:	Jamaluddin
Drafting:	Jamaluddin, Nizamuddin
Data Analysis:	Abid Shah
Revisiting Critically:	Nizamuddin, Abid Shah
Final Approval of version:	Jamaluddin

Conflict of Interest: The study has no conflict of interest to declare by any author.

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