



Incidence and Risk Factors of Hyperuricemia during Anti-Tubercular Treatment – A Trivial Issue or a Tempest in a Teacup?

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ABSTRACT

We studied the incidence and risk factors leading to hyperuricemia among the patients who were started on anti-tubercular therapy. We found that age, sex, seasonal variations, Body Mass Index, socio-economic factors all played a part in determining the frequency of symptoms in this patient cohort. The type of Tuberculosis (pulmonary vs extra-pulmonary) also determined whether the symptoms were mild or severe.

Keywords: Tuberculosis, Hyperuricemia, Anti-tubercular Treatment

1. INTRODUCTION

There has been a dramatic increase in the cure rate of TB since the introduction of the RIPE regimen in 1974[1]. But this victory has not been devoid of problems. The 4 drugs Rifampin, INH, pyrazinamide (PZA) and ethambutol (EMB) not only have to be taken for a long duration, but are also associated with a myriad of adverse effects, ranging from hepatotoxicity to peripheral neuropathy and blindness.

One particularly innocuous side effect of both PZA and EMB is hyperuricemia. For the last 70 years, there has been a debate whether this finding merited therapeutic intervention or could be ignored if the patient was asymptomatic. Even though the number of reported cases of hyperuricemia due to ATT which progressed to gouty arthralgia or urate nephropathy and required pharmacological control with allopurinol, febuxostat or probenecid were low, in a country like India, with 26 lakh cases of TB[2], even a 1% chance of symptomatic hyperuricemia will translate to an increase in morbidity and lead to treatment non compliance, giving rise to MDR-TB and relapse.

Prompt identification of at risk patients and preemptive prophylaxis will ensure that severe symptoms warranting discontinuation of either PZA or EMB doesn't develop and the patient is cured in the shortest time possible without complications.

In this study, we sought to identify the incidence of hyperuricemia and identify risk factors for symptomatic hyperuricemia

Materials and methods

This study was conducted in our hospital for a period of 1 year. Both male and female patients were recruited for the study after ethical board clearance and taking informed consent, via the following inclusion criteria:

1. Individuals 18 years and above with pulmonary or extrapulmonary TB confirmed by trueNat, X-ray or culture
2. Those who consented to repeated blood draws for measuring uric acid levels
3. Motivated individuals with strong family support who had a good chance of adhering to the regimen

Exclusion criteria:

1. Those on drugs known to cause hyperuricemia (thiazides, cyclosporin, chemotherapy)
2. Those with abnormal renal function tests
3. Those suffering from comorbidities which lead to gout like chronic alcoholism, recent surgery, congestive heart failure

Patients were instructed to report to the hospital for regular blood draws at 1, 2, 4, 6 weeks and to also come to hospital if they started experiencing symptoms like arthralgia, arthritis, swelling of joints, flank pain

All data was statistically analysed using SPSS25

Result

36 males(36%,total =100) and 48 females (48%,total=100)were afflicted with symptomatic hyperuricemia ,ranging from joint stiffness to pain in great toe and urate nephropathy.

the age range in males varied from 25 to 63 years,with 16 pts > 50 years old(44%) ,whereas in females it ranged from 23 to 61 years,with 14 pts > 50 years (29%)

33% of the relapsed males suffered from hyperuricemia,whereas it was 66% for relapsed females.The distribution of pulmonary and extrapulmonary cases in males was almost similar at 35.48% and 36.84% respectively,but for females,only 44.44% of pulmonary cases were affected,compared to 54.54% of extrapulmonary cases

The mean serum uric acid for symptomatic patients peaked at 2 months and was (10.81 +-8.42) for men and (10.55 +-9.37) for women

The most common symptoms of hyperuricemia were arthralgia and joint stiffness(80%),16% of patients complained of great toe pain and 4% developed urate nephropathy

There was a peak incidence of cases in during the summer and another smaller peak during winter

There was a direct relationship between BMI and risk of hyperuricemia(table 1)

Table 1 – relationship between BMI and hyperuricemia

BMI (kg/m ²)	No of Cases
< 18	11
18-25	20
26-30	23
>30	1. 26

Socioeconomic status inversely correlates with incidence of hyperuricemia(table 2)

Table 2 – relationship between socioeconomic status and hyperuricemia

Kuppuswamy scale	Cases
Upper class	9
Upper middle	11
Lower middle	15
2. Upper lower	3. 22
4. Lower	5. 37

Discussion

The occurrence of hyperuricemia in patients taking ATT was first elucidated by Cullen et al [3],who showed that PZA caused hyperuricemia.Attention was further drawn to the fact by [4],who even went on to question the position of pyrazinamide in the short term anti TB regime,due to this adverse effect that it associated with, and the discovery was consolidated by [5].That this seemingly harmless presentation could manifest as a serious illness was documented by [6].Soon,the fact that ethambutol was also a likely culprit was pointed out by Postlethwaite et al and other workers[7][8][9][10][11].

From our study we observe that 42% of the patients went on to develop symptomatic hyperuricemia,a significant number. Serum urate levels peaked in the 2nd month[12][13] and were similar for both genders.Female patients had a much higher risk of suffering from symptomatic hyperuricemia than males,most likely due to lesser S.urate clearance.This is counter intuitive since males are generally at a greater risk of developing hyperuricemia and gout.

The most common symptoms were joint stiffness,shoulder,knee or elbow arthralgia and in some patients,pain in the great toe,resembling gout.6 patients ended up with urate nephropathy.This mirrors the work of [14].Patients of all age group were affected,which was clearly reflected in our study with the youngest patient being 23 and the oldest being 63,but there was a slight preponderance for elderly males and younger female patients.Also there was a higher incidence of symptoms in female patients who had relapsed,compared to their male counterparts.The serum uric acid was the highest 2 months from the commencement of treatment,similar to findings of [13] and was around the same in both genders.

A noteworthy finding was that creatinine clearance drastically improved for all the patients,suggesting that ATT should be continued regardless of symptomatic hyperuricemia.This was in accordance with [12].The distribution of cases was equal between pulmonary and extrapulmonary male patients,but females with extrapulmonary TB,were at a greater risk of displaying symptoms.Majority of the patients showed a direct correlation with the

serum uric acid level and severity of symptoms, which echoed the results outlined by [5]. Interestingly, some of the patients with arthralgia had near normal serum uric acid levels, confirming the work of [15].

Regarding seasonal variation, we observed that there was a major peak during the summer months (March-June) and a smaller peak in winter (Nov-Jan). This was in agreement with [16] and [17] and is due to the fact that serum urate levels are highest during summer, and the winter peak is due to high intake of purine rich foods and alcohol consumed during the holidays. We studied the role of BMI with degree of hyperuricemia and noticed that as the BMI increased, so did the risk for developing symptoms. This is to be expected since it is a well-known fact that obesity is a risk factor for hyperuricemia and gout [18][19]. Lastly, we tried to correlate socioeconomic condition of our patients with their symptoms and found that those belonging to poorer section of society were more likely to be affected. This matches the finding of [20] and [21].

Conclusion

From our study, we conclude that there is a high risk of developing hyperuricemia in pts on ATT. The most common symptoms are arthralgia and joint stiffness. Younger aged females sex and older aged males, females with extrapulmonary TB and females who had relapsed are at higher risk. There is also a higher chance during summer and winter months, patients belonging to lower socioeconomic status and those with higher BMI.

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References

- [1] East African/British Medical Research Council. 1974. Controlled clinical treatment of short course (6 months) regime of chemotherapy for treatment of pulmonary tuberculosis. Third report. *Lancet* 2: 237-248
- [2] <https://tbfacts.org/tb-statistics-india/>
- [3] CULLEN JH, EARLY LJ, FIORE JM. The occurrence of hyperuricemia during pyrazinamide-isoniazid therapy. *Am Rev Tuberc*. 1956 Aug;74(2 Part 1):289-92. doi: 10.1164/artpd.1956.74.2-1.289. PMID: 13340157
- [4] Koumbaniou C, Nicopoulos C, Vassiliou M, Manda-Stachouli C, Sakellariou K, Demou GS, Constantopoulos SH. Is pyrazinamide really the third drug of choice in the treatment of tuberculosis? *Int J Tuberc Lung Dis*. 1998 Aug;2(8):675-8. PMID: 9712283
- [5] Taki H, Ogawa K, Murakami T, Nikai T. Epidemiological survey of hyperuricemia as an adverse reaction to antituberculous therapy with pyrazinamide. *Kekkaku*. 2008 Jul;83(7):497-501. PMID: 18709966
- [6] Gupta S, Gupta V, Kapoor B, Kapoor V. Pyrazinamide induced hyperuricaemia presenting as severe bilateral leg cramps. *J Indian Med Assoc*. 2007 Jun;105(6):341-2. PMID: 18232182
- [7] Postlethwaite AE, Kelley WN. Studies on the mechanism of ethambutol-induced hyperuricemia. *Arthritis Rheum*. 1972 Jul-Aug;15(4):403-9. doi: 10.1002/art.1780150411. PMID: 5046470
- [8] Self TH, Fountain FF, Taylor WJ, Sutliff WD. Acute gouty arthritis associated with the use of ethambutol. *Chest*. 1977 Apr;71(4):561-2. doi: 10.1378/chest.71.4.561b. PMID: 852331
- [9] Khanna BK. Acute gouty arthritis following ethambutol therapy. *Br J Dis Chest*. 1980 Oct;74(4):409-10. PMID: 7213543
- [10] Louthrenoo W, Hongsongkiat S, Kasitanon N, Wangkaew S, Jatuworapruk K. Effect of Antituberculous Drugs on Serum Uric Acid and Urine Uric Acid Excretion. *J Clin Rheumatol*. 2015 Oct;21(7):346-8. doi: 10.1097/RHU.000000000000297. PMID: 26398460
- [11] Pham AQ, Doan A, Andersen M. Pyrazinamide-induced hyperuricemia. *P T*. 2014 Oct;39(10):695-715. PMID: 25336865; PMCID: PMC4189695
- [12] Adebisi SA, Oluboyo PO, Okesina AB. Effect of drug-induced hyperuricaemia on renal function in Nigerians with pulmonary tuberculosis. *Afr J Med Med Sci*. 2000 Sep-Dec;29(3-4):297-300. PMID: 11714010
- [13] Khanna BK, Gupta VP, Singh MP. Ethambutol-induced hyperuricaemia. *Tubercle*. 1984 Sep;65(3):195-9. doi: 10.1016/0041-3879(84)90075-8. PMID: 6207648
- [14] Inoue T, Ikeda N, Kurasawa T, Sato A, Nakatani K, Ikeda T, Yoshimatsu H. [Hyperuricemia and arthralgia during pyrazinamide treatment]. *Nihon Kogyaku Gakkai Zasshi*. 1999 Feb;37(2):115-8. Japanese. PMID: 10214039
- [15] Jenner PJ, Ellard GA, Allan WG, Singh D, Girling DJ, Nunn AJ. Serum uric acid concentrations and arthralgia among patients treated with pyrazinamide-containing regimens in Hong Kong and Singapore. *Tubercle*. 1981 Sep;62(3):175-9. doi: 10.1016/0041-3879(81)90003-9. PMID: 7314249
- [16] Choi HJ, Lee CH, Lee JH, Yoon BY, Kim HA, Suh CH, Choi ST, Song JS, Joo H, Choi SJ, Lee JS, Shin K, Jun JB, Baek HJ. Seasonality of gout in Korea: a multicenter study. *J Korean Med Sci*. 2015 Mar;30(3):240-4. doi: 10.3346/jkms.2015.30.3.240. Epub 2015 Feb 16. PMID: 25729244; PMCID: PMC4330476

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- [17] Elliot AJ, Cross KW, Fleming DM. Seasonality and trends in the incidence and prevalence of gout in England and Wales 1994-2007. *Ann Rheum Dis.* 2009;68:1728–1733. doi: 10.1136/ard.2008.096693
- [18] Sivakumar K, Thamarai R, Pragatha RJ. Screening of Serum Uric Acid in Obese Individuals in Rural Population. *International Journal of Scientific Study.* 2014; Vol 2 | Issue 2
- [19] Gulab Kanwar and Rahul Kabra. Serum uric acid level and obesity: An association. *International Journal of healthcare Sciences.* 2016; 4(1):52–55
- [20] Gardner MJ, Power C, Barker DJ, Paddy R. The prevalence of gout in three English towns. *Int J Epidemiol.* 1982 Mar;11(1):71-5. doi: 10.1093/ije/11.1.71. PMID: 7085182
- [21] Taylor W, Smeets L, Hall J, McPherson K. The burden of rheumatic disorders in general practice: consultation rates for rheumatic disease and the relationship to age, ethnicity, and small-area deprivation. *N Z Med J.* 2004 Oct 8;117(1203):U1098. PMID: 15477922