



CHANGES IN BIOCHEMICAL MARKERS OF RENAL FUNCTION IN SUBCLINICAL AND OVERT HYPOTHYROIDISM

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Abstract: The present study aimed to determine whether thyroid dysfunction has deleterious effects on renal function. Both renal function tests (urea, creatinine and uric acid) and thyroid function tests (TSH, fT_3 and fT_4) were conducted in 100 patients with euthyroid status and 50 patients with subclinical and overt hypothyroidism respectively. A statistically significant rise in the levels of urea and creatinine has been observed in patients with subclinical and overt hypothyroidism as compared to euthyroid subjects. Also, a positive correlation been observed between the rise in TSH levels and creatinine in patients with overt hypothyroidism. A statistically significant rise in uric acid levels has been observed in patients with overt hypothyroidism as compared to controls. These observations are suggestive of monitoring the renal function in patients with hypothyroidism.

Key Words: Overt Hypothyroidism, Renal function tests, Subclinical Hypothyroidism creatinine, thyroid function tests.

INTRODUCTION

The interplay between thyroid and the kidney in each other's functions is known for many years (1). Thyroid hormones affect renal function by both pre-renal and direct renal effects. Pre-renal effects are mediated by the influence of thyroid hormones on the cardiovascular system and the renal blood flow (RBF). The direct renal effects are mediated by the effect of thyroid hormones on glomerular filtration rate (GFR) (2). Thyroid dysfunction affects renal physiology and development, whereas kidney disease could result in thyroid dysfunction. Long standing hypothyroidism can cause significant changes in renal function such as a decrease in sodium reabsorption in the proximal tubule, impairment in the concentrating and diluting capacities of the distal tubules, a decrease in the urinary urate excretion and a decrease in the renal blood flow and glomerular filtration rate (GFR) (3,4). These renal abnormalities occur because the deficiency of thyroid hormones (TH) reduces the cardiac output leading to generalized hypodynamic state of the circulatory system (5).

Hypothyroidism also results in increased glomerular capillary permeability to proteins (6). The consequent proteinuria often precedes the reduction in GFR in hypothyroidism (7).

Very few studies have reported the effect of hypothyroidism on renal function tests especially creatinine (8,9,10). Some studies have also reported hyperuricemia leading to gout in hypothyroid subjects (11,12). Not much data is available on the impact of hypothyroidism on renal function tests in this region. This study was therefore planned to study about the changes in biochemical markers of renal function in patients with subclinical and overt hypothyroidism and

to correlate these values with the thyroid profile of the patient.

MATERIALS AND METHODS

The present study was conducted on 200 patients who visited the hormone clinic of our hospital and were in the age group 20 to 70 years. Brief clinical history was taken to rule out hypertension, diabetes mellitus or any other medical condition, which can affect renal function. 6ml of fasting venous blood sample was taken for analysis. After centrifugation, the serum was divided into 2 aliquots for renal function tests (urea, creatinine and uric acid) and thyroid function tests (TSH, fT_3 and fT_4). Both the aliquots were analyzed immediately by different technicians who were unaware of the results of other organ function tests.

Renal function tests

Serum urea was analyzed by enzymatic urease-glutamate dehydrogenase method, creatinine by modified jaffe's method and serum uric acid by urease-peroxidase method on fully automated analyser BS-480 (Mindray) using mindray kits.

Thyroid function tests

Serum TSH, fT_3 and fT_4 were analyzed on Liaison whose working is based on chemiluminescence. Reference ranges are TSH (0.25-5.25 μ IU / ml), fT_3 (2.0-4.0 pg/ml) and fT_4 (0.7-1.7 ng/dl).

The study included 100 patients having euthyroid status (TSH < 6 μ IU / ml, normal fT_3 and fT_4 levels) who were taken as controls and 100 patients having hypothyroidism (TSH levels > 6.0 μ IU / ml). The hypothyroid group further included 50 patients with

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subclinical hypothyroidism (TSH 6.1-9.9 μ IU / ml with normal fT_3 and fT_4) and 50 patients with overt hypothyroidism (TSH >10 μ IU / ml with abnormal fT_3 and fT_4)(13).

Statistical analysis

The continuous data was presented as mean \pm SD. Normality of quantitative data was checked by measures of kolmogorov Smirnov tests of normality. Analysis of normally distributed continuous variable (age) was done by One Way ANOVA followed by Post-Hoc Multiple Comparisons. For skewed data, Kruskal Wallis test was applied. Mann-Whitney U test was used for statistical analysis.

RESULTS

In the present study, majority of the patients who reported to the thyroid clinic were females. Mean age of the euthyroid group was 33.6 ± 12.3 years and of the hypothyroid group was 41.08 ± 11.8 years with a significant p value ($p < 0.001$). Hypothyroid group consisted of 80% females whereas the euthyroid group consisted of 85% females.

Serum TSH levels in the euthyroid group were $2.396 \pm 0.9 \mu$ IU/ml (Table 1). Patients with both subclinical hypothyroidism (7.128 ± 1.3) and overt hypothyroidism (46.38 ± 58.1) showed statistically significant rise in TSH levels ($p < 0.001$) as compared to controls.

Table 1: Comparison between TSH, fT_4 and fT_3 values obtained in hypothyroid and euthyroid subjects

Parameters	Controls	Subclinical hypothyroidism	Overt hypothyroidism
TSH (μ IU/ml)	2.396 ± 0.92	$7.12 \pm 1.32^{**}$	$46.38 \pm 58.06^{**}$
fT_4 (ng/dl)	0.98 ± 0.08	$0.89 \pm 0.14^{**}$	$0.52 \pm 0.26^{**}$
fT_3 (pg/ml)	3.08 ± 0.29	$2.84 \pm 0.12^{**}$	$1.89 \pm 0.58^{**}$

**p value vs controls $p < 0.001$

The levels of fT_4 decreased significantly in patients with subclinical hypothyroidism (0.89 ± 0.1 ng/dl, $p = 0.001$) as compared to those with euthyroid status (0.98 ± 0.1 ng/dl) whereas the decrease has been highly significant in patients with overt hypothyroidism (0.52 ± 0.3 ng/dl) ($p < 0.001$, Table 1).

The levels of fT_3 in patients with subclinical hypothyroidism (2.84 ± 0.1 pg/ml) as well as in patients with overt hypothyroidism (1.89 ± 0.6 pg/ml) showed a highly significant decrease ($p < 0.001$) as compared to controls (3.08 ± 0.3 pg/ml) (Table 1). Mean levels of serum urea in both subclinical hypothyroidism (24.7 ± 9.2 mg/dl) and overt hypothyroidism (28.36 ± 10.9) showed a statistically significant rise as compared to controls (19.92 ± 4.5 mg/dl) (Table 2).

Table 2: Comparison of renal function tests between hypothyroid and euthyroid subjects

Tests	Controls	Subclinical hypothyroidism	p value ^a	Overt hypothyroidism	p value ^b
Urea	19.92 ± 4.52	24.7 ± 9.15	0.004**	28.36 ± 10.89	$< 0.001^{**}$
Creatinine	0.75 ± 0.15	0.89 ± 0.23	$< 0.001^{**}$	1.05 ± 0.36	$< 0.001^{**}$
Uric acid	4.04 ± 0.92	4.37 ± 1.28	0.157	5.06 ± 1.55	$< 0.001^{**}$

p value^a Subclinical hypothyroidism vs controls

p value^b Overt hypothyroidism vs controls

Similarly, serum creatinine levels in patients with subclinical hypothyroidism (0.89 ± 0.2 mg/dl) and overt hypothyroidism (1.05 ± 0.4) were higher than in controls (0.75 ± 0.2 mg/dl) and the rise was statistically significant ($p < 0.001$) (Table 2). The mean levels of uric acid in patients with overt hypothyroidism (5.06 ± 1.6 mg/dl) showed a statistically significant rise ($p < 0.001$) as compared to controls (4.04 ± 0.9 mg/dl) (Table 2).

When subclinical and overt hypothyroid cases were compared, TSH, fT_4 and fT_3 showed a statistically significant change ($p < 0.001$). Also the differences in renal function parameters were also statistically significant (Urea 0.038^* , creatinine 0.008^{**} , and uric acid 0.004^{**}). (* $p < 0.05$, ** p value < 0.001).

Correlation coefficients (r) between thyroid function tests and renal function tests were also calculated in subclinical and overt hypothyroidism to find out if any association exists between them (Table 3). TSH did not show any statistically significant correlation with any of the renal function parameters in subclinical hypothyroidism but fT_3 and fT_4 showed a positive correlation with urea (Table 3).

Table 3: Correlation of renal function tests in patients with subclinical hypothyroidism

	TSH		fT_4		fT_3	
	r value	p value	r value	p value	r value	p value
Urea	-0.115	0.433	0.294	0.04*	0.312	0.029*
Creatinine	0.217	0.135	0.162	0.268	0.054	0.711
Uric acid	0.052	0.721	0.035	0.814	0.085	0.559

* $p < 0.05$

In patients with overt hypothyroidism, TSH showed a significant positive correlation with serum creatinine levels whereas fT_4 and fT_3 did not show any significant correlation with any of these renal function parameters (Table 4).

Table 4: Correlation of renal function tests in patients with overt hypothyroidism

	TSH		fT_4		fT_3	
	r value	p value	r value	p value	r value	p value
Urea	0.047	0.744	-0.077	0.594	-0.182	0.205
Creatinine	0.302	0.035*	0.1	0.488	-0.127	0.378
Uric acid	0.048	0.741	-0.066	0.649	-0.07	0.627

* $p < 0.05$

DISCUSSION

The purpose of the present study was to evaluate the effect of subclinical and overt hypothyroidism on parameters of renal function and to compare it with euthyroid subjects and also to study the correlation of TSH, fT_4 and fT_3 with urea, creatinine and uric acid.

The present study shows that there is a statistically significant rise in the levels of urea and creatinine in patients with subclinical and overt hypothyroidism as compared to euthyroid subjects. A positive correlation has been observed between the rise in TSH levels and creatinine in patients with overt hypothyroidism. It has also been seen that primary hypothyroidism is associated with a reversible elevation of serum creatinine in both adults (10,14,15) and children (16,17) and this increase is observed in more than half (~55%) of adults with hypothyroidism (8). Similar results have also been reported in case studies and few other studies involving lesser number of hypothyroid subjects (12, 17, 18). It has been thought that renal impairment with hypothyroidism may be due to reduced cardiac output and increased systemic and renal vasoconstriction leading to reduced renal blood and plasma flow and decreased GFR. Also, hypothyroidism results in a reversible elevation in serum creatinine due to the reduction in GFR as well as possible myopathy and rhabdomyolysis (7). So, it can be said that hypothyroidism can be considered either as a cause of kidney disease or a factor responsible for deterioration of renal function.

A statistically significant rise in uric acid levels has been observed in patients with overt hypothyroidism as compared to controls. But the rise did not correlate with any of the thyroid function tests. Hyperuricemia has been observed in hypothyroid patients in other studies also (11, 15, 19, 20, 21). In hypothyroidism, the hyperuricemia occurs secondary to decreased renal plasma flow and impaired glomerular filtration (15, 19).

It can thus be concluded that increasing degree of hypothyroidism is associated with deteriorating renal function. So, it becomes very important for the treating clinician to understand the association between renal function and hypothyroidism. It is emphasized here that there should be regular monitoring of renal function in patients with hypothyroidism so that declining renal function may be detected. However, further studies are needed to understand the effects of hypothyroidism on renal function.

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