ORIGINAL ARTICLE

Evaluation of Serum Uric Acid Levels in Patients with Thyroid Disorders in A Tertiary Care Hospital of Kolkata, India

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ABSTRACT

An analytical, case-control study was conducted in the Department of Biochemistry of R. G. Kar Medical College & Hospital, West Bengal, India, to evaluate changes in serum uric acid levels in patients with thyroid disorders. 50 newly diagnosed cases of primary hypothyroidism and hyperthyroidism in each group, both males and females aged 15-60 years (before starting any kind of thyroid medications) were taken as cases. 50 age and sex matched apparently healthy euthyroid individuals were taken as controls. Our exclusion criteria were: children, older individuals (>60 years), thyroid disorders other than primary hypothyroidism and hyperthyroidism, chronic kidney disease etc. Serum uric acid levels were observed 4.19±0.74 mg/dL, 7.07±1.15 mg/dL, and 4.33±1.01 mg/dL in euthyroid control group, hypothyroid and hyperthyrod patients respectively. Serum uric acid level was found increased in hypothyroid patients as compared to hyperthyroid patients and control individuals. A significant positive correlation was found between serum TSH and uric acid levels in primary hypothyroidism cases ($r = +0.765$; $p<0.05$). Besides, a significant negative correlation was observed between serum FT_4 and uric acid levels in primary hypothyroidism cases ($r = 0.664$; $p<0.05$). Association of serum uric acid with TSH levels in primary hyperthyroid cases did not follow normal distribution pattern; however, it showed statistically non-significant negative correlation ($r = 0.223$; $p>0.05$). No differences were observed in serum uric acid levels in cases of primary hyperthyroidism compared to age and sex matched euthyroid controls ($p>0.05$). However, higher serum uric acid levels were observed in primary hypothyroidism compared to primary hyperthyroidism patients ($p<0.05$).

Keywords: Primary hypothyroidism, primary hyperthyroidism, uric acid, hyperuricemia

International Journal of Human and Health Sciences Vol. 10 No. 02 April'26

DOI:https://doi.org/10.31344/ijhhs.v10i2.938

INTRODUCTION

Thyroid disorders are very familiar now-a-days thereby becoming a burden to the society. Hypo-functioning of thyroid gland will lead to hypothyroidism. When TSH level is high but FT_4 level is low then this condition is known as primary hypothyroidism. Primary hyperthyroidism develops when there is hyperfunctioning of thyroid gland which elevates FT_4 and FT_3 levels with reduction of TSH level.[1] Thyroid hormones affect various metabolic pathways including carbohydrate, lipid, protein as well as nucleotide metabolism. They also affect brain development, respiratory, cardiovascular and nervous system functions, muscle strength, skin dryness, menstrual cycles, maintenance of body temperature and body weight, etc.[1] Thyroid hormones play crucial role in growth, cell differentiation and cellular metabolism.[2]

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Thyroid hormones affect both renal morphology and function, thus they are essential for kidney growth and development. Thyroid deficiency state (hypothyroidism) results in decreased renal plasma flow and glomerular filtration rate (GFR).[3]

Hyperuricemia is a common metabolic disorder. It is associated with various metabolic disorders like hypertension, diabetes, insulin resistance and dyslipidemia. Risk factors of hyperuricemia are purine rich diet, alcohol consumption, smoking, sedentary lifestyle and lack of physical activity.[4] Purine rich diet includes meat, pulses, legumes, green leafy vegetables, etc. Hyperuricemia is the independent risk factor for gout.[4] Epidemiological data suggest that hyperuricemia is more prevalent in developed countries than developing countries for increased intake of non-vegetarian diet in the former.[5]

Evidence suggests that hypothyroidism is associated with decreased myocardial contractility, reduced stroke volume and increased peripheral vascular resistance, leading to the reduction of effective renal plasma flow and glomerular filtration rate (GFR) and decreased clearance of uric acid, thus promoting elevation of serum uric acid level in hypothyroidism.[6] As the local Bengal population mostly thrive on non-vegetarian food, including fish, mutton, beef, chicken, egg etc., purine rich diet, might aggravate hyperuricemia. The effects of hyperthyroidism on the kidney are usually opposite to the effects of hypothyroidism. Hyperthyroidism increases GFR and renal blood flow due to increased cardiac output, decreased systemic vascular resistance.[7] Therefore, a relation exists between hemodynamic changes resulting from thyroid disoreders and uric acid metabolism, as disturbance in thyroid hormones affect purine metabolism. Those phenomena together lead to alteration in the uric acid levels in thyroid patients. Hence, this study was designed for estimation and observation of changes in serum uric acid levels in patients with thyroid disorders.

METHODS

This analytical, case-control study was conducted in the Department of Biochemistry of R. G. Kar Medical College & Hospital, West Bengal, India. 50 newly diagnosed cases of primary hypothyroidism and hyperthyroidism in each group, both males and females aged 15–60 years (before starting any kind of thyroid medications) were taken as cases. 50 age and sex matched apparently healthy euthyroid individuals were taken as controls. Both cases (primary hypothyroidism and primary hyperthyroidism) and control subjects were selected from the same geographical area. All patients with raised TSH and reduced FT4 values considered as primary hypothyroidism and reduced TSH and raised FT4 considered as primary hyperthyroidism along with presence of clinical symptoms. Our exclusion criteria were: children, older individuals (>60 years), thyroid disorders other than primary hypothyroidism and hyperthyroidism. Any other disorders known to cause rise in urea, creatinine and uric acid, e.g., chronic kidney disease, were also excluded from the study. Finally, following the above inclusion and exclusion criteria, 50 cases each in primary hypothyroidism and hyperthyroidism and 50 euthyroid subjects were selected in the control group.

Blood samples were collected in a clot vial from the study subjects in aseptic manner following the appropriate protocol. Serum was separated and measured immediately after centrifugation at 3000 rpm for 15 mins. Thyroid profile (TSH, FT_4, FT_3) along with uric acid, urea, creatinine was measured for this study. Then, serum TSH, FT_4 and FT_3 were measured by chemiluminescent immunoassay (CLIA) technique with Centaur XP autoanalyzer. If TSH (>4.78 µIU/mL) and FT_4 (<0.89 ng/dL), these subjects were classified as primary hypothyroidism and TSH (<0.55 µIU/mL) and FT_4 (>1.76 ng/dL) as primary hyperthyroidism. Serum uric acid was estimated by end point uricase method which was measured by KONELAB Prime 60i chemistry autoanalyzer in cases of primary hypothyroidism, hyperthyroidism and control group.

Data obtained was analyzed for comparison of serum uric acid level in cases (both primary hypothyroidism and hyperthyroidism) and age and sex matched euthyroid control group. The details of each patient on clinical visit were recorded in pre-formed data sheet. For statistical analysis data was entered into a Microsoft excel spreadsheet and then analyzed by using SPSS version 26.0 for Windows. Kruskal-Wallis test was applied. Moreover, Spearman correlation coefficient was done. A p-value <0.05 was considered statistically significant.

RESULTS

Serum uric acid levels were observed 4.19±0.74 mg/dl, 7.07±1.15 mg/dl, and 4.33±1.01 mg/

dl in euthyroid control group, hypothyroid and hyperthyrod patients respectively. Serum uric acid level was found increased in hypothyroid patients as compared to hyperthyroid patients and control individuals (Table 1). A significant positive correlation was found between serum TSH and uric acid levels in primary hypothyroidism cases (r =+0.765; p<0.05) (Table 2). A significant negative correlation was observed between serum FT_4 and uric acid levels in primary hypothyroidism cases (r=0.664; p<0.05) (Table 3). Association of serum uric acid with TSH levels in primary hyperthyroid cases did not follow normal distribution pattern; however, it showed statistically non-significant negative correlation (r=0.223; p>0.05) (Table 4). No differences were observed in serum uric acid levels in cases of primary hyperthyroidism compared to age and sex matched euthyroid controls (p>0.05). However, higher serum uric acid levels were observed in primary hypothyroidism compared to primary hyperthyroidism patients (p<0.05) (Table 5).

Table 1: Serum uric acid levels in study subjects (N=150)

Group	Mean±SD	Median (IQR)	Kruskal-Wallis H value	p-value
Control (n=50)	4.19±0.74	4.30 (1.2)	92.730	<0.05[S]
Hypothyroid (n=50)	7.07±1.15	7.15 (1.5)		
Hyperthyroid (n=50)	4.33±1.01	4.45 (1.7)		

Kruskal- Wallis test was applied; S=significant

Table 2: Correlation between serum TSH and uric acid levels in primary hypothyroidism

Variables	Mean±SD	Median (IQR)	Correlation coefficient (Spearman rho)	p-value
TSH (µIU/ml)	48.54±40.20	32.70 (54.6)	+0.765	<0.05[S]
Uric acid (mg/dl)	7.07±1.15	7.15 (1.5)		

Spearman correlation coefficient was applied; S=significant.

Table 3: Correlation between serum FT_4 and uric acid levels in primary hypothyroidism

Variables	Mean±SD	Median (IQR)	Correlation coefficient (Spearman rho)	p-value
FT_4 (ng/dl)	0.59±0.14	0.60 (0.1)	–0.664	<0.05[S]
Uric acid (mg/dl)	7.07±1.15	7.15 (1.5)		

Spearman correlation coefficient was applied; S=significant.

Table 4: Correlation between serum TSH and uric acid levels in primary hyperthyroidism

Variables	Mean±SD	Median (IQR)	Correlation coefficient (Spearman rho)	p-value
TSH (µIU/ml)	0.14±0.06	0.10 (0.1)	–0.223	>0.05[NS]
Uric acid (mg/dl)	4.33±1.01	4.45 (1.7)		

Spearman correlation coefficient was applied; NS=not significant.

Table 5: Comparison of serum uric acid levels in euthyroid controls, primary hypothyroidism and hyperthyroidism cases (N=150)

Group	Mean±SD	Median (IQR)	Donn Bonferroni value	p-value
Control (n=50)	4.19±0.74	4.30 (1.2)	Euthyroid vs. Hyperthyroid 0.040	>0.05^{NS}
Hypothyroid (n=50)	7.07±1.15	7.15 (1.5)		
Hyperthyroid (n=50)	4.33±1.01	4.45 (1.7)	Hypothyroid vs. Hyperthyroid 70.560	<0.05^{S}

Donn Bonferroni test was applied; S=significant, NS=not significant.

DISCUSSION

Thyroid disorders affect almost all the organs in the human body including kidney. Thyroid disorders are associated with altered serum uric acid level predominantly hyperuricemia, leading to numerous comorbidities including hypertension, type 2 diabetes mellitus and metabolic syndrome, which will hamper day to day activities.[8] Uric acid is the essential parameter to be measured as it involves "cardio-nephro metabolic" disorders. Various study have reported a relation between alteration of serum uric acid level and cardiovascular risk factors such as hypertension, diabetes mellitus and metabolic syndrome suggesting possible pathophysiologic link between these conditions with hyperuricemia.[9] Hypothyroidism may be associated with cardiovascular mortality. There is a need for an effective treatment to manage the disease.[10]

Our study showed that the mean serum uric acid level is much more increased in case of primary hypothyroid cases than hyperthyroid cases. It also showed a significant positive correlation between serum TSH and uric acid levels and significant negative correlation between serum FT4 and uric acid levels in cases of primary hypothyroidism. Hypothyroidism leads to considerable changes in renal function which results in decreased renal blood flow, decrease in glomerular filtration rate (GFR) and decrease in sodium reabsorption in proximal convoluted tubules.[11] The significant elevation of serum uric acid levels in hypothyroid group was attributed to reduced renal plasma flow and impaired glomerular filtration rate, which should be observed periodically for chronic kidney disease as well as gout and coronary heart disease. In hypothyroidism the hyperuricemia is secondary to a decreased renal plasma flow and impaired glomerular filtration.[3] Several mechanisms including reduced cardiac output, increased peripheral vascular resistance, intrarenal vasoconstriction, decreased renal response to vasodilators, and decreased expression of renal vasodilators such as vascular endothelial growth factor and insulin-like growth factor-1, contribute to reduction of renal blood flow and decline in GFR in hypothyroidism. In hypothyroidism, reduced renal blood flow may also be caused by pathologic modifications to the glomerular structure, such as thickening of the glomerular basement membrane and expansion of the mesangial matrix. GFR may also be reduced as a result of decreased sensitivity to adrenergic stimulation, decreased renin release, decreased angiotensin II, and diminished renin angiotensin system action.[11,12] The action of thyroid hormone on renal function thus could be explained by its influence on maturation of the renin angiotensin aldosterone system (RAAS). Plasma renin activity and plasma levels of angiotensinogen, angiotensin II and aldosterone are directly associated to plasma levels of thyroid hormones.[13] Hypothyroidism is associated with low plasma renin, which may cause an increase in uric acid levels.[14]

In cases of primary hyperthyroidism, we observed a non-significant negative correlation was present between serum TSH and serum uric acid level. Elevation of serum uric acid is a precipitating factor for gout and nephrolithiasis along with it is a strong risk factor for metabolic syndrome as well as cardiovascular disease. The main causes for higher serum uric acid are lower excretion, higher synthesis, or both. The explanation for

developing hyperuricemia on the basis of diet is still not sufficient, but high intake of fructose-rich industrialized food and high alcohol intake (particularly beer) may induce serum uric acid level.[15] Increased amount of purine rich non-vegetarian diet of local Bengal population, including fish, egg, chicken, mutton and even beef in a particular community may be an aggravating factor of hyperuricemia in primary hypothyroidism cases.

In our study, we found significantly higher levels of serum uric acid in cases of primary hypothyroidism as compared to primary hyperthyroidism ($p<0.05$). The deiodination process, one of the steps of thyroid hormone synthesis helps to convert FT_4 to FT_3 mainly in the kidney; therefore, it may alter the serum uric acid level in cases of primary hypothyroidism and primary hyperthyroidism. Abnormal elevation of uric acid in the blood results in arthritis and gout. Gout is an independent risk factor to develop many cardiovascular diseases associated with higher cardiovascular mortality. It was seen that treatment of hyperuricemia as well as gout with urate-lowering agents improves cardiovascular outcomes.[8]

Various epidemiological studies reported positive correlation between serum uric acid levels with cardiovascular diseases such as hypertension, atherosclerosis, atrial fibrillation and heart failure. Allopurinol, a xanthine oxidase (XO) inhibitor, helps to improve cardiovascular outcomes in patients with HF, coronary heart disease (CHD), type 2 diabetes mellitus. The incidence of hyperuricemia is increasing now a days associated with unhealthy lifestyles and it is considered as the "fourth highest" morbidity and mortality indicator after hypertension, hyperglycemia, and hyperlipidemia. By early detection of hyperuricemia at the primary care level, the high risk population can thus be educated on the deleterious effect of UA and could be advised on the health promoting behavior such as lifestyle modification with respect to avoiding uric acid rich diet particularly egg, beer, wine, liquor, soft drinks, poultry, potatoes and meat products.[16,17]

CONCLUSION

To conclude, we found that our study subjects, who are thriving mostly on non-vegetarian diet containing purine rich eggs, fish, chicken, mutton and even beef, had increased serum uric acid levels along with decreased serum FT_4 and elevated serum TSH in cases of primary hypothyroidism in comparison to healthy individuals as well as cases of primary hyperthyroidism. In addition to the dietary factor, reduced renal plasma flow resulting from decreased GFR in primary hypothyroidism, is supposed to be the most important factor for increased serum uric acid level. Hence, we may opine from this study that, routine measurement and screening of serum uric acid level in primary hypothyroidism should be done, so that necessary actions can be taken at the earliest to prevent some of its complications, namely, gout, renal stones and ureteric stones.

Conflict of interest: The authors declared that there was no conflict of interest related to this study.

Funding statement: There was no external funding for this study.

Ethical approval: Ethical approval was obtained from West Bengal University of Health Sciences and the Institutional Ethics Committee of R. G. Kar Medical College & Hospital, Kolkata, West Bengal, India.

Authors' contribution: Concept and design of the study: D Majumder, J De, A Sur; Patient selection, data collection, compilation and analysis: D Majumder, J De, A Sur, TG Ray; Manuscript preparation, editing and final submission: D Majumder, J De, A Sur, TG Ray.

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