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Assessment Of The Relation Between Serum Uric Acid And Electrolytes Levels InSubclinical And Overt Hypothyroidism Patients

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ABSTRACT

Background: *A common endocrine condition known as hypothyroidism is characterized by insufficient thyroid hormone production by the thyroid gland. Approximately all tissues need thyroid hormones for optimal growth, development, and operation,and the kidneys particularly 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 con[1]nection 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 Medicine Departments, Makkah hospital, Saudi Arabia. 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 healthypeople (control individuals).* ***Results:*** *A statistically significant difference existed between the groups that were being researched in uric acid level. Posthoc 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

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The most prevalent endocrine condition is thyroidillness conditions in the globe. According to reports, almost 42 million of people struggle with thyroid issues [1]. The most frequent underlying cause of hypothyroidismis 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 T3are 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 incidenceof 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 beena 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 thyroidproblems can have an impact on the physiology anddevelopment 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 purinesare 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 isinfluenced 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 hypothyroid patients' renal perfusion and glomerularfiltration rate (GFR) are decreased [8, 13].

PATIENTS AND METHODS

This case control comparative study was conducted at Medicine Departments, Makkah hospital, Saudi Arabia. The study involved 126 adult individuals (42 healthy controls of the same age andsex and 84 the hypothyroid patients). The study wascarried out from March 2022 to January 2023.

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

- **Group I:** 42 Patients diagnosed with primaryhypothyroidism.
- **Group II:** 42 Patients diagnosed with subclinicalhypothyroidism.
- **Group III:** 42 Healthy control individuals.

Inclusion criteria:

Low serum T3 and T4 levels in conjunction withelevated 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 recognized 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 secondaryhypothyroidism.
- 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 thatincluded their age and gender, history of hypertension ordiabetes, history of drug use, any chronic illnesses, familyhistory 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 ethical approval was obtained

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).

Variable		othyroidism(n=42)		hical 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 analysisshowed 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).

Variable	othyroidism(n=42)	Subclinical hypothyroidism (n=42)	Control(n=42)	KW/F	P	PostHoc

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]

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 andATG 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).

Variable		**Hypothyroidism (n=42)**	**Subclinical hypothyroidism (n=42)**	**Control(n=42)**	**KW**	**P**	**PostHoc**
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]

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

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 amonghypothyroidism and subclinical hypothyroidism groups (Table 5).

Variable	Hypothyroidism Uric acid(n=42)		Subclinical hypothyroidismUric 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 subclinicalclinical hypothyroidism (Table 6).

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% indifferentiation between subclinical and clinical hypothyroidism among cases groups (Table 7).

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 ourstudy, **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 oneanother.

In the current study, in terms of free T3, free T4,and TSH, statistically, there was a distinction between thestudied 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 highlystatistical 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 TSHlevels 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 wasstatistically more significant.

We demonstrated between the studied groups thatthere 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 asversus 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 significantincrease in uric acid, according to a post hoc analysis. Additionally, the subclinical hypothyroidism group's uricacid level increased statistically significantly when compared to the control group. In addition, **Saini et al.** [17]showed that significant difference in serum levels of uricacid 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 termsof 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 etal.** [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 differencesin uric acid levels between SCH and control groups. Thisvariation 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 parametersamong the hypothyroidism and SCH cases groups. This isin agreement with **Noureen et al.** [16] study, which indicated a strong positive relationship between the levelsof TSH and serum UA in hypothyroidism groups (r =0.53and p0.001). When UA was linked to TSH and FT4 in theSCH and control groups, no significant beneficial relationship was identified. **Jat et al.** [20] showed that whencorrelated 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 inwhich 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 andserum 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 andserum 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 wasshown to have a relationship with fT3 (poor directionalitycorrelation) 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 theirfindings.

In the current study uric acid at cut off 5.3 mg/dlhad sensitivity of 70.2%, specificity

71.4% and accuracy70.6% in diagnosis of subclinical and clinicalhypothyroidism. 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 fordistinguishing 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 hadincreased 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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