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Correlation between Uric Acid and Thyroid Hormones in Patients with Thyroid Disorders. A Case Control Study

Mona Youssry Helmy
Department of Internal Medicine, Faculty of Medicine, Cairo University, Egypt
***Corresponding Author:** Mona Yousry Helmy, **Tel:** (+20)1004389020, Email: mona55508@yahoo.com

ABSTRACT

Background: Thyroid disease influences the purine metabolism, which may increase serum uric acid (UA) level. Previous studies showed a high incidence of hyperuricemia in patients with thyroid disorders but with low thyroid stimulating hormone (TSH)-to-serum uric acid association.

Objective: Aim of this work was to investigate the serum uric acid relationship to thyroid hormones in patients with primary thyroid disorder.

Subjects and Methods: This case-control study included a total of 105 patients, 35 healthy participants as a control group and 70 patients with primary thyroid disorders, attending at the Endocrinology Outpatient Clinic, Kasr El Ainy, Cairo University. The included subjects were divided into three groups; **(Group I)** consisted of 35 patients with primary hypothyroidism, **(Group II)** consisted of 35 patients with primary hyperthyroidism and **(group III)** consisted of 35 subjects representing the control group. Waist circumference and the BMI have been calculated. TSH, free T4 (FT4; thyroxine) and free T3 (FT3; triiodothyronine), fasting lipids, creatinine, urea, eGFR and uric acid were evaluated.

Results: On comparing the three studied groups a statistical significant difference in UA level was found ($p < 0.05$), being highest in group I followed by group II then group III (6.59± 1.32mg/ dl, 6.38± 0.88mg/ dl and 5.48± 0.47mg/ dl respectively). Among hyperthyroid patients, there was a statistical negative significant correlation between UA and TSH (r -0.733-) and a positive significant correlation between Uric acid and FT3 (r 0.541) and FT4 (r 0.482).

Conclusion: A significant negative correlation between uric acid and TSH and significant positive correlation between it and FT3 and FT4 among hyperthyroid patients were found. Focusing more on the possible correlation of uric acid and primary thyroid diseases.

Keywords: Uric acid; Thyroid hormones; Primary thyroid disorders.

INTRODUCTION

Uric acid (UA) is water soluble and antioxidant which is mainly produced by the liver [(1)]. It inhibits the harm done by the free radicals and also protect cell membranes and DNA [(2)]. Among important biochemical parameters, uric acid is functioning as antioxidant agents which affected by thyroid function [(3)] and also, thyroid dysfunction affects the purine metabolism that may increase uric acid concentration [(4)].

There are few reports about the association of thyroid dysfunction and metabolism of UA, with a contradictory evidence. There was a poor relationship between TSH and serum uric acid (SUA) levels [(5, 6)]. Previous research, however, documented a high prevalence of elevated levels of UA in hypothyroidism [(7)] and hyperthyroidism [(7, 8)]. This may be attributed to elevated rate of purine metabolism in primary hyperthyroidism and reduced renal perfusion and glomerular filtration rate (GFR) in primary hypothyroid patients [(9, 10)].

As to thyroid dysfunction, the elevated levels of SUA are also accompanied with other co-morbid conditions including hypertension, metabolic syndrome, chronic kidney disease and type 2 diabetes mellitus [(11, 12)]. This may be attributed to increased purine metabolism in primary hyperthyroidism and reduced renal perfusion and glomerular filtration (GFR) in primary hypothyroid patients. The elevated uric acid (UA) levels is thought to be an intermediate factor in adipose tissue. Also, it regulates endocrine disorders that promote inflammation which can be an important factor leading to dyslipidemia and atherosclerosis [(13)].

Previous research has attempted to discover the link between these two conditions because thyroid dysfunction also alters UA concentration together with other metabolic deranges [(7, 14)]. Because the competition of deranged rates of SUA in primary thyroid diseases patients can not only elevate the risk of all-cause mortality, but can also impact disease management and prognosis [(12)]. However, the results of such studies were inconsistent and the association between thyroid disease and SUA concentrations is still unclear.

So, this study was aimed at evaluating the connexion between uric acid and thyroid hormones in patients with primary thyroid disorders in order to close this gap in the literature.

SUBJECTS AND METHODS

This case-control study included a total of 105 patients aged 20 to 60 years, 35 healthy participants as a control group and 70 patients with primary thyroid disorders, attending at the Endocrinology Outpatient

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Clinic, Kasr El Ainy, Cairo University. This study was conducted between July 2019 to July 2020. Written informed consent of all the subjects was obtained.

***Ethical Consideration*:**

This study was ethically approved by Ethics Board of Faculty of Medicine, Cairo University.

The included subjects were divided into three groups; **(Group I)** consisted of 35 patients with primary hypothyroidism, **(Group II)** consisted of 35 patients with primary hyperthyroidism and **(group III)** consisted of 35 subjects representing the control group.

Exclusion criteria included Patients with secondary thyroid dysfunction, pregnancy, history of Renal or Hepatic disease, history of other endocrine disorders and history of medications that can affect UA or thyroid hormones level.

Full medical history was taken from all subjects, emphasizing on age, gender, the duration of thyroid dysfunctions and family history of thyroid disease. Full clinical examination included blood pressure measurement, weight, height, body mass index (BMI) (kg/m2), waist circumference (WC) and goiter presence.

Laboratory investigations: Fasting lipids {total cholesterol (TC), triglycerides (TAG), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C)}, urea, creatinine, e GFR and uric acid, F T3, F T4 and TSH, levels were assessed.

The venous blood was drawn after 12-hour overnight fasting for examining of serum creatinine, urea, uric acid and lipids including triglyceride (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), TSH, F T3 and F T4.

Determination of serum total cholesterol, serum triglyceride, serum LDL and serum HDL were carried out on Dimension RxL Max analyzer, (Siemens Healthcare GmbH - Henkestr. 127, 91052 Erlangen, Germany) by colorimetric techniques.

Kidney Function Tests (Uric Acid, creatinine and Urea) were measured by a full-auto Olympus AU 400 Analyzer (Olympus Diagnostics GmbH, Germany) using standard reagent kits from Randox Laboratory (Crumlin, United Kingdom).

Estimated glomerular filtration rate was calculated using Cockraft and Gault formula. eGFR (mL/min)= [(140 - age) × Wt / (0.814 × S.Cr in μmol/L)] × (0.85 if female) [(15)].

T3, T4 and TSH were analyzed by Immunoturbidometric method [(16)]. All bio-chemical tests were performed using Backman coulter AU680, fully automated analyzer.

Statistical analysis

Data were coded and entered using the Social Sciences statistical package (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was summed using frequencies (number of cases) and relative frequencies (percentages) for categorical variables and mean+/- standard deviation for quantitative variables. Comparisons between groups were done using analysis of variance (ANOVA) with multiple comparisons, post hoc test in normally distributed quantitative variables while non-parametric Kruskal-Wallis test and Mann-Whitney test were used for non-normally distributed quantitative variables [(17)]. The categorical data was contrasted using the Chi square test (2). Exact test was carried out when the frequency is expected to be < 5 [(18)]. For correlations between quantitative variables, the Pearson correlation coefficient [(19)] was used. P-values < 0.05 have been recognized as statistically important.

RESULTS

Our study groups included group I having 35 patients with hypothyroidism, 29 (82.85 %) were females and 6 (17.14 %) were males with their mean age (47.60± 11.51) years, group II included 35 hyperthyroid patients, 30 (85.7%) were females and 5 (14.28 %) were males with their mean age (46.30±9.83) years and group III included 35 healthy control subjects, 28 (80 %) were females and 7 (20 %) were males with their mean age (37.67 ± 10.41) years with significant statistically difference between studied groups regarding the age (P < 0.001), presence of goiter (P < 0.001) and HTN (Tables 1, 2).

Table (1): Comparison of parameters among the three studied groups.

Variable		Group I Hypothyroidism		Group II Hyperthyroidism		Group III Controls		P value
		Count	%	Count	%	Count	%	
Sex	M	6	17.14%	5	14.28%	7	20.0%	0.787
	F	29	82.85%	30	85.7%	28	80.0%	
FH of thyroid	yes	7	23.3%	6	20.0%	4	13.3%	0.602
	No	23	76.7%	24	80.0%	26	86.7%	
BP(mmHg)	normal	15	50.0%	26	86.7%	25	83.3%	0.002
	HTN	15	50.0%	4	13.3%	5	16.7%	
Goiter	Yes	9	30.0%	11	36.7%	0	0.0%	0.001
	NO	21	70%	19	63.3%	30	100.0%	

*P < 0.05 is significant, M, male, F, female, FH, family history, BP, blood pressure.

On comparing three studied groups, a significant statistical difference were found regarding weight and BMI (*P*< 0.001) and disease duration mean were (7.36±5.71) in hypothyroid group and (1.14±0.67) in hyperthyroid group with significant statistical difference when compared to controls (*P*< 0.001). There were significant statistical differences between the studied groups regarding T. cholesterol, Triglycerides, HDL –C, LDL-C, urea, creatinine, e GFR, uric acid, TSH, F T3 and FT4 (*P*< 0.001).(Table 2).

Table (2): Comparison of parameters among the three studied groups.

Variable	Group I Hypothyroidism		Group II Hyperthyroidism		Group III Controls		P value
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	
Age (years)	47.60	11.51	46.30	9.83	37.67	10.41	0.001
Disease duration (years)	7.36	5.71	1.14	0.67	.	.	< 0.001
Weight(Kg)	90.57	17.18	61.03	5.57	70.90	12.60	< 0.001
Height (cm)	163.80	7.65	162.77	6.02	164.70	7.18	0.565
BMI (kg/m2)	33.40	6.23	22.92	1.09	26.01	4.77	< 0.001
WC (cm)	112.50	14.53	81.60	6.95	95.77	15.60	< 0.001
T.cholesterol (mg/dl)	217.60	34.03	187.40	25.51	190.00	22.94	< 0.001
Triglycerides (mg/dl)	181.63	38.31	144.77	18.73	152.93	30.99	< 0.001
HDL-C (mg/dl)	43.33	8.73	54.20	11.02	55.27	8.22	< 0.001
LDL-C (mg/dl)	124.13	16.78	103.73	13.97	100.20	9.83	< 0.001
Urea (mg/dl)	36.37	7.54	27.33	3.13	29.71	4.92	< 0.001
Creatinine (mg/dl)	0.91	0.21	0.68	0.07	0.75	0.13	< 0.001
eGFR (ml/min/1.73m2)	112.84	14.19	100.86	9.59	117.36	9.73	< 0.001
Uric acid (mg/dl)	6.59	1.32	6.38	0.88	5.48	0.47	< 0.001
TSH (ul /ml)	15.25	21.54	1.00	0.39	2.38	0.18	< 0.001
FT3 (pmol / L)	2.87	0.41	7.48	1.07	3.12	0.71	< 0.001
FT4 (pmol / L)	0.95	0.21	3.21	0.11	1.48	0.10	< 0.001

Values are expressed as means ± SD, *P < 0.05 is significant, WC, waist circumference, BMI, Body mass index, HDLC, high-density lipoprotein cholesterol, LDLC, low-density lipoprotein cholesterol ; e GFR, estimated glomerular filtration rate, TSH, thyroid stimulating hormone, F T3, free triiodothyronine, F T4, free thyroxine.

Comparisons between hypothyroid and hyperthyroid patients using Post Hoc pair wise and Kruskal-Wallis method found a significant difference regarding weight, BMI, WC, T.cholesterol, triglycerides, HDL –C, LDL –C, Urea, Creatinine, eGFR, TSH, F T3 and F T4. Also, a Significant difference regarding Age, weight, BMI, WC, T. cholesterol, triglycerides, HDL –C, LDL –C, Urea, Creatinine, uric acid, TSH, FT3 and FT4 were shown between hypothyroid patients and controls. In addition, A significant difference were found between hyperthyroid patients and controls according to Age, weight, BMI, WC, uric acid, TSH, F T3 and F T4 (Tables 3, 4, 5).

Table (3): Post Hoc pair wise comparisons of clinical parameters (between each 2 groups).

Variable		Group I Hypothyroidism	Group II Hyperthyroidism	Group III Controls
Age (years)	Hypothyroidism		1.000	0.001
	Hyperthyroidism	1.000		0.007
	Controls	0.001	0.007	
Weight (kg)	Hypothyroidism		< 0.001	< 0.001
	Hyperthyroidism	< 0.001		0.010
	Controls	< 0.001	0.010	
BMI (kg/m2)	Hypothyroidism		< 0.001	< 0.001
	Hyperthyroidism	< 0.001		0.031
	Controls	< 0.001	0.031	
WC (cm)	Hypothyroidism		< 0.001	< 0.001
	Hyperthyroidism	< 0.001		< 0.001
	Controls	< 0.001	< 0.001	

*P < 0.05 is significant, WC, waist circumference, BMI, Body mass index.

Table (4): Post Hoc pair wise comparisons of laboratory parameters (between each 2 groups).

Variable		Group I Hypothyroidism	Group II Hyperthyroidism	Group III Controls
Cholesterol(mg/dl)	Hypothyroidism		< 0.001	0.001
	Hyperthyroidism	< 0.001		1.000
	Controls	0.001	1.000	
Triglycerides(mg/dl)	Hypothyroidism		< 0.001	0.001
	Hyperthyroidism	< 0.001		0.905
	Controls	0.001	0.905	
HDL-C(mg/dl)	Hypothyroidism		< 0.001	< 0.001
	Hyperthyroidism	< 0.001		1.000
	Controls	< 0.001	1.000	
LDL-C(mg/dl)	Hypothyroidism		< 0.001	< 0.001
	Hyperthyroidism	< 0.001		0.975
	Controls	< 0.001	0.975	
Urea(mg/dl)	Hypothyroidism		< 0.001	< 0.001
	Hyperthyroidism	< 0.001		0.293
	Controls	< 0.001	0.293	
Creatinine(mg/dl)	Hypothyroidism		< 0.001	< 0.001
	Hyperthyroidism	< 0.001		0.165
	Controls	< 0.001	0.165	
eGFR(ml/min/1.73m2)	Hypothyroidism		< 0.001	0.381
	Hyperthyroidism	< 0.001		< 0.001
	Controls	0.381	< 0.001	
uric acid(mg/dl)	Hypothyroidism		1.000	< 0.001
	Hyperthyroidism	1.000		0.001
	Controls	< 0.001	0.001	

*P < 0.05 is significant, WC, waist circumference, BMI, Body mass index, HDLC, high-density lipoprotein cholesterol, LDLC, low-density lipoprotein cholesterol ; e GFR, glomerular filtration rate.

Table (5): Kruskal-Wallis comparisons of thyroid function tests.

Variable		P value
TSH (ul /ml)	**Hyperthyroid VS control**	0.007
	Hyperthyroid VS Hypothyroid	< 0.001
	Control VS Hypothyroid	< 0.001
F T3 (pmol / L)	**Hypothyroid VS Control**	0.009
	Hypothyroid VS Hyperthyroid	< 0.001
	Control VS Hyperthyroid	0.001
F T4 (pmol / L)	**Hypothyroid VS Control**	0.002
	hypothyroid VS Hyperthyroid	< 0.001
	Control VS Hyperthyroid	0.001

*P < 0.05 is significant, TSH, thyroid stimulating hormone, F T3, free triiodothyronine, F T4, free thyroxine.

Among hyperthyroid patients, we found negative significant correlation between uric acid and T cholesterol, LDL-C and TSH and positive significant correlation between it and HDL –C, F T3 and F T4 (Table 6).

Table (6): Correlation between uric acid and other parameters in hyperthyroid patients.

Variable	Uric acid(mg/dl)		
	r	P value	N
BMI (kg/m2)	-0.295-	0.113	35
WC (cm)	-0.274-	0.143	35
T. cholesterol (mg/dl)	-0.618-	0.000	35
Triglycerides**(mg/dl)**	-0.325-	0.080	35
HDL-C(mg/dl)	0.400	0.029	35
LDL-C(mg/dl)	-0.431-	0.017	35
Urea(mg/dl)	0.006	0.974	35
Creatinine(mg/dl)	-0.021-	0.911	35
eGFR(ml/min/1.73m2)	0.033	0.864	35
TSH (ul /ml)	-0.733-	<0.001	35
FT3 (pmol / L)	0.541	0.002	35
FT4 (pmol / L)	0.482	0.007	35

*P < 0.05 is significant, r, Correlation Coefficient, BMI, Body mass index, WC, waist circumference, HDLC, high-density lipoprotein cholesterol, LDLC, low-density lipoprotein cholesterol, e GFR, estimated glomerular filtration rate ; TSH, thyroid stimulating hormone FT4, free thyroxine, F T3, free triiodothyronine

Among hypothyroid patients, we did not find significant correlation between uric acid and kidney function tests, obesity parameters and thyroid functions (Table7).

Table (7): Correlation between Uric acid and other parameters in hypothyroid patients.

Variable	Uric acid (mg/dl)		
	r	P value	N
BMI (kg/m2)	-0.065-	0.731	35
WC (cm)	-0.060-	0.752	35
T.cholesterol (mg/dl)	0.145	0.445	35
Triglycerides **(mg/dl)**	0.293	0.116	35
HDL-C(mg/dl)	0.006	0.974	35
LDL-C(mg/dl)	0.057	0.763	35
Urea(mg/dl)	-0.218-	0.246	35
Creatinine(mg/dl)	-0.156-	0.412	35
eGFR(ml/min/1.73m2)	0.105	0.581	35
TSH (ul /ml)	0.046	0.808	35
FT3 (pmol / L)	-0.001-	0.996	35
FT4 (pmol / L)	-0.185-	0.326	35

*P < 0.05 is significant, r, Correlation Coefficient, BMI, Body mass index, WC, waist circumference, HDLC, high-density lipoprotein cholesterol, LDLC, low-density lipoprotein cholesterol, e GFR, glomerular filtration rate ; TSH, thyroid stimulating hormone, F T3, free triiodothyronine, F T4, free thyroxine.

DISCUSSION

This case-control research was aimed to examine the

relationship between UA and thyroid hormones in patients with primary thyroid disorder, as previous studies attempted to investigate this connexion. However, their results were inconsistent. Our results supported our hypothesis that in subjects with primary thyroid dysfunction, UA levels were higher than controls, and the UA levels in hypothyroid patients were significantly higher than in hyperthyroid patients. Significant negative correlation between UA and TSH was reported among patients with hyperthyroid as well as a significant positive correlation between it and F T3 and F T4. Also, significant association was recorded among hyperthyroid patients between UA and T cholesterol, LDL-C and HDL-C.

In our research, uric acid levels in patients with primary thyroid disorders were higher than controls. The uric acid level was substantially higher in hypothyroid patients than in hyperthyroid patients. In agreement with our results, studies by **Rafat *et al.* [20], Khan *et al.* [21] and Giordano *et al.* [7].** On the contrary, study by **Abebe *et al.* [22]** reported low serum UA levels in both hypothyroid and hyperthyroid patients. A case-control study of **Sato *et al.* [8]** also found that serum UA levels in patients with overt hyperthyroidism were significantly elevated and decreased in patients with overt hypothyroidism.

The disagreement between these finding and our results can be attributed by the differences in the studied population and in sample size. The significant elevation of uric acid level in hypothyroid group was attributed to reduced glomerular filtration rate and so such patients should also be monitored closely for gout and coronary heart disease.

The current study found that creatinine and urea were higher in hypothyroid patients than other studied groups with significant difference. In agreement with our findings. The study by **Sidhu *et al.* [23]** reported a significant increase in hypothyroidism of both urea and creatinine compared to hyperthyroidism. Also, studies by **Rafat *et al.* [20], Saini *et al.* [5] and Khan and Majumder [24]** found similar results. On the opposite hand, **Rashead and Hamid[25]** didn't find this association.

Histological anomalies in nephrons, especially basement membrane thickening, were demonstrated in both hypothyroid rats and humans. These changes may result in physiological effects including alterations in renal hemodynamics, decrements in renal blood flow and GFR and hence reduced clearance of creatinine and uric acid **[26],** in addition to hypothyroid myopathy. For chronic kidney disorders such patients should be closely monitored as well.

In this regard, decreases in uric acid excretion, increase in creatinine and creatinine clearance decrease have been described in patients with hypothyroidism. For chronic kidney disorders such patients should be closely monitored as well. However, non-significant correlation was revealed between UA and kidney function tests among our hypothyroid and hyperthyroid patients.

The association between UA level and thyroid disorders has been investigated in many studies, which provided conflicting results. Among our hyperthyroid patients, a significant negative correlation between UA and TSH and positive significant correlation between it and F T3 and F T4 were found indicating that the FT4 and FT3 may increase purine nucleotide turnover by their action on kidneys as has been suggested by studies of **Giordano *et al.* [7] and Sato *et al.* [8]** in hyperthyroidism.

Also, In the current study, among hypothyroid patients, we did not find significant correlation between UA and thyroid functions tests. On the contrary, **Arora *et al.* [27]** found a negative correlation between UA with T3 levels among hypothyroid.

The link between TSH and UA serum has been poor by studies of **See *et al.* [14], Saini *et al.* [5] and Raber *et al.* [6].**

The disagreement between these finding and our finding can be explained by the differences in the studied population and in sample size.

Our findings showed that in hypothyroid patients: BMI, waist circumference, T.Cholesterol, triglycerides were a higher than in hyperthyroid patients with significant difference. This agreed with finding of **Rafat *et al.*[20].** Abnormal lipid profile in thyroid disorders is common. **Abbas *et al.* [28] and Abrams and Grundy [29]** clarified this by reducing LDL receptor function resulting in reduced LDL and intermediate density lipoprotein catabolism and induction of cholesterol synthesis as well as effect on biliary lipid metabolism and elevated levels of uric acid were found to contribute to the risk of obesity and obesity through an unrevealed process.

Obesity is proposed to be accompanied by elevated SUA levels by excess production and impaired renal removal. Study by **Matsuura *et al.* [30],** conducted by participants with visceral fat obesity, showed that increased uric acid levels are heavily affected by overproduction, with decreased urinary urate excretion and clearance. In addition, visceral fat deposition causes a strong influx of free fatty acids into the liver and hepatic portal veins, which stimulates triglyceride synthesis accompanied by a related increase in uric acid output via activation of pathway of UA synthesis as recorded by **Fabregat *et al.* [31].**

A significant positive relation between SUA and obesity in Chinese population was shown by **Chen *et al.* [32],** in Iraq by **Essa *et al.* [33]** and in United States by **Choi *et al.* [34].**

In spite this, among hyperthyroid patients of our current study, we showed a significant correlation between UA and T cholesterol, LDL-C and HDL –C and no significant correlation between it and BMI and WC. Also, in hypothyroid patients, we found no significant association between UA and obesity parameters.

CONCLUSION

It could be concluded that in subjects with primary thyroid dysfunction, UA levels were higher than controls and UA levels in patients with hypothyroid were substantially higher than patients with hyperthyroid. Creatinine and urea levels were higher in hypothyroid patients than other studied groups with significant

difference. Significant correlation was found between UA and T cholesterol, LDL-C and HDL –C among hyperthyroid patients. Significant negative correlation between UA and TSH and positive significant correlation between it and F T3 and F T4 among hyperthyroid patients were reported. Increasing the concern to the possible association between UA level and thyroid dysfunctions. This research indicates a thyroid function test might be needed for patients with hyperuricemia, IHD, and CKD.

RECOMMENDATIONS

We believe that further studies with larger samples should be carried out, to determine the role of hyperuricemia in patients with primary thyroid disorders.

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