Research Article

Effect of diet, body mass index, and proton pump inhibitors on antitubercular therapy–induced hyperuricemia in patients of tuberculosis

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Abstract

Background: Risk factors for developing hyperuricemia other than inherited abnormalities are obesity, moderate to heavy alcohol intake, high blood pressure, and abnormal kidney function. Factors that increase urate formation are excess dietary purine intake, increased nucleic acid turnover, obesity, and exercise. Factors that decrease urate excretion are kidney disease, diabetic ketoacidosis, hypertension, drugs, and trisomy 21. **Objectives:** To see the effect of diet, body mass index (BMI), and proton pump inhibitors (PPIs) in antitubercular therapy (ATT)–induced hyperuricemic tubercular patients. **Materials and Methods:** This prospective study was conducted at a tertiary care teaching hospital of Rajasthan in tubercular patients aged 18–65 years of either sex. Serum uric acid level was estimated at weekly interval after starting ATT for 2 months along with baseline value. Patients developing hyperuricemia were finally included in the study. Patients were divided into vegetarian and nonvegetarian groups. BMI of all the patients was calculated. All the patients were grouped into two categories on the basis of those receiving or not receiving PPI. Appropriate statistical tests were used to compare the data. **Results:** Out of the total 123 hyperuricemic patients, 71 patients were on vegetarian diet while 52 patients were on nonvegetarian diet. Difference between the serum uric acid levels of vegetarian and nonvegetarian groups was found to be insignificant. Out of the total, 90 patients were underweight, 28 were having normal weight while 5 were overweight. Pearson's correlation test showed no correlation between BMI and serum uric acid levels. PPIs were taken by 72 patients. Difference between serum uric acid levels of patients receiving PPIs and those not receiving PPIs was found to be insignificant. **Conclusion:** The serum uric acid level was not found to be affected by diet, BMI, and use of PPI in ATT-treated tubercular patients probably due to some altered physiology in these patients.

KEY WORDS: Diet; Body Mass Index; Proton Pump Inhibitors; Antitubercular Therapy; Hyperuricemia

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Introduction

Uric acid is the final breakdown product of purine degradation in human beings having no physiological role.[1,2] Presence of abnormally high level of uric acid in blood is known as hyperuricemia. In humans, the normal upper limit of serum uric acid is 6 mg/dL for women and 7 mg/dL for men.[3] Some authors consider normal upper limit as 6.5 mg/dL. Hyperuricemia can result from increased production or decreased excretion of uric acid or from a combination of the two.

Risk factors for developing hyperuricemia besides inherited abnormalities are obesity, moderate to heavy alcohol intake, high blood pressure, and abnormal kidney function. Factors that increase urate formation are excess dietary purine intake, increased nucleic acid turnover, obesity, and exercise. Factors that decrease urate excretion are kidney disease, diabetic ketoacidosis, hypertension, drugs, and trisomy.[4]

Diet contributes to the serum urate level.[5] Recent research by Choi and others had shown that purines from meat and fish clearly increase risk of gout, while purines from vegetables do not.[6] Dairy foods actually appear to lower risk of Gout.[6] Recent studies have confirmed association of hyperuricemia with high intake of meat, seafood, and alcohol (especially beer) but not with "high-purine vegetables" such as beans, peas, and lentils.[7–10]

Hyperuricemia has been associated with obesity. Body mass index (BMI) is a simple index of weight for height that is commonly used to classify underweight, overweight, and obesity in adults The BMI values are age independent and the same for both sexes.[11] More is the obesity more are the chances of raised serum uric acid levels.[12] The association of obesity with overweight has a number of effects on urate metabolism, which include decreasing urate clearance and increasing urate production.[13]

Drugs also alter uric acid metabolism. A large number of drugs affect the production of uric acid or a decrease in uric acid excretion, while others lower serum uric acid level by an increase in uric acid excretion and decrease in absorption. Diuretics and pyrazinamide are the most common hyperuricemic agents.[14] Ethambutol is also known to cause hyperuricemia.[15,16] Both pyrazinamide and ethambutol are antitubercular drugs routinely prescribed in antitubercular therapy (ATT) as per WHO guidelines 1997. Two case reports have suggested that omeprazole, a proton pump inhibitor (PPI), may rarely cause increased uric acid levels and acute gout attack.[17] A study was conducted to evaluate the incidence rates of newly diagnosed gout cases among omeprazole based on the case reports describing patients who developed a first episode of acute gout while being treated with the PPI omeprazole.[18] Two recent case reports of first-time acute gout during use have raised concern over a possible causal association.[19] Both patients developed gout within the first 2 weeks of omeprazole treatment.[19] In addition to these reports, the manufacturer has received 21 spontaneous reports over the last 10 years about patients suffering from gout during omeprazole treatment.[18] No formal studies have been published evaluating the frequency of newly diagnosed gout among users of omeprazole. PPIs are commonly used to treat unwanted gastrointestinal symptoms due to antitubercular drugs in tubercular patients. So this study was planned to see the effect of diet, BMI, and the use of PPIs in ATT-induced hyperuricemia in tubercular patients.

Materials and Methods

This study was conducted in a tertiary care teaching institute located in Rajasthan, which is not only catering to rural population residing around but also funneling patients from nearby places. Approval from Institutional Ethics Committee was taken before starting the study. Data were collected in the approved proforma after taking written consent. Patients diagnosed with tuberculosis and aged between 18 and 65 years of either gender except pregnant and lactating women, with no comorbidities, were recruited for the study. Baseline value of serum uric acid level was estimated. Serum uric acid level was monitored at weekly interval after starting ATT for 2 months. Uric acid analysis was done by fully automatic analyzer after proper calibration and quality control by Caraway method (colorimeter method) in the Central Laboratory of the Hospital. Patients developing hyperuricemia at any point of the study were finally included in the study. Patients were divided into vegetarian and nonvegetarian groups on the basis of their diet. BMI of all the patients was calculated and the patients were subdivided into three subgroups on the basis of classification of overweight and obesity according to their BMI, that is, <18.5 (underweight), 18.5–24.99 (normal), and >25 (overweight). All the patients were grouped into two categories on the basis of those receiving or not receiving PPI. Appropriate statistical tests were done by calculating the mean and SD to compare baseline and hyperuricemic values of serum uric acid. Correlation between BMI of the patients and serum uric level was also determined.

Results

Total number of patients included in this study was 183; out of which 60 patients were lost for follow-up. Henceforth 123 patients were followed for a period of 2 months. Out of these 123 patients on ATT, 90 patients developed hyperuricemia, and in 33 patients, serum uric acid level was normal throughout the 2-month duration. Out of total 123 patients, 76 were male and 47 female. Seventy one patients were on vegetarian diet while 52 patients were on nonvegetarian diet. Ninety patients were underweight, 28 patients were having normal weight while 5 patients were overweight. Out of the 123 patients PPI was taken by 72 patients.

The serum uric acid levels of vegetarian and nonvegetarian groups were compared by *t*-test, which was found insignificant (Table 1).

There was no correlation between BMI and serum uric acid level on Pearson's correlation test. The value of r was -0.0123. Thus, negligible correlation was found between BMI and serum uric acid level. Coefficient of determination (r^2) was found to be 0.0002, which concludes that there was no variability of response of data around its mean (Figure 1).

Comparison of serum uric acid level of patients receiving PPI with those not prescribed PPI was found to be insignificant after applying *t*-test (Table 2).

Discussion

Hyperuricemia develops during ATT due to pyrazinamide and ethambutol, which sometimes warrants withdrawal of the

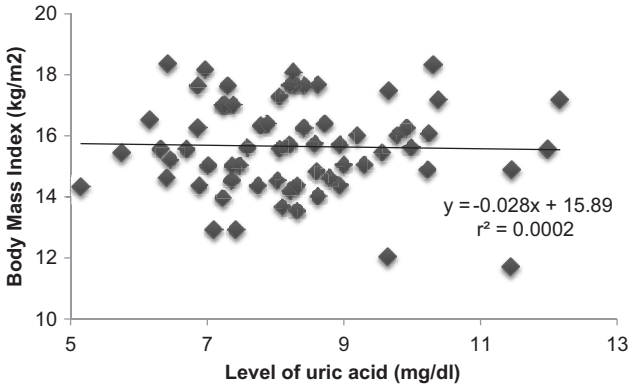

Figure 1: Correlation between BMI and uric acid level.

drugs because of severe painful arthralgia. In this study, we tried to evaluate whether there is possible relationship between development of hyperuricemia and other factors such as diet and BMI, which are associated with its development.

Effect of dietary habit on serum uric acid level was found to have an add-on effect in causing hyperuricemia, though no detailed history of dietary habits was taken. According to Schmidt JA, there can be different diet groups as vegetarians, meat eaters, vegans, and fish eaters.[5] Some take more vegetables and fruits, few take more dairy products among which some take cheese in more quantity and some like milk. In the above study, it was found that the four diet groups also differed significantly in their nutrient intake. It was found that there were significant differences between the diet groups in mean BMI; meat eaters had the highest BMI followed by vegetarians, fish eaters, and vegans. The comparison of uric acid concentration between vegetarians and nonvegetarians showed no significant difference in our study. Possible explanation to this could be differences in diet groups within the broad groups; vegetarian and nonvegetarian was not considered in our study. Detailed history of dietary intake was not taken. Moreover, tuberculosis is usually found in malnourished people and in those of low socioeconomic status. In our study of 123 patients, 90 patients were underweight. Further, few patients are likely to give false history of being vegetarian due to religious or family restrictions.

Hyperuricemia has been associated with obesity. According to a study, the prevalence of gout demonstrated a dose–response pattern in relation to BMI, being greater among higher BMI categories. For example, while approximately 1%–2% of the participants with a normal BMI value reported a diagnosis of gout, the proportion was 3% among the overweight participants, 4%–5% among those with class I obesity, and 5%–7% among individuals with class II or class III obesity. Graphically, at higher BMI values, the proportion of patients with gout steadily increased. Furthermore, across the full spectrum of BMI, the proportion of individuals with hyperuricemia exceeded the proportion with gout, at any given BMI value.[20] In this study, no correlation was found between BMI of the patients and increase in serum uric acid level. In another study, a graded increase of serum uric acid level was found.[21] Difference in both the study could be explained because that study considered fat distribution along with body weight which was not considered in our study. Hence it could be another search area for future researchers.

The results of our study do not show any association of PPIs with increase in serum uric acid levels. Although there have been two case reports and 21 spontaneous adverse drug event reports to the manufacturer in which omeprazole has been associated with onset of gout,[18,19] similar results have been found in the study by Meier and Jick.[18] According to that study, omeprazole use was not indicated with a substantial increased risk of developing gout. The incidence rate of newly treated gout was relatively low in users of ulcer-healing drugs. But they

Table 1: Mean serum uric acid levels with dietary habit in patients on ATT

Serum uric acid levels	Dietary habits	Number of patients	Mean	SD	*p* Value*
Baseline value	Vegetarian	71	4.829	1.3753	> 0.05
	Nonvegetarian	52	4.607	1.1612	
Hyperuricemic value	Vegetarian	53	9.125	3.2220	> 0.05
	Nonvegetarian	37	8.495	2.8578	

*p Value > 0.05 (nonsignificant).

Table 2: Serum uric acid with PPI and without PPI in patients on ATT

Serum uric acid levels	PPI	Number of patients	Mean	SD	*p* Value*
Baseline value	No	51	4.832	1.3443	>0.05
	Yes	72	4.667	1.2531	
Hyperuricemic value	No	38	8.959	3.2822	>0.05
	Yes	52	8.788	2.9444	

*p Value > 0.05 (nonsignificant).

also stated that there is no evidence to assume that the lack of an omeprazole effect on gout incidence in previously healthy subjects was due to small statistical power and other known risk factors such as higher age, male gender, overweight, and so on. While there was no substantial evidence to support the hypothesis that omeprazole use is consistently associated with an increased risk of developing gout. This could be because omeprazole may rarely cause or trigger gout in particular individuals, although there is no obvious plausible biological mechanism. Furthermore, hyperuricemia has been mentioned as one of the rare side effects of omeprazole and pentoprazole in the Physicians' Desk Reference.[22]

Conclusion

We can conclude that the serum uric acid level was not affected by diet, BMI, and addition of PPI in ATT-treated tubercular patients. This could be probably due to some altered physiology in these patients, which could be explored further in future research.

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