Correlation of Serum uric acid with Thyroid hormones in patients in a tertiary care hospital in Northern India

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Abstract

Background: Thyroid hormones regulate the rate of metabolism, affect growth and modulate energy utilization. Uric acid plays a predominant role due to its involvement in cardio-nephro-metabolic disorders. There are conflicting results regarding relationship between thyroid function and uric acid levels. Few studies have been done to establish the relationship of uric acid with thyroid function among the normal subjects. Current cross-sectional study is an attempt by the authors to address this gap in literature.

Aim: The study was planned to observe the association of serum uric acid levels with thyroid hormones in apparently healthy patients.

Material & Methods: Study population included apparently healthy participants in age group 18-50 years attending the Outpatient Department of the hospital during the study period.Free triiodothyronine (FT3), free thyroxine (FT4), and thyroid - stimulating hormone and Serum uric acid (SUA) were measured. The participants were divided into 4 quartiles based on serum uric acid levels.

Results: The results showed that SUAwas significantly correlated with thyroid hormones only in the last quartile (>5.7 mg/dL). Present study hypothesised that there was a linear correlation between FT3 and FT4 and uric acid even in normal patients without overt thyroid dysfunction.

Conclusion: Uric acid levels are affected by thyroid hormones and hence they must be evaluated routinely in association with clinical manifestations for better prognosis and management of patients.

Keywords: Free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), and Serum uric acid (SUA).

Introduction

Thyroid gland is one of the largest endocrine glands in the body secreting thyroxine (T4) and triiodothyronine (T3) hormones. The production of T4 and T3 is regulated by the hypothalamus and pituitary gland. Thyroid hormones (T4 and T3) regulate the rate of metabolism, affect growth, and modulate energy utilization by increasing the basal metabolic rate, increasing oxygen consumption, and facilitating heat production[1].

Uric acid (UA) is the final product of endogenous and dietary purine metabolism in human beings, and serum UA levels reflect the balance between purine breakdown and UA excretion rates[2].

It plays a predominant role due to its involvement in cardio-nephro-metabolic disorders. Several epidemiological studies have reported a relation between serum UA levels and traditional cardiovascular risk factors, including hypertension, metabolic syndromeand diabetes mellitus, suggesting a possible pathophysiologic link between these conditions[3-6].

Physiological interactions exist between thyroid hormones and uric acid synthesis and excretion and even minor degree of altered thyroid leads to adverse effects in various tissues, even though clinically the patients are euthyroid. The first association between hypothyroidism and hyperuricemia was described in 1955 by Kuzell et al[7]. Several subsequent studies were done in patients with thyroid dysfunction but few in normal subjects[8,9,10].

Thus, the potential association of thyroid hormones

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on UA metabolism is still ambiguous. Current cross-sectional study is an attempt by the authors to address this gap in literature. The study was planned to observe the association of serum uric acid levels with thyroid hormones in apparently healthy patients.

Material and Methods

This cross-sectional observational study was conducted in central research laboratory of a Tertiary care Hospital in Northern India after permission of institutional Ethical committee review board (File no 134 X/11/13/2022- IEC/41) of the Hospital. Informed written consent was taken from each study participant before enrolment. The study included 1450 patients attending the Outpatient Department of the hospital during the study period and considered as the study population.

The study included apparently healthy participants in age group 18-50 years attending OPD Patients, Attendants, and Health care workers. Patients who were known cases of heart diseases, diabetes, hypertension, renal failure (acute and chronic), hepatic disorders, bone disorders, malignancies, or were on chemotherapy or radiotherapy, were pregnant were excluded from the study. Further, patients with hyperuricemia or gout who continued to receive medication, with a history of thyroid cancer or thyroid nodules or previous thyroid surgery or radioactive iodine intake and patients unwilling to participate were also excluded from the study. A complete history regarding demographic details, present and past medical/surgical history was taken after institutional ethical approval and written informed consent from the participants. The study variables included Free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), and Serum uric acid (SUA).Normal TSH levels were 0.465-4.68 mIU/L, Normal FT3 levels were 2.71-5.27 pg/mL, and normal FT4 levels were 0.78-2.19 ng/dL. Serum uric acid 3.5-8.5 mg/dL (M), 2.5-6.2mg/dL (F)**.**Detailed clinical and demographical data including, relevant clinical history in case study form after written informed consent. 5mL of venous blood samples was collected with strictly aseptic measures in Plain vacutainer for serum thyroid profile (FT3, FT4, TSH, Uric acid). The plain vacutainer sample was allowed to clot for 30 minutes and will be centrifuged properly for 3000 rpm 10 minutes and serum separated was used for analysis in fully automated VITROS XT 7600 integrated system analyzers.

Statistical analysis

The Parameters were presented as Mean ± Standard deviation/median (inter quartile range). Correlation between uric acid and variables were be analyzed by Regression. All Statistical analysis was performed using SPSS for windows version 21.0. 'p' value <0.05 was considered statistically significant.

Results

A total of 1450 patients were enrolled for the study.

Table 1: Characteristics of subjects according to Quartiles of Uric acid

Descriptives					
Parameters	**Quartiles of Uric Acid**	**Mean**	**Std. Deviation**	**Sig**	**N**
Age	1.00	38.43	14.475		358
	2.00	41.44	14.446		409
	3.00	43.08	14.599		346
	4.00	43.17	15.837		337
	Total	41.49	14.928	.000	1450
Free T3 (2.77-5.27 pg/mL)	1.00	3.15	.611		358
	2.00	3.28	1.175		409
	3.00	3.34	.669		346
	4.00	3.48	1.640		337
	Total	3.31	1.106	.001	1450
Free T4 (0.78-2.19 ng/dL)	1.00	1.07	.252		358
	2.00	1.10	.404		409
	3.00	1.10	.334		346
	4.00	1.16	.541		337
	Total	1.11	.396	.013	1450
TSH (0.465-4.68 mIU/L)	1.00	2.59	1.326		358
	2.00	2.68	1.402		409
	3.00	2.62	1.372		346
	4.00	2.49	1.336		337
	Total	2.60	1.362	.305	1450

Uric acid (UA) 3.5-8.5 mg/dL M 2.5-6.2mg/dL F	1.00	3.00	.542		358
	2.00	4.17	.286		409
	3.00	5.13	.291		346
	4.00	6.76	1.113		337
	Total	4.71	1.493	.000	1450
Creatinine (0.6-1.2mg/dL)	1.00	.60	.502		358
	2.00	.64	.378		409
	3.00	.74	.408		346
	4.00	.92	.660		337
	Total	.72	.508	.000	1450
Urea(15-40mg/dl)	1.00	20.70	9.068		358
	2.00	22.92	11.688		409
	3.00	24.13	11.811		346
	4.00	27.46	15.029		337
	Total	23.71	12.245	.000	1450
Random Blood sugar (140-200 mg/dL)	1.00	109.48	50.239		358
	2.00	111.70	54.100		409
	3.00	116.30	59.084		346
	4.00	106.17	37.728		337
	Total	111.01	51.297	0.369	1450
Alanine Transaminase (ALT) (8-45U/L)	1.00	28.44	23.322		358
	2.00	30.81	18.716		409
	3.00	35.91	21.942		346
	4.00	39.87	23.654		337
	Total	33.51	22.288	0.000	1450
Aspartate transaminase (AST) (8-50U/L)	1.00	33.78	17.154		358
	2.00	35.19	12.048		409
	3.00	37.66	13.963		346
	4.00	40.42	23.086		337
	Total	36.63	17.026	0.000	1450
Alkaline Phosphatase (ALP) (40-120 U/L)	1.00	86.17	25.065		358
	2.00	93.12	26.239		409
	3.00	93.76	26.016		346
	4.00	91.90	24.572		337
	Total	91.23	25.663	0.000	1450
Triglycerides (TG) (<150mg/dL)	1.00	132.90	55.741		358
	2.00	137.81	55.676		409
	3.00	151.63	60.676		346
	4.00	159.64	62.601		337
	Total	144.92	59.447	0.000	1450
Cholesterol (<200mg/dL)	1.00	174.29	36.774		358
	2.00	176.62	30.039		409
	3.00	180.38	21.551		346
	4.00	180.43	30.567		337
	Total	177.81	9.779	.113	1450
LDL Cholesterol <100mg/dL)	1.00	92.92	36.543		358
	2.00	95.07	37.316		409
	3.00	97.36	40.065		346
	4.00	99.58	40.043		337
	Total	96.12	38.475	.123	1450
HDL (40-60mg/dL)	1.00	50.59	13.293		358
	2.00	48.44	13.650		409
	3.00	46.62	13.121		346
	4.00	44.73	12.695		337
	Total	47.68	13.372	0.000	1450

The mean age of the study population was 41.5 years and 56% were males. The mean TSH, FT4 and FT3 levels were 2.6 mIU/L, 1.1 ng/dL, 3.31 pg/mL. The mean serum uric acid level was 4.71mg/dL. (Table 1).

The participants were divided into 4 quartiles based on serum uric acid levels. First quartile uric acid levels <3.7 mg/dL, second quartile 3.7-4.6mg/dL, third quartile 4.7-5.6 mg/dL and fourth quartile> 5.7 mg/dL. There was significant difference in Urea, uric acid, creatinine, AST, ALT, ALP, TG, Chol, LDL, and HDL levels amongst all the uric acid groups. (Table1)

Table 2: Results of multiple linear regression of Uric acid with all biochemical parameters

Model		Standardized Coefficients	Sig.	95.0% Confidence Interval for B	
		Beta		Lower Bound	Upper Bound
1	(Constant)		.000	3.030	5.332
	Age	.164	.000	.008	.026
	Sex	-.285	.000	-1.228	-.597
	FT3	-.054	.493	-.197	.095
	FT4	.108	.175	-.140	.766
	TSH	-.017	.707	-.121	.082
	Creatinine	.215	.000	.327	1.147
	Urea	.094	.125	-.004	.030
	Blood sugar	-.023	.613	-.004	.002
	Alanine Transaminase (ALT)	.090	.204	-.004	.018
	Aspartate transaminase (AST)	.001	.985	-.016	.017
	Alkaline Phosphatase (ALP)	-.030	.507	-.007	.003
	Cholesterol	.134	.626	-.015	.024
	LDL	-.043	.852	-.021	.018
	VLDL	.057	.538	-.016	.031
	HDL	-.097	.352	-.032	.011
Dependent variable Uric acid					

The above table depicts the results of multiple linear regression of Uric acid with all biochemical parameters. On multiple linear regressions no significant relationship was found between uric acid levels and Thyroid hormones (Table 2).

Table 3: Results of multiple linear regression of Uric acid with all biochemical parameters in Quartile 1 uric acid <3.7mg/dL

Model		Standardized Coefficients	Sig.	95.0% Confidence Interval for B	
		Beta		Lower Bound	Upper Bound
1	(Constant)		.032	.244	5.249
	Age	.069	.595	-.009	.015
	Sex	-.109	.383	-1.216	.474
	Ft3	.118	.352	-.134	.370
	FT4	-.030	.817	-.741	.587
	TSH	.190	.159	-.033	.200
	Creatinine	-.063	.637	-1.442	.889
	Urea	.025	.859	-.016	.019
	Blood sugar	-.099	.449	-.006	.003
	Alanine Transaminase (ALT)	.254	.120	-.003	.030
	Aspartate transaminase (AST)	-.123	.434	-.031	.013
	Alkaline Phosphatase (ALP)	.004	.973	-.005	.005
	Cholesterol	.291	.769	-.017	.022
	LDL	-.904	.763	-.109	.081
	VLDL	1.005	.713	-.077	.112
	HDL	.436	.707	-.077	.113
Dependent variable Uric acid					

The relationship between uric acid levels and Thyroid hormones were further confirmed in different quartiles of uric acid. The above table (Table 3) shows the results obtained when multiple linear regression of Uric acid was done with all biochemical parameters in Quartile 1 uric acid <3.7mg/dL

Table 4: Results of multiple linear regression of Uric acid with all biochemical parameters in Quartile 2 uric acid 3.7mg/dL-4.6 mg/dL

Model		Standardized Coefficients	Sig.	95.0% Confidence Interval for B	
		Beta		Lower Bound	Upper Bound
1	(Constant)		.000	3.449	4.734
	Age	.148	.121	-.001	.007
	Sex	-.063	.591	-.221	.127
	FT3	-.078	.683	-.075	.050
	FT4	.042	.826	-.178	.222
	TSH	-.197	.035	-.088	-.003
	Creatinine	.154	.193	-.168	.824
	Urea	-.011	.921	-.009	.008
	Blood sugar	.044	.677	-.001	.002
	Alanine Transaminase (ALT)	.108	.528	-.004	.007
	Aspartate transaminase (AST)	-.170	.311	-.011	.004
	Alkaline Phosphatase (ALP)	-.124	.197	-.004	.001
	Cholesterol	1.430	.013	.002	.019
	LDL	-1.086	.029	-.018	-.001
	VLDL	-.335	.078	-.020	.001
	HDL	-.592	.013	-.021	-.003
Dependent variable Uric acid					

The relationship between uric acid levels and Thyroid hormones were further confirmed in different quartiles of uric acid. The above table shows the results of multiple linear regression of Uric acid with all biochemical parameters in Quartile 2 uric acid 3.7mg/dL-4.6 mg/dL.

Table 5: Results of multiple linear regression of Uric acid with all biochemical parameters in Quartile 3 uric acid 4.6mg/dL-5.7 mg/dL

Model		Standardized Coefficients	Sig.	95.0% Confidence Interval for B	
		Beta		Lower Bound	Upper Bound
1	(Constant)		.000	4.256	5.873
	Age	.121	.295	-.002	.008
	Sex	.066	.604	-.121	.207
	FT3	.032	.784	-.095	.126
	FT4	-.152	.234	-.409	.101
	TSH	-.027	.824	-.071	.057
	Creatinine	.306	.051	-.001	.623
	Urea	-.030	.842	-.011	.009
	Blood sugar	-.112	.377	-.002	.001
	Alanine Transaminase (ALT)	.022	.888	-.005	.006
	Aspartate transaminase (AST)	-.023	.878	-.010	.009
	Alkaline Phosphatase (ALP)	.126	.288	-.001	.004
	Cholesterol				
	LDL	.056	.645	-.002	.003
	VLDL	-.053	.681	-.008	.005
	HDL	-.196	.096	-.010	.001
Dependent variable Uric acid					

The relationship between uric acid levels and Thyroid hormones were further confirmed in different quartiles of uric acid Table (3, 4, 5, 6). In order to better determine the correlation between the level of metabolic indicators and TSH, FT3, and FT4, we conducted a linear regression analysis (table 5). Gender, age, FBG, blood lipid, liver function, SUA. Lipid profile was included in the multiple linear regression analysis. The results showed that SUA were significantly correlated with FT3 and FT4 but in the last quartile.

Table 6: Results of multiple linear regression of Uric acid with all biochemical parameters in Quartile 2 uric acid >5.7 mg/dL

Model		Standardized Coefficients	Sig.	95.0% Confidence Interval for B	
		Beta		Lower Bound	Upper Bound
1	(Constant)		.000	3.861	8.309
	Age	-.078	.532	-.023	.012
	Sex	-.051	.701	-.715	.484
	FT3	.609	.031	.453	.927
	FT4	.642	.027	.113	1.843
	TSH	-.135	.249	-.290	.077
	Creatinine	-.275	.173	-.915	.168
	Urea	.576	.006	.013	.071
	Blood sugar	.072	.535	-.004	.007
	Alanine Transaminase (ALT)	-.040	.838	-.022	.018
	Aspartate transaminase (AST)	.190	.301	-.014	.046
	Alkaline Phosphatase (ALP)	-.152	.237	-.019	.005
	Cholesterol	.145	.288	-.003	.008
	LDL	.058	.885	-.017	.020
	VLDL	-.075	.826	-.021	.017
	HDL	-.011	.949	-.032	.030
Dependent variable Uric acid					

The above table shows the results of multiple linear regression of Uric acid with all biochemical parameters in Quartile 2 uric acid >5.7 mg/dL. The regression coefficients of SUA in the FT3, and FT4 regression models were B = 0.609 (95% CI 0.453-0.927, p = 0.031), B = 0.642 (95% CI.113-1.843, p 0.027), respectively (Table 6), suggesting that SUA could affect the levels of FT3, and FT4 in higher range greater than 5.7 mg/dL.

Discussion

Despite several cross-sectional studies to establish the relationship between thyroid function and uric acid levels the results still remain controversial. There is paucity in literature exploring relationship of UA with thyroid function among the normal subjects. As a result, the current cross-sectional study was an attempt by the authors to address this gap in literature.

The present study enrolled 1450 participants who were classified into quartiles based on uric acid levels. Significant differences were observed in the levels of FT3, FT4, and TSH between different uric acid quartiles. Further multivariate linear regression analysis, it was observed that FT3 and FT4 were significantly correlated with uric acid in fourth quartile UA > 5.7 mg/dL, but no significant association between TSH and uric acid levels.

Similar findings were reported by Ye et al[11], who also observed that UA content was associated with FT4 in healthy individuals with a significant high risk of hyperuricemia in higher FT4 quartiles but not with FT3 or T3 in subjects without overt thyroid dysfunction. Wang et al 2020[12] has also demonstrated a relationship of FT3 with UA contents among the general population with no obvious thyroid dysfunction.

Hypothyroid hyperuricemia is due to a reduction in renal plasma flow and glomerular filtration secondary to thyroid hormone deficiency leading to decreased uric acid clearance and increased SUA concentration. Several studies have proposed the correlation between overt hypothyroidism and hyperuricemia[13-16,10]. Hyperuricemia in Hyperthyroidism may be due to accelerated purine nucleotide turnover or a decrease in uric acid tubular excretion due to direct thyroxine action [17-20].Among hyperthyroid patients a significant negative correlation between TSH and positive with FT3 and FT4 has been observed. Uric acid levels were increased and associated with T3 and T4 hormone levels as suggested by Giardano[8]and Sato[19] et al.

However, Raber et al[9] did not find any association between UA and T 3and T4 hormone contents in patients suffering from thyroid dysfunction. Weak association between TSH and UA has been observed by Saini et al [10], and Raber et al.

The disagreement between studies and contradictory results could be attributed to several factors. Such as the heterogeneities in study population (healthy subjects versus patients), region of study, ethnicity, laboratory approaches for defining FT3/FT4 level and TSH, statistical approaches, sample size and different grouping methods[21].

Present study opined that under normal thyroid function, there is a close relationship between different uric acid levels and TSH, FT3, and FT4 levels. Further analysis confirmed that the uric acid level was linearly correlated with FT3 and FT4, but not with TSH. It can be speculated that thyroid hormones can alter level of cytokines produced by oxidative stress and inflammation, and the change of thyroid hormones can affect enzyme like xanthine oxidase and dehydrogenase level and finally affect the uric acid level. It could be hypothesized that FT3 and FT4 effects on uric acid may be through the transformation of purine nucleotides and uric acid excretion; therefore, this necessitates prospective studies are needed to confirm these findings[22].

Reactive oxygen species (ROS) are oxidizing agents implicated in tissue damage whose production is inevitably linked to ATP synthesis in turn related to the rate of cell respiration. Thyroid hormones (THs) are an important regulator of metabolic and respiratory rates. They are related to oxidative stress by stimulation of metabolism as well as their effects on antioxidant mechanisms. Controversial and insufficient data are available of OS in thyroid dysfunction. Uric acid has both antioxidant and pro-oxidant properties in vitro by scavenging and production of reactive oxygen species (ROS)[23]. So, increase in FT3 and FT4 may lead to increased oxidative stress and free radicals and uric acid might play its antioxidant role to scavenge free radicals. Uric acid positive correlation with FT3 and FT4 in higher range may be accounted by this.

In present study UA levels was divided into quartiles to study its association with Thyroid hormones. Stringent exclusion criteria were set according to routine laboratory findings and medical histories, adjusting the potential confounders to minimise physiologic impacts of UA on thyroid function. Certain limitations of the study were the cross-sectional study design, lack of follow up and diet history which may impact TH. The causal relationship of the UA with thyroid dysfunction could not be determined. Studies on thyroid function have gone deep into epigenetics, but the association between thyroid function and uric acid is still controversial and remains undeciphered. Further studies on large population is required to explore the relation of uric acid and thyroid hormones with follow up in patients to delineate the connexion between thyroid function and uric acid along with other renal function tests.

Altered purine nucleotide metabolism and altered renal function seen in thyroid dysfunction can worsen uric acid levels and gout in future. Therefore, in patients with increased serum uric acid levels thyroid hormones evaluation must be done before the patients develop altered thyroid hormone status.

In present study it is evident that the UA levels in serum are related to FT3, and FT4 in concentration >5.7mg/ but not TSH in apparently healthy patients without any thyroid dysfunction. Various studies indicate the profound influence of thyroid hormone on renal function but the results inconsistent and relation remains debatable. This information would avoid unnecessary investigations, treatment cost, and worry in patients presenting with either increased uric acid or with undetermined thyroid status. The thyroid function should, therefore, be routinely assessed for evaluation of patients presenting with deranged renal function and vice versa. Therefore, the present study emphasizes the importance of the routine evaluation of serum uric acid in patients with altered thyroid function.

Conclusion

In conclusion, the increase in uric acid has been linked to a variety of cardio metabolic nephrotic diseases; the uric acid level is affected by many factors, including epigenetics. Present study hypothesised that there was a linear correlation between FT3 and FT4 and uric acid even in normal patients without overt thyroid dysfunction. Uric acid levels are affected by thyroid hormones and hence they must be evaluated routinely in association with clinical manifestations for better prognosis and management of patients.

Recommendations

To account for the limitations of current study; further follow up studies are recommended in hospital settings recruiting patients with other comorbidities. Also, community-based studies are required to explore the causal associations of uric acid and thyroid hormones with follow up in normal population and thyroid disorder patients. The physicians are also recommended to assess patients with thyroid disorder with renal function and vice versa in clinical settings.

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