ORIGINAL ARTICLE

Correlation of Serum Uric Acid, Thyroid-Stimulating Hormone and Free-Thyroxine in Subclinical and Overt Hypothyroidism

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ABSTRACT

Objective: To correlate the serum uric acid, Thyroid-stimulating hormone (TSH) and free-thyroxine (FT4) in overt and subclinical hypothyroidism.

Study Design: Cross sectional comparative.

Place and Duration of Study: Capital Development Hospital, Islamabad from January 2019 to June 2019.

Materials and Methods: Total 114 participants, recruited through convenient non-probability sampling technique, were sub-divided in three groups, comprising 38 participants each. Group I included patients of overt hypothyroidism. Group II had patients with subclinical hypothyroidism and Group III included healthy controls. Serum uric acid levels were measured for all participants. For data analysis, SPSS 21 was used. Statistical significance was estimated using one way ANOVA. *p* value of < 0.05 was considered significant. Correlation between numerical variables was determined by Pearson correlation coefficient.

Results: Mean serum uric acid level in overt hypothyroid patients (7.5±0.84 mg/dL) was significantly raised than the patients in the subclinical hypothyroid and control group (4.7±0.82, 4.6±1.09 mg/dL respectively) with *p* value <0.001. However, there was no significant difference of mean uric acid levels between subclinical hypothyroid group and the control group (*p* value =0.95).

A significantly positive relation was observed between serum uric acid and TSH in group I only (r = 0.53 and *p* < 0.001).

Conclusion: Uric acids levels are increased in hypothyroidism more profoundly in case of overt hypothyroidism, less so when subclinical hypothyroidism is present. In patients of overt hypothyroidism, serum TSH and uric acid levels should be monitored regularly to prevent renal complications in these patients.

Key Words: *Hypothyroidism, Thyroid Stimulating Hormone, Thyroxine, Uric Acid.*

Introduction

Clinically, the commonest endocrine disorder is hypothyroidism. It results from an insufficiency of the thyroid hormones, leading to generalized impairment of various metabolic processes. [1]

Prevalence of hypothyroidism is 3.8%–4.6% in Asian population.[2]

T3 and T4 are the two related hormones synthesized by the thyroid gland. These hormones serve an imperative role in cell differentiation, regulation of thermogenesis and metabolic homeostasis in adults.[3]

Numerous mechanistic links exist between thyroid hormones and the renal system. The kidneys cause local deiodination of T4 by enzyme T4-5 - deiodinase, resulting in production of T3, a more potent form biologically.[4] Conversely, thyroid hormones are crucial for the development of renal system and its physiology. They have effects, both pre renal as well as intrinsic renal, which in turn cause increased renal blood flow and glomerular filtration rate (GFR).[5]

Hypothyroid state causes hemodynamic changes, including a decline in both renal plasma flow and GFR, which may cause derangement of renal function.[6] Also, purine metabolism is affected by lower levels of T3 and T4, which may cause a modification in uric acid (UA) levels.[7]

There are numerous remaining gaps in knowledge with respect to the interactions between thyroid and kidney dysfunction.[6] Previous studies carried out to

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Funding Source: NIL; Conflict of Interest: NIL
Received: July 19, 2019; Revised: May 30, 2020
Accepted: June 01, 2020

inquire the link between hypothyroidism and UA levels have shown contrary findings.[8,9] Therefore, the present study was designed to correlate the serum uric acid, Thyroid-stimulating hormone (TSH) and free-thyroxin (FT4) in overt and subclinical hypothyroidism.

Materials and Methods

It was a cross-sectional study conducted at Capital Development Hospital, Islamabad after getting approval from institutional Ethical Review Committee.

The study extended over 6 months from January 2019 to June 2019. A total of 114 participants were enrolled and were divided in three groups comprising of 38 participants each. Groups I included overt hypothyroid patients (TSH >4.5 µIU/ml and FT4 < 0.78ng/dL). Group II included subclinical hypothyroid subjects (TSH > 4.5 µIU/mL and normal FT4) and euthyroid individuals were labeled as Group III. Participants from both genders were enrolled through non-probability convenient sampling after taking informed consent. Known patients of diabetes, hypertension, renal and hepatic disorders, patients on treatment of hyperuricemia and pregnant women were excluded from this study. Age group < 18 years was also excluded as reference ranges of TSH and FT4 are universally different depending on age group. Serum TSH was done of clinically diagnosed patients who visited Medical OPD and who were admitted in wards. Subjects who had raised serum TSH levels > 4.5 µIU/mL were further tested for serum FT4. Participants who had TSH > 4.5 µIU/mL and FT4 less than 0.78 ng/dL were labeled as overt hypothyroid. Subjects having raised serum TSH but normal serum FT4 value were recruited as cases of subclinical hypothyroidism. Age and gender matched controls with normal serum TSH level (0.4 – 4.5 µIU/mL) were enrolled.

Venous blood sample was collected. Centrifugation of blood samples was done at 15000 rpm x g for about 15 minutes and serum was separated. Serum was stored at -70° C, until analysis of serum TSH, FT4 and UA was performed for all participants.

Serum TSH and FT4 test was performed using the VitrosECi Immunodiagnostic Systems using FDA approved kits of Johnson's and Johnson's. Serum UA was performed by uricase method on semi-automated chemistry analyzer micro-lab 300.

Data analysis was done by SPSS 21. Frequencies and percentages were computed for each categorical variable such as gender, whereas mean and standard deviation was estimated for numerical variables like age, serum TSH, serum FT4 and serum UA levels. To compare serum TSH, FT4 and uric acid levels in overt hypothyroidism, subclinical hypothyroidism and euthyroid groups, One way ANOVA was performed. Pearson correlation was calculated to find relationship of serum uric acid with serum TSH and FT4 in all the three groups.

Results

Mean age (years) of participants in group I, II and III were 47.5±9.92, 39.6 ±7.39 and 39.2±11.77 respectively. There were 21.1%, 44.7% and 52.6% males and 78.9%, 55.3% and 47.4% females in three groups respectively (Table I). The mean serum TSH, FT4 and UA levels in all three groups are summarized in Table II.

In group I, 58% patients had higher than normal serum uric acid levels for their gender. In group II, all the participants had normal serum uric acid levels while in group III, 8% participants had higher than normal serum uric acid level for their gender.

Among the three groups I, II and III, there was a statistically significant difference (p <0.001) in mean serum TSH levels (48.3±28.24, 23.5±33.11, 3.2±0.54 µIU/mL respectively), serum FT4 (0.42±0.20, 1.08±0.26, 1.54±0.40 ng/dL respectively) and serum UA (7.5±0.84, 4.7±0.82, 4.6±1.09 mg/dL respectively) as determined by one way ANOVA for each of these parameters(Table II).

Post HOC comparison using the Tukey test indicated that mean value of serum UA in overt hypothyroid patients (7.5±0.84 mg/dL) was raised significantly than the patients of the subclinical hypothyroidism and controls (4.7±0.82, 4.6±1.09 mg/dL) with p value <0.001. However, there was no significant difference in UA levels between the subclinical hypothyroid group and the control group (p value =0.95).

There was a significant positive relation between serum UA and TSH levels in group I (r =0.53 and p<0.001). No significant positive relation was found when TSH and FT4 were correlated with UA in each of the groups II and III. (Table III)

Discussion

This study indicates a worsening pattern for serum UA levels from euthyroid condition to overt

Table I: Descriptive Statistics of Age and Gender in Study Groups (N=114)

Variable	Group I (n=38)	Group II (n=38)	Group III (n=38)
Mean Age (years)	47.5±9.92	39.6±7.39	39.2±11.77
% Male Female	8 (21.1%) 30 (78.9%)	17(44.7%) 21(55.3%)	20 (52.6%) 18 (47.4%)

Table II: Comparison of Biochemical Parameters among Study Groups (N=114)

Parameters	Group I (n=38)	Group II n=38)	Group III (n=38)	*p* value (ANOVA)
TSH (µIU/mL)	48.33±28.24	23.53±33.11	3.21±0.54	0.000*
FT4 (ng/dL)	0.422±0.20	1.08±0.26	1.54±0.40	0.000*
Uric acid(mg/dL)	7.5±0.84	4.7±0.82	4.6±1.09	0.000*

*p<0.05 was taken as level of significance

Group I: Overt hypothyroid patients

Group II: Subclinical hypothyroid patients

Group III: Healthy adults

Table III: Correlation of Uric acid with serum TSH, FT4 in three Groups (N=114)

Variables	Uric acid					
	Group I (n=38)		Group II (n=38)		Group III (n=38)	
	r	*p* value	r	*p* value	r	*p* value
TSH	0.539*	0.000*	-0.250	0.130	0.117	0.486
FT4	-0.124	0.442	-0.119	0.476	0.151	0.364

r= correlation coefficient

p<0.05 was taken as level of significance

hypothyroidism. Previous studies investigating the relationship of overt hypothyroidism with hyperuricemia have shown contrary findings[8,9] Therefore, this study was designed to measure uric acid levels in hypothyroidism in our setup.

Our study demonstrated a significant increase in serum UA levels in overt hypothyroid patients when compared to the controls. This finding is in agreement with results of Marwah et al[8], Kaur et al[10], Karanikas[11], Khan et al[12] and Abebe et al.[13] The results of our study indicate a possible effect of thyroid abnormalities, mainly overt hypothyroidism, over purine nucleotide metabolism. This suggests that a reduction in renal blood flow and GFR in hypothyroidism may lead to hyperuricemia.[8] On the contrary, the results of an African study indicated that serum UA levels are reduced in both overt hypothyroidism and hyperthyroidism.[13] Similarly, a study conducted on a large cohort of 2359 patients diagnosed with thyroid dysfunction (hypothyroidism and hyperthyroidism) could not ascertain any positive relation between serum UA and TSH levels.[9] The disagreement between these findings and our study results can be explained through differences in sample size and study population of these studies.

The results of our study demonstrated that there was no significant difference in the mean serum UA levels between the subclinical hypothyroid group and the control group. This finding is in agreement with the results of Ye Y et al[14] who showed that the prevalence of hyperuricemia in euthyroid and subclinical hypothyroid groups had no significant difference (22.8 % vs 21.9% respectively). Similarly the work of K Ashizawa et al[15] demonstrated no significant association between hyperuricemia and subclinical hypothyroidism.

The possible reason that why the subclinical hypothyroid group did not show considerable change in serum uric acid levels when compared with euthypothyroid group can be explained by the gradual deterioration of thyroid function in subclinical hypothyroid patients , which might not be linked with metabolic complications at this stage of subclinical hypothyroidism.[16]

In our study, a significantly positive relation between serum UA and TSH in overt hypothyroid patients was observed. This finding is in agreement with the findings of Marwah et al[8] and Saini et al.[17] The reason for this rise in the levels of UA in case of hypothyroidism may either be an increased generation of uric acid due to hypothyroidism-associated myopathy or a deficient renal clearance resulting from reduced GFR.[17] This relationship may be of significance while evaluating patients having gout, because the excretion of uric acid in these patients might stem from a hypothyroid state. However our results are contrary to Arindam et al[18] who demonstrated no association between UA levels and TSH/FT4 in overt hypothyroidism.

Our study revealed no significant correlation of uric acid with either TSH or FT4 in the subclinical and euthyroid participants. This finding is supported by the results of Raber et al[9] which also did not establish any correlation of TFTs with uric acid in these groups. This might occur because the

derangement of thyroid function is less severe in patients of sub-clinical hypothyroidism as compared to overt hypothyroids.[16]

Limitations

The limitation of this study is that it was a uni-centred, cross sectional study, so it did not help to determine cause and effect relationship between hypothyroidism and uric acid.

Future Recommendations

Further multi-centred studies with larger sample size are recommended. Moreover other biochemical markers for renal functions (serum urea and creatinine along with muscle markers i.e serum aldolase and creatinine kinase) can be considered in relation to hypothyroidism when similar study is planned.

Conclusion

Uric acids levels are increased in hypothyroidism more profoundly in case of overt hypothyroidism, less so when subclinical hypothyroidism is present. A positive correlation of serum TSH and UA in overt hypothyroid patients calls for regular monitoring of serum UA levels in these patients to prevent renal complications.

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