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Research Article

Evaluation of the Correlation of Urea, Creatine, and Uric Acid Levels with TSH in Patients with Newly Diagnosed Overt and Subclinic Hypothyroidism

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Abstract

Objectives: Renal function is influenced by thyroid status. Changes in routine clinical chemical indicators of renal function in the hypothroid status are not well characterized, and are infrequently discussed in standart internal medicine textbooks. This study was done to determine the relationship between renal function and different degrees of thyroid dysfunction.

Methods: In this cross-sectional retrospective study, thyroid and kidney function tests were analyzed in 201 patients of whom 120 were subclinical hypothyroidism and 81 patients were overt hypothyroidism. These were compared with 203 age-and sex-matched euthyroid control group.

Results: Overt hypothyroid subjects showed significantly raised serum urea, creatinin and uric acid levels as compared to controls but subclinical hypothyroid patients did not showed significant increased levels of serum urea, uric acid and creatinin levels.

Conclusion: Hypothyroid state is associated with significant derangement in biochemical parameters of renal function. Therefore, the renal function should be regularly monitored in hypothyroid patients.

Keywords: Creaitine, hypothyroidism, urea, uric acid, tsh

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Hypothyroidism is defined as a decrease in thyroid hormone production as a result of a defect in any part of the hypothalamic-pituitary-thyroid axis. As a laboratory finding, high TSH, low T4 and T3 are detected. Subclinical hypothyroidism is a common endocrine disorder characterized by normal T3, T4 level, increased TSH level, usually without clinical manifestations.[1] The kidneys play a role in the metabolism and elimination of thyroid hormones, at the same time the kidneys are organs where the effects of thyroid hormones are present. The effects of hypothyroidism on the kidney are well understood and are associated with water and electrolyte balance and tubular dysfunction.[2,3] How renal routine biochemical markers change in hypothyroidism is not well characterized, and changes in urea and creatinine levels are not mentioned in standard reference texts.[4,5] In uncomplicated primary hypothyroidism, urea and creatinine levels increase reversibly in children and adults.[6-9] In some studies, hyperuricemia and thus a predisposition to gout

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were found in hypothyroid patients.[10] Studies and data on renal functions in hypothyroidism are limited.[8,9]

In this study, we aimed to investigate whether there is a significant change in the biochemical renal function parameters that we use in daily practice in subclinical hypothyroidism and overt hypothyroidism and whether these values are correlated with the thyroid hormone profile.

Methods

The files of patients with overt hypothyroidism and subclinical hypothyroidism diagnosed in general internal medicine outpatient clinics between 2010 and 2013 were retrospectively reviewed. The diagnosis of subclinical hypothyroidism was made with increased TSH value (between 6.1 and 9.9 mIU/ML) and normal fT4 and fT3 values. The diagnosis of overt hypothyroidism was made with increased TSH (>10mIU/Ml), decreased fT3 and fT4 values. Exclusion criteria from the study: pregnancy, hepatic or renal dysfunction, hypertension, heart failure, obesity, use of contrast material in the last month, use of lithium or amiodarone, use of methimazole or propylthiuracil due to hyperthyroidism, and other inflammatory conditions.

The healthy control group, which was matched in terms of age and gender distribution, was included in the patient group among the healthcare professionals who had their routine examinations done for general control.

All patients included in the study had TSH, fT4, fT3, urea, creatine and uric acid values. TSH, fT4,s T3 electrochemiluminescence immunoassay (ECLIA) was studied on the Roche Eleycsys Modular Analystic E170 autoanalyzer. Urea, creatine, uric acid and other routine biochemical tests were also performed using the automated technique (Siemens Advia 2400, Tarrytown, New York, United States).

The basic statistics and the characteristics of the patients are summarized. Mean, median, standard deviation, minimum and maximum values in summarizing numerical parameters; number and percentage values were used for categorical variables. The statistical significance limit (p) was determined as 0.05. Statistical analyzes were performed with SPPS (SPSS Inc. Chicago, IL, USA) ver 12.0 program. Parametric or non-parametric statistical methods were used in comparisons, depending on whether the variable was normally distributed or not. Oneway ANOVA was used for comparisons between three groups for normally distributed numerical parameters, and Tukey HSD was used as a post-hoc test. Chi-square was used to compare categorical variables. Pearson correlation was used for the relationship between numerical variables showing symmetrical distribution.

Results

A total of 201 patients, 81 of whom were overt and 120 subclinical, were included in the study. Twelve of the patients with subclinical hypothyroidism were male and 108 were female. Of the patients with overt hypothyroidism, 17 were male and 64 were female. A control group consisting of 203 healthy individuals with similar age and gender distribution were included in the study. There is no difference between the groups according to gender.

TSH level was found to be 2.524±0.21 mIU/Ml in the control group. TSH value was higher in patients with subclinical hypothyroidism (7.812±0.13 mIU/Ml). This difference was more pronounced in patients with overt hypothyroidism (44,501±4.51 mIU/Ml). Serum fT3 (3.09±0.07 pg/dl) and fT4 levels (0.84±0.03 ng/dl) were statistically significantly lower in patients with subclinical hypothyroidism compared to the control group. This decrease was statistically more significant in patients with overt hypothyroidism (fT3: 2.65±0.07 pg/dl, fT4: 0.402±0.02 ng/dl).

In the study, mean urea: 30.5±14.8mg/dl, creatinine: 0.7±0.1mg/dl, uric acid: 4.1±1.1mg/dl in the control group. Serum urea level was found to be 35.6±7.1mg/dl in patients with overt hypothyroidism, which was statistically significantly higher than the control group (p=0.002).

The creatinine value in patients with overt hypothyroidism was found to be 0.8±0.1mg/dl, and it was significantly higher than the control group (p=0.001). The uric acid level was also found to be 5.5±1.3mg in patients with overt hypothyroidism and was significantly higher than the control group (p<0.001). In patients with subclinical hypothyroidism, urea: 31.5±6.4mg/dl, creatinine: 0.7±0.2 mg/dl, uric acid: 4.3±1.1mg/dl. it was not significantly higher than the control group (p= 0.708, p= 0.934, p= 0.334) (Table 1).

Table 1. Urea, creatinine and uric acid comparisons by groups

Variables	Control	Overt	p[1]	Subclinical	p[2]
Urea	30.5±14.8	35.6±7.1	0.002	31.5±6.4	0.708
Creatinine	0.7±0.1	0.8±0.1	0.001	0.7±0.2	0.934
Uric acid	4.1±1.1	5.5±1.3	<0.001	4.3±1.1	0.334

[1] overt vs. control; [2] Subclinical vs. control.

In the post-hoc analysis performed by Tukey HSD method, urea, creatinine, and uric acid values were significantly different in overt hypothyroid patients compared to the control group and subclinical hypothyroid patients. The urea, creatinine, and uric acid values found in patients with subclinical hypothyroidism were not significantly different from the control group (Table 2).

Considering all patients, each parameter was correlated with TSH; however, no statistically significant correlation was found with TSH for each parameter in the groups (Table 3).

When the correlation of urea, creatinine, and uric acid values between fT3, fT4, TSH values was examined, it was found that Urea and fT4, Uric acid and fT3 and fT4 were correlated in the whole group (weakly inversely significant relationship); In the control group, creatinine and uric acid were found to be correlated with fT3 (weak correlation in the same direction); however, no correlation was found between urea, creatinine, uric acid values and fT3, fT4, TSH values in patients with subclinical hypothyroidism and overt hypothyroidism (Tables 3, 4).

Table 2. Urea, creatinine and uric acid comparisons by groups

Variables	Groups	*P
Urea	Overt vs. Subclinical	0.033
	Overt vs. Control	0.002
	Subclinical vs. Control	0.708
Creatinine	Overt vs. Subclinical	0.010
	Overt vs. Control	0.001
	Subclinical vs. Control	0.934
Uric acid	Overt vs. Subclinical	<0.001
	Overt vs. Control	<0.001
	Subclinical vs. Control	0.334

*Tukey HSD.

Table 3. Correlation of urea, creatinine, and uric acid with TSH

	TSH	
	R	P
All Groups		
Urea	0.147	0.003
Creatinine	0.137	0.006
Uric acid	0.341	<0.001
Overt hypothyroidism		
Urea	0.058	0.607
Creatinine	-0.041	0.715
Uric acid	0.009	0.933
Subclinical hypothyroidism		
Urea	0.013	0.888
Creatinine	0.115	0.210
Uric acid	-0.042	0.648
Control		
Urea	0.042	0.549
Creatinine	0.082	0.245
Uric acid	0.012	0.864

Discussion

The relationship between kidney and thyroid functions has been known for years.[11,12] Thyroid hormones are necessary for the development of the kidney and for maintaining the water and electrolyte balance. In addition, the kidney plays a role in the metabolism and elimination of thyroid hormones. In clinical practice, hypo- and hyperthyroidism is effective in electrolyte and fluid metabolism and also in cardiovascular functions.[5,6] Impairment in kidney functions may lead to changes in the synthesis, secretion and elimination of thyroid hormones.[12] The most common renal dysfunction in hypothyroid patients is increased serum creatinine level, decreased glomerular filtration rate (GFR) and renal blood flow, impaired free water excretion, and hyponatremia.[3]

Our aim in this study was to determine whether basic kidney function tests (urea, creatinine, uric acid) were affected in hypothyroidic patients. Although the increase in urea and creatinine values in hypothyroidism is not mentioned in the reference texts, there are many publications showing the increase in urea and creatinine values in uncomplicated hypothyroidism. Verhelst j et al. showed that creatinine values also increased in patients with subclinical hypothyroidism.[13]

In some studies, a reversible creatinine elevation was found

Table 4. Correlation of urea, creatinine and uric acid with fT3 and fT4

	fT3		fT4	
	R	P	R	P
All Groups				
Urea	-0.088	0,076	-0.118	0.018
Creatinine	-0.071	0.155	-0.057	0.251
Uric acid	-0.243	<0.001	-0.244	<0.001
Overt hypothyroidism				
Urea	-0.074	0.513	-0.047	0.679
Creatinine	-0.048	0.668	0.029	0.798
Uric acid	-0.061	0.587	0.032	0.778
Subclinical hypothyroidism				
Urea	0.052	0.570	0.110	0.234
Creatinine	0.097	0.294	0.063	0.494
Uric acid	0.037	0.691	0.042	0.647
Control				
Urea	0.093	0.185	-0.027	0.700
Creatinine	0.169	0.016	0.127	0.072
Uric acid	0.241	0.001	0.059	0.402

in primary hypothyroidism.[8,9] There are two mechanisms related to kidney dysfunction in hypothyroidism: direct effects of thyroid hormones on the cardiovascular system (increase in peripheral arterial resistance, decrease in myocardial contraction and stroke volume) and metabolic effects (hyperlipidemia) and indirect effects with paracrine and endocrine mediators (IGF I, VEGF).[14-16] A mild proteinuria may be observed in patients with hypothyroidism due to the increase in capillary passage of proteins.[17] Therefore, hypothyroidism may be a factor that worsens renal function in patients with already renal failure. GFR is lower in one third of patients with myxedema than in euthyroid patients. It can return to normal with thyroxine replacement therapy.[18] In a study conducted by Hammami et al to investigate the effect of acute hypothyroidism on GFR and serum creatinine levels in patients with thyroid cancer when they discontinued T4 therapy for 4 weeks while they were preparing for treatment or screening, they measured serum creatinine values in 191 hypothyroid phases in 116 patients. They found that there was an increase in serum creatinine level due to the temporary discontinuation of thyroxine treatment, and that the increase in serum creatinine was more pronounced in young male patients with very elevated TSH levels (>150 mU/L). It has been shown that GFR and serum creatinine values returned to normal levels with the re-initiation of thyroxine treatment.[19] In the study of Georgias et al., it was observed that glomerular functions returned to normal rapidly with hormone replacement therapy in which GFR decreased in acute severe hypothyroidism cases.[9] In patients who have undergone total thyroidectomy due to thyroid carcinoma, levothyroxine treatment is discontinued as a preparation for radioactive iodine treatment. In this case, urea and creatinine levels increase and drugs with renal excretion may accumulate in the body.[20] Vandana Saini, Amita Y et al. found that serum urea and creatinine values were increased in patients with overt and subclinical hypothyroidism compared to the control group.[21] In our study, similar to the studies mentioned above, urea and creatinine values were found to be significantly higher in patients with overt hypothyroidism compared to the healthy control group (p=0.002 for urea, p=0.001 for creatinine). Urea and creatinine values were not significantly different in patients with subclinical hypothyroidism compared to the control group (p=0.708 for urea, p=0.934 for creatinine). Vandana et al., in their study, found that TSH and serum creatinine and uric acid levels were positively correlated in patients with overt hypothyroidism, and fT4 level and uric acid were negatively correlated.[21] In our study, when the control and patient groups were considered as a whole, TSH and creatinine values were found to be correlated; however, it was determined that TSH was not correlated with urea and creatinine values in the patient groups with overt and subclinical hypothyroidism. When the correlation of urea, creatinine, and uric acid values between fT3, fT4, and TSH values was examined, it was found that urea and fT4, uric acid and fT3 and fT4 were correlated in the whole group (weakly significant inverse relationship); creatinine and uric acid were found to be correlated with fT3 in the control group (weak correlation in the same direction); however, no correlation was found between urea, creatinine, uric acid values and fT3, fT4 and TSH values in patients with subclinical hypothyroidism and overt hypothyroidism.

It has been shown in some studies that there may be hyperuricemia in patients with uncomplicated hypothyroidism.[23,24] Giardano et al. proved that gout due to hyperuricemia is more common in hypothyroid patients.[23] In this study, uric acid levels were found to be significantly higher in patients with overt hypothyroidism ($p<0.001$). In patients with subclinical hypothyroidism, there was no significant difference with the control group. Considering the whole group, uric acid level was found to be correlated with TSH ($p<0.001$), and fT3 level and uric acid level were found to be correlated in the whole group ($p<0.001$). The elevation of uric acid in patients with overt hypothyroidism was found to be more significant than the elevation of urea and creatinine ($p<0.001$). The increase in uric acid production may be responsible for this increase due to myopathy in hypothyroidism. At the same time, decreased GFR and decreased renal blood flow reduce the renal clearance of uric acid, which may be the second cause of increased uric acid.[24]

In our study, urea, creatinine and uric acid levels were significantly higher in patients with overt hypothyroidism compared to the control group and patients with subclinical hypothyroidism; however, these values were still within normal limits. High levels of urea, creatinine, and uric acid in newly diagnosed outpatients with overt hypothyroidism and their increase as the degree of hypothyroidism increases may suggest that these values should be used in renal monitoring in daily practice in hypothyroid patients. Thyroid functions should be closely monitored in patients with existing chronic renal failure, and replacement should be performed immediately in case of thyroid hormone insufficiency. It has been found that GFR and renal perfusion flow increase with levothyroxine treatment in primary hypothyroidism.[3,8] Likewise, it has been shown that thyroid hormone replacement significantly increases GFR in patients with chronic renal failure with hypothyroidism.[13]

Limiting points of our study; The fact that we can evaluate renal functions more objectively is that values such as GFR and proteinuria were not checked. At the same time,

it has not been prospectively investigated whether these values decrease to normal after levothyroxine treatment in patients with overt hypothyroidism with increased urea, creatinine and uric acid values.

Conclusion

In conclusion, prospective studies with biochemical markers and parameters and larger patient groups that we can evaluate renal functions more objectively are needed in order to better understand the physiological changes seen in the kidneys in hypothyroidism.

Disclosures

Ethics Committee Approval: The study was performed in accordance with the declaration of Helsinki. The patients give a written informed consent before the study. Both patient consent and the approval of the Health Sciences University, Istanbul Training and Research Hospital ethics committee approval were received. (Approval Number: 3543-12/17).

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