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Assessment of Serum Uric Acid and Electrolytes Levels in Subclinical and Overt Hypothyroidism Patients

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ABSTRACT

Background: A common endocrine condition known as hypothyroidism is characterised by insufficient thyroid hormone production by the thyroid gland. Nearly all tissues need thyroid hormones for optimal growth, development, and operation, and the kidneys especially depend on them for healthy growth and operation. Thyroid dysfunction and uric acid (UA) metabolism may be related, according to some studies. A rise in serum uric acid (UA) levels may result from thyroid disease's impact on the purine metabolism.

Objective: To examine the connection between thyroid hormones and blood uric acid in people with primary hypothyroidism.

Patients and methods: This case-control comparative study was carried out at the Internal Medicine Department, Faculty of Medicine, Zagazig University. 126 subjects with similar age and sex distribution participated in the study. They were divided into three groups: 42 people with subclinical hypothyroidism, 42 people with overt hypothyroidism, and 42 healthy people (control individuals).

Results: A statistically significant difference existed between the groups that were being researched in uric acid level. Post hoc test showed that there was a highly statistical significance increase in uric acid in hypothyroidism group compared to the subclinical hypothyroidism and control. In addition, there was a statistically significant rise in uric acid levels in the subclinical hypothyroidism group compared to the control group.

Conclusion: Compared to euthyroid controls, blood uric acid levels are higher in overt hypothyroid and subclinical hypothyroid individuals.

Keywords: Uric acid, Subclinical, Overt, Hypothyroidism.

INTRODUCTION

The most prevalent endocrine condition is thyroid illness conditions in the globe. According to reports, almost 42 million of people struggle with thyroid issues [(1)]. The most frequent underlying cause of hypothyroidism is iodine deficiency [(2, 3)].

The term "hypothyroidism" refers to a condition in which the hypothalamic-pituitary-thyroid axis is compromised, resulting in a decrease in the synthesis of thyroid hormones. High TSH, low T4 and T3, and low T3 are discovered in the laboratory. Common endocrine disorders such as subclinical hypothyroidism are characterised by normal T3, T4 levels, elevated TSH levels, and typically no clinical symptoms. The incidence of primary hypothyroidism, which affects 0.5-2.0% of women and 0.2% of males, is a common syndrome. According to numerous publications, there has lately been a 2.1% increase in the number of people with autoimmune illnesses and hypothyroidism [(4, 5)].

Constipation, cold intolerance, and weight gain are all symptoms of hypothyroidism. Important biological effects of thyroid hormones include the modulation of body hemodynamics, thermoregulation and many metabolic processes. It affects practically all bodily metabolisms, including those for carbohydrates, proteins, lipids, and the well-known regulation of water and electrolyte homeostasis. Both kidney diseases and thyroid problems can have an impact on the physiology and development of the kidneys [(6)].

Humans produce uric acid (UA) as endogenous and as dietary purine metabolism byproduct. Blood uric acid levels are a good indicator of how efficiently purines are broken down and how quickly UA is excreted [(7)].

The liver primarily produces uric acid (UA), an antioxidant that is water soluble. It prevents the harm causes free radical while also protecting DNA and cell membranes [(8, 9)]. Uric acid serves as an antioxidant and is influenced by thyroid function. Additionally, thyroid failure affects the purine metabolism, which can lead to an increase in uric acid content [(10)].

According to some evidence, thyroid dysfunction and UA metabolism are related.

Kuzell *et al.* [(11)] were the first to link hypothyroidism with hyperuricemia. In a cross-sectional investigation by **Ashizawa *et al.*** [(12)] it was discovered in women's serum where UA levels were related to subclinical hypothyroidism. However, previous research demonstrated that hypothyroidism and hyperthyroidism are frequently related with higher UA values. This Possibly due to the fact that primary hyperthyroid patients' purine metabolism is raised and that primary

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hypothyroid patients' renal perfusion and glomerular filtration rate (GFR) are decreased [8, 13].

PATIENTS AND METHODS

This case control comparative study was conducted at Internal Medicine Department, Faculty of Medicine, Zagazig University. The study involved 126 adult individuals (42 healthy controls of the same age and sex and 84 the hypothyroid patients). The study was carried out from January 2022 to December 2022.

Study population: The study includes 126 participants. They were split into three groups.

- **Group I:** 42 Patients diagnosed with primary hypothyroidism.
- **Group II:** 42 Patients diagnosed with subclinical hypothyroidism.
- **Group III:** 42 Healthy control individuals.

Inclusion criteria:

Low serum T3 and T4 levels in conjunction with elevated TSH values were used to make the diagnosis. FreeT3 (normal range: 2.4-4.2 pg/ml), freeT4 (normal range: 0.7-1.4 ng/dl), and TSH (normal range: 0.34-4.25 IU/ml) levels, all hypothyroid individuals were recognised and confirmed by the doctor. Subclinical hypothyroidism was diagnosed based on increased TSH (5-10 IU/ml) and normal free T4 levels **[14].** Both males and females were included. Older than 18 years old.

Exclusion criteria:

- Patients suffering from secondary hypothyroidism.
- Pregnancy.
- A history of kidney or liver illness, bone disease, persistent drinking, or gout.
- Previous history of another endocrine disorder.
- A history of drugs that may have an effect on serum uric acid, thyroid hormone levels, or electrolytic abnormalities.
- A history of diabetes, severe hypertension, and cancer.

All patients underwent a thorough history taking that included their age and gender, history of hypertension or diabetes, history of drug use, any chronic illnesses, family history of thyroid disorders, complete clinical examination that included blood pressure measurement and pulse, the presence of goitre and neck examination, and laboratory investigations that included FT3, FT4, TSH, uric acid, anti TPO and anti TG antibodies.

Ethical consideration:

Patients provided written informed permissions after being briefed about the treatment and its potential risks, and IRB approval was obtained from Faculty of Medicine, Zagazig University.

Statistical Analysis

Data were computerised and statistically evaluated with the software programme for social sciences version 27.0 (IBM, 2020). The Chi square test, ANOVA F-test, the Kruskall-Wallis test, Pearson's correlation coefficient, and ROC curve analysis were used.

RESULTS

Age or sex distribution did not statistically differ significantly amongst the groups under study (Table 1).

Table (1): Demographic data of the studied groups.

Variable		Hypothyroidism (n=42)		Subclinical hypothyroidism (n=42)		Control (n=42)		F	P
Age: (years)	**Mean ± SD** **Range**	35.74±9.78 24-57		41.07±11.65 25-62		38.79±10.07 24-60		2.71	0.07 NS
Variable		**No**	**%**	**No**	**%**	**No**	**%**	χ^2	**p**
Sex:	**Male** **Female**	13 29	31 69	19 23	45.2 54.8	21 21	50 50	3.39	0.18 NS

In terms of free T3, free T4, and TSH, there was a statistically significant difference between the groups. When the hypothyroidism group was compared to the subclinical hypothyroidism group and the Control group, post hoc analysis showed that free T3 and free T4 levels were noticeably lower in the group with hypothyroidism than they were in the subclinical hypothyroidism group and control group. TSH levels in the hypothyroidism group were likewise substantially higher than they were in the subclinical hypothyroidism group and the control group. TSH levels were also considerably higher in the subclinical hypothyroidism group than in the control group (Table 2).

Table (2): Thyroid function tests results of the studied groups

Variable		Hypothyroidism (n=42)	Subclinical hypothyroidism (n=42)	Control (n=42)	KW/F	P	Post Hoc
Free T3: (ng/dl)	**Mean±SD**	0.09 ± 0.01	0.3 ±0.05	0.3±0.08	205.8	**<0.001****	**<0.001**[1] **<0.001**[2] 0.9 NS[3]
Free T4: (ng/dl)	**Mean±SD**	0.63 ± 0.09	1.43±0.24	1.37±0.23	**210.9**	**<0.001****	**<0.001**[1] **<0.001**[2] 0.35 NS[3]
TSH: (UIu/ml)	**Mean±SD**	29.78±5.16	9.61±1.70	3.16±0.59	**102.55**	**<0.001****	**<0.001**[1] **<0.001**[2] **<0.001**[3]

Post hoc: P1: Hypothyroidism versus Subclinical hypothyroidism, P2: Hypothyroidism versus control P3: Subclinical hypothyroidism versus control.

Regarding anti TPO and anti TG, there was a statistically significant difference between the studied groups. When compared to the subclinical hypothyroidism and control groups, a post hoc analysis showed highly statistically significant increase in ATPO and ATG in the hypothyroidism group. Additionally, the subclinical hypothyroidism group's ATPO and ATG levels increased significantly when compared to the control group. There was a statistically significant difference in uric acid levels between the tested groups. When compared to the groups with subclinical hypothyroidism and the control group, a post hoc analysis showed a highly statistically significant increase in uric acid in the hypothyroidism group. Additionally, in comparison with the control group, the subclinical hypothyroidism group experienced a statistically significant increase in uric acid levels (Table 3).

Table (3): Anti thyroid peroxidase (ATPO), anti-thyroglobulin (ATG) and uric acid of the studied groups

Variable		Hypothyroidism (n=42)	Subclinical hypothyroidism (n=42)	Control (n=42)	KW	P	Post Hoc
ATPO: (IU/ml)	**Mean±SD**	228.69±43.72	59.5±7.74	6.76±1.38	**100.98**	**<0.001****	**<0.001**[1] **<0.001**[2] **<0.001**[3]
ATG: (IU/ml)	**Mean±SD**	331.21±28.58	156.4±27.2	13.49±2.75	**89.65**	**<0.001****	**<0.001**[1] **<0.001**[2] **<0.001**[3]
Uric acid (mg/dl)	**Mean±SD**	7.2±1.77	5.47±1.41	4.73±1.08	**32.40**	**<0.001****	**<0.001**[1] **<0.001**[2] **0.04***[3]

Post hoc: P1: Hypothyroidism versus Subclinical hypothyroidism, P2: Hypothyroidism versus control P3: Subclinical hypothyroidism versus control.

There was a statistical significance +ve correlation between uric acid and TSH, ATPO & ATG among the studied cases groups and negative correlation between UA and FT4 (Table 4).

Table (4): Correlation between uric acid level and age & Laboratory parameters among cases groups

Variable	Uric acid (n=84)	
	r	P
Age (years)	0.02	0.84 NS
Free T3: (ng/dl /L)	0.12	0.26 NS
Free T4: (ng/dl/L)	**-0.36**	**0.001***
TSH: (UIu/ml)	**0.45**	**<0.001****
ATPO: (IU/ml)	**0.58**	**<0.001****
ATG: (IU/ml)	**0.57**	**<0.001****

There was no statistical significance correlation between uric acid and any of the studied parameters among hypothyroidism and subclinical hypothyroidism groups (Table 5).

Table (5): Correlation between uric acid level and age & Laboratory parameters among Hypothyroidism and subclinical hypothyroidism groups

Variable	Hypothyroidism Uric acid (n=42)		Subclinical hypothyroidism Uric acid (n=42)	
	r	P	r	P
Age (years)	0.10	0.52 NS	0.06	0.71 NS
Free T3: (ng/dl /L)	0.14	0.49 NS	0.02	0.94 NS
Free T4: (ng/dl /L)	0.18	0.37 NS	0.14	0.37 NS
TSH: (UIu/ml)	0.06	0.73 NS	0.10	0.54 NS
ATPO: (IU/ml)	0.27	0.09 NS	0.29	0.07 NS
ATG: (IU/ml)	0.11	0.49 NS	0.26	0.09 NS

Uric acid at cut off 5.3 mg/dl had sensitivity of 70.2%, specificity of 71.4% and accuracy of 70.6% in diagnosis of subclinical clinical hypothyroidism (Table 6).

Table (6): Validity of uric acid in diagnosis of subclinical clinical hypothyroidism among the studied groups

Cut off	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Accuracy	P
>5.3 mg/dl	0.77 0.69-0.85	70.2%	71.4%	83.1%	54.5%	70.6%	**<0.001****

Uric acid at cut off > 6.15 mg/dl had sensitivity of 71.4%, specificity of 73.8% and accuracy of 75% in differentiation between subclinical and clinical hypothyroidism among cases groups (Table 7).

Table (7): Validity of uric acid in differentiation between subclinical and clinical hypothyroidism among the studied cases groups.

Cut off	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Accuracy	P
>6.15	0.78 0.68-0.87	71.4%	73.8%	75%	75%	75%	0.002*

DISCUSSION

Our results showed that the age and sex distributions did not differ statistically significantly amongst the studied groups. This is in agreement with our study, **Akagunduz *et al*.** [5] showed that regarding gender, there is no difference between the groups. In addition, **Sayari *et al*.** [15] showed that age and sex between the studied groups were comparable (P=0.278 and P=0.629, respectively), and they couldn't be distinguished from one another.

In the current study, in terms of free T3, free T4, and TSH, statistically, there was a distinction between the studied groups. According to a post hoc analysis, the hypothyroidism group's free T3 and free T4 levels were much greater than those of the control group, while TSH levels of subclinical hypothyroidism group and the control group were significantly lower than those of the mild hypothyroidism group. Also there was a highly statistical significance increase in TSH in the subclinical hypothyroidism group compared to the control group. This is in agreement with the study of **Noureen *et al*.** [16], which showed that one way ANOVA for each of these measures showed that there was a difference that was statistically significant ($p < 0.001$) between groups I, II, and III in terms of the average serum TSH levels. (48.3±28.24, 23.5±33.11, 3.2±0.54 IU/mL, and serum FT4 (0.42±0.20, 1.08±0.26, 1.54±0.40 ng/dL, respectively). Also, **Akagunduz *et al*.** [5] showed that patients with subclinical hypothyroidism had higher TSH levels than control group. Those who clearly have hypothyroidism had a difference that was more noticeable. Patients with subclinical hypothyroidism had statistically substantially lower serum fT3 (3.09±0.07 pg/dl) and fT4 (0.84±0.03 ng/dl) levels than the control group. When someone has overt hypothyroidism (fT3: 2.65±0.07 pg/dl, fT4: 0.402±0.02 ng/dl), this decline was statistically more significant.

We demonstrated between the studied groups that there was is statistically significant alteration in ATPO & ATG. Post hoc test showed that there was a highly statistical significance increase in ATPO & ATG in hypothyroidism group in comparison with the control group and the subclinical hypothyroidism group. Additionally, the subclinical hypothyroidism group's ATPO & ATG levels were significantly increased as versus the control group.

We showed that the difference was statistically significant in the levels of uric acid between the studied groups. In comparison with the subclinical hypothyroidism group (SCH), the hypothyroidism group and the control group had a highly statistically significant increase in uric acid, according to a post hoc analysis. Additionally, the subclinical hypothyroidism group's uric acid level increased statistically significantly when compared to the control group. In addition, **Saini *et al*.** [17] showed that significant difference in serum levels of uric acid between the cases and controls were observed. **Helmy** [8] found that there were substantial statistical differences in uric acid levels between the studied groups ($P < 0.001$) and there was a significant difference in terms of uric acid (P 0.001), TSH, FT3 and FT4 between hypothyroid patients and controls. **Shabana *et al*.** [18] showed in terms of clinical and laboratory data that the comparison of patients with SCH and those without revealed that SCH patients had significantly higher UA levels (6.1 ± 1.8 versus 4.8 ± 1.7, $p < 0.001$). **Desideri *et al*.** [19] showed that in SCH group the average serum UA level was 5.0±1.3 mg/dL, characterised by hyperuricemia (serum UA levels more than 6 mg/dL) occurred in 22.6% of the population. In disagreement with our study, **Sayari *et al*.** [15] showed that there were no discernible differences in uric acid levels between SCH and control groups. This variation could be related to a difference in sample size.

In the current study, statistical significant +ve correlation was found between uric acid and TSH, ATPO & ATG among the whole studied cases groups and negative correlation between UA and FT4. We showed that there was no statistical significance correlation between uric acid and any of the studied parameters among the hypothyroidism and SCH cases groups. This is in agreement with **Noureen *et al*.** [16] study, which indicated a strong positive relationship between the levels of TSH and serum UA in hypothyroidism groups (r =0.53 and p0.001). When UA was linked to TSH and FT4 in the SCH and control groups, no significant beneficial relationship was identified. **Jat *et al*.** [20] showed that when correlated with serum TSH levels, serum uric acid of >7 were found in 15 patients in which TSH levels of >5.5 was seen in 12 patients. When correlated with serum T3 levels, serum uric acid of > 7 was found in 15 patients in which T3levels of < 9 was seen in 6 patients. When correlated with T4 levels, serum uric acid of > 7 was found in 15 patients in which T4 level of < 3.5 was seen in 8 patients. **Bhattarai *et al*.** [21] found that thirty-five% of thyroid dysfunction patients had hyperuricemia. The rate in hypothyroid patients was 26.1%. **Desideri *et al*.** [19] found that there was also a minor yet substantial FT3 and serum correlation of UA levels (r =0.241, p =0.0026). TSH and serum uric acid had a substantial positive connection, according to **Sinha *et al*.** [6]**. Jat *et al*.** [20] discovered a strong correlation (P=0.001) between T4 and serum uric acid. **Akagunduz *et al*.** [5] reported that when the relationship between uric acid readings was examined, fT3, fT4, TSH levels, it was discovered that fT4, uric acid, fT3 and fT4 were associated throughout the group (weakly negatively significant association). Uric acid was shown to have a relationship with fT3 (poor directionality correlation) in the control group, nonetheless, there was

no link found between uric acid and levels and fT3, fT4 and TSH levels in both overt and covert hypothyroid individuals. In disagreement with our study, **Sayari *et al*. [(15)]** TSH, T3, and T4 had no discernible relationship with any aspect of renal function indicators, according to their findings.

In the current study uric acid at cut off 5.3 mg/dl had sensitivity of 70.2%, specificity 71.4% and accuracy 70.6% in diagnosis of subclinical and clinical hypothyroidism. Also, uric acid at cut off > 6.15 mg/dl had sensitivity of 71.4%, specificity of 73.8% and accuracy of 75% in differentiation between subclinical and clinical hypothyroidism among cases groups. This is in agreement with study of **Torkian *et al*. [(22)]** where they discovered that uric acid had a considerable prediction for distinguishing SCH patients from the euthyroid group. Uric acid's optimum cut-off point, sensitivity, and specificity for differentiating patients were 4.70, 55%, and 52%, respectively.

CONCLUSION

Overt and subclinical hypothyroid individuals had increased serum uric acid levels than in euthyroid controls. This demonstrated the negative impact of hypothyroidism on renal function. As a result, it is advised to examine the renal state both at the time of hypothyroidism diagnosis and during the follow-up period. Thyroid screening is recommended for anyone who has certain biochemical abnormalities.

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