

Study on Effect of Levothyroxine Replacement Therapy on Some Biochemical Markers of Renal Function in Hypothyroid Patients in Tertiary Care Centre of Kumaon Region

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ABSTRACT

Introduction- Thyroid hormones are essential for energy metabolism, growth and development of various body organs including kidneys. The literature concerning the association between renal function changes with the severity of hypothyroidism and the effects of levothyroxine replacement therapy is unclear.

Aims and objectives- This study was therefore conducted with aim to assess the derangements in biomarkers of renal function in hypothyroid patients as well as to observe the effects of thyroxine treatment in these subjects.

Materials and methods- 215 subjects were enrolled in the study. 135 newly diagnosed cases of hypothyroidism were divided into 2 groups; subclinical hypothyroids (GII; n=75) and overt hypothyroid (GIII; n=60). The results were compared with 80 euthyroid controls (GI; n=80).

83 selected subjects; 38 of subclinical hypothyroidism and 45 overt hypothyroid cases were followed up with repeat of renal and thyroid function tests after 3 months of thyroxine replacement therapy (L-T4 therapy).

Serum sample for TSH, T3 and T4 was analysed on autoanalyser e411 of Roche diagnostics. Serum urea, creatinine and uric acid estimation was done on cobas 501c of Roche diagnostics.

Results- Mean levels of serum creatinine and uric acids were raised in overt hypothyroid & subclinical cases as compared to controls. The levels of serum creatinine ($p<0.001$) & uric acid ($p<0.05$) were significantly elevated in OH cases when compared with SH cases. No significant change was observed in serum urea levels in SCH and OH cases in comparison to euthyroid controls. There was a significant reduction in levels of Serum creatinine, uric acid levels in SCH and OH cases after 3 months of levothyroxine replacement therapy, while there was no change in serum urea levels.

A significant positive correlation of creatinine ($p<0.0242$) and uric acid ($p<0.0281$) with TSH and negative correlation of urea and T4 was observed in hypothyroid group as whole before therapy.

Conclusions - This study concludes that there is deterioration in renal function with progression of hypothyroidism and the derangements are reversible with restoration of thyroid hormone levels by levothyroxine replacement therapy. Thus, clinicians can advise the renal function tests while screening and treating hypothyroid patients.

Key words- Subclinical hypothyroidism), Overt Hypothyroidism, Creatinine, Uric Acid, Levo- thyroxine therapy

INTRODUCTION

Thyroid hormones, tetra-iodothyronine (T4) or thyroxine and tri-

iodothyronine (T3) produced by thyroid gland, play an important role in various biochemical pathways, growth, development

& differentiation of different tissues including kidneys. (1-3) The biosynthesis of thyroid hormones is regulated and controlled by Thyroid stimulating hormone (TSH) secreted by pituitary, thyroid releasing hormone (TRH) released from hypothalamus according to body requirements. (4,5)

The deficiency of thyroid hormones may occur due to reduced production, derangement in distribution or lack of effects, leading to clinical syndrome called as hypothyroidism. (6-8) According to severity the hypothyroidism, can be classified as clinical or overt hypothyroidism, characterized by elevated levels of TSH along with reduced levels of both T3, T4 and mild or subclinical in which there is only subtle elevation of TSH, T3 & T4 levels are within reference range. (9-11)

Hypothyroidism has been associated with derangements of various kidney functions. (12-14) Thyroid hormones may have direct effects on embryonic structure, development, glomerular filtration, tubular secretion, absorption, electrolyte pumps and pre renal or indirect effects mediated by the influence on cardiovascular system and renal blood flow. (12-19)

In the treatment of hypothyroidism, synthetic T4 hormone as levothyroxine is used as replacement therapy. Studies conducted in hypothyroidism to evaluate the effects on renal function tests and responses to levothyroxine treatment have shown controversial results. (17-22) Hence the present study was conducted with aims

1. To study derangements in biochemical markers of renal function tests in different grades of hypothyroidism patients
2. To quantitate the effects of levothyroxine replacement therapy after 3 months on parameters of thyroid and renal function tests

STATISTICAL ANALYSES: - The data were compiled and entered in MS Excel sheet and the analysis was carried out using the Statistical Package for the Social Sciences (SPSS 19.0.2) program for windows. Paired “t” test was used to analyze

all the data for statistical significance. Correlation and regression coefficient were also calculated among relevant parameters.

MATERIALS AND METHODS

After approval from Institutional Ethical Committee, the present study was conducted in Department of biochemistry at Susheela Tiwari Medical College and Hospital, Haldwani between November 2016 to April 2018. A total of 215 subjects, age and sex matched attending the medical OPD after giving written informed consent were enrolled in the study. Out of these 80 subjects (euthyroids; TSH, T3, T4 within normal reference range) were taken as controls (Group -I). 75 newly diagnosed patients with lab values of elevated TSH and T3 and T4 within normal range were included as subclinical hypothyroidism patients (SCH; Group-II). 60 patients having elevated TSH and decreased both T3 and T4 levels were enrolled as overt hypothyroidism (group III).

Patients with previous history of any thyroid disorder, renal disease, diabetes mellitus, hypertension, tuberculosis, any other acute or chronic illness were excluded from the study. Patients on levothyroxine and other drugs like oral contraceptives, steroids, antiepileptics, pregnant females and infants were also excluded from the study.

Selected 83 subjects, 38 patients of SCH and 45 cases of OH were followed with a repeat of thyroid (TSH, T3, T4) and renal function tests (serum urea, creatinine, uric acid) parameters after 3 months of levothyroxine replacement therapy.

METHODS- After an overnight fast of 10-12 hours, 5-6 ml of venous blood sample was collected, centrifuged and separated sera was divided into 2 aliquots. The one for kidney function test parameters including serum urea, creatinine, uric acid was analyzed immediately on a fully automated Cobas 501 of Roche diagnostics. The other one for thyroid profile tests in which TSH, T3 and T4 was included was analyzed on Cobas e411 of Roche diagnostics based on the principle of Electrochemiluminescence.

RESULTS

Table –I: Shows baseline profile (age, sex, BMI) of the study subjects (n=135).

Parameters	Euthyroid controls (n=80)	Subclinical hypothyroid patients(n=75)	Overt hypothyroid patients(n=60)	Total (n=135)
Age (years)	43.56 ± 10.76	44.64 ± 11.44	45.76 ± 12.65	45.20 ± 11.74
% of males	21.11%	20.89%	18.76%	19.82%
% of females	78.89%	79.11%	81.24%	80.18%
BMI(kg/m ²)	23.62 ± 10.21	24.93 ± 4.45	26.89 ± 4.87	25.91 ± 4.67

Table II: Comparison of biochemical parameters of thyroid function tests and renal function tests in euthyroid controls (group I), subclinical hypothyroids (group II) and overt hypothyroids (group III) along with their normal reference range

Biochemical parameters	Normal range	Euthyroid controls: G I (n=80)	Subclinical hypothyroids: GII (n=75)	Overt hypothyroids: GIII (n=60)	P value G I vs GII	P value GI vs GIII	P value GII vs GIII
TSH	0.27-4.20 µIU/ml	2.71 ± 0.77	9.51 ± 3.18	42.67 ± 4.78	<0.0001	<0.0001	<0.0001
T3	0.85-2.0ng/ml	1.37 ± 0.24	1.23 ± 0.41	0.62 ± 0.29	=0.54	<0.001	<0.001
T4	5.13-14.06µgdl	9.45 ± 1.48	6.43 ± 2.17	3.91 ± 1.55	=0.225	<0.0001	<0.001
Urea	10-40 mg/dl	19.84 ± 4.78	21.49 ± 4.81	23.09 ± 5.94	=0.876	=0.098	=0.589
Creatinine	0.6-1.4 mg/dl	0.63 ± 0.12	0.84 ± 0.32	1.20 ± 0.34	<0.05	<0.001	<0.001
Uric acid	3.5-7 mg/dl	3.54 ± 0.57	4.89 ± 0.54	6.68 ± 1.25	0.032	<0.001	<0.05

The study subjects were divided into 3 groups according to their thyroid function tests.

Group I(GI): euthyroid controls; TSH, T3, T4 within normal reference range. Group II(GII): subclinical hypothyroids(SCH); increased TSH with normal levels of T3 &T4. Group III (GIII): overt hypothyroids (OH); higher levels of TSH and decreased levels of both T3, T4.

The mean ± SD values of TSH in euthyroid controls (GI), subclinical hypothyroids (GII) & overt hypothyroids were 2.71 ± 0.77, 9.51 ± 3.18 and 42.67 ± 4.78 µIU/ml respectively. The p value obtained on comparison among three groups; (GI vs GII <0.0001, GI vs GIII <0.0001 & GII vs GIII <0.0001) were highly significant. Mean T3 levels in SCH cases (GII) when compared to control (GI) were not significantly reduced (1.37 ± 0.24 vs 1.23 ± 0.41ng/ml, p value=0.54), whereas T3 levels were significantly reduced in GIII(0.62 ± 0.29ng/ml) when compared to GI &GII ; p value< 0.001. No significant difference in T4 level in SCH cases (GII) when compared with controls (GI) was seen (9.45 ± 1.48 vs 6.43 ± 2.17 µg/dl, p value=0.225). However when T4 levels in overt hypothyroids (GIII, 3.91 ± 1.55 µg/dl) compared with controls (p value < 0.0001) and SCH (p value < 0.001) were significantly reduced.

The mean serum urea, creatinine & uric acid levels in controls (GI) were 19.84 ± 4.78 mg/dl, 0.63 ± 0.12 mg/dl & 3.54 ±

0.57mg/dl respectively. In SCH cases (GII) serum urea, creatinine & uric acid levels were observed to be 21.49 ± 4.81 mg/dl, 0.84 ± 0.32 mg/dl & 0.84 ± 0.32 mg/dl respectively. Whereas in overt hypothyroids (GIII) the levels of above mentioned parameters were 23.09 ± 5.94 mg/dl, 1.20 ± 0.34 mg/dl & 6.68 ± 1.25 mg/dl.

No significant difference was there in urea levels among three groups (p value in GI vs GII=0.876, GI vs GIII=0.098, GII vs GIII=0.589). However, urea levels were found to be negatively correlated with T4 levels in hypothyroids subjects as a whole.

Mean levels of serum creatinine were within normal reference range in both subclinical hypothyroids and overt hypothyroids. However, serum creatinine levels in subclinical hypothyroids were significantly elevated on comparison with controls (p value <0.05). In OH patient levels of serum creatinine were significantly raised than both controls & SCH groups; p values GI vs GII <0.001, GII vs GIII<0.0001

In this study the serum uric acid levels in SCH patients were within normal range but significantly raised than controls (p value GI vs GII=0.032).In OH group uric acid value were significantly high on comparison with euthyroids (p value <0.001 and SCH cases (p value<0.05)

TABLE III: shows correlation studies between thyroid profile and renal function tests in hypothyroid group as a whole

Lab values	TSH	T4	T3
Urea	$r = -0.1962$ $p = .3425$	$r = -0.4241$ $p = 0.0184$	$r = -0.0268$ $p = 0.6825$
Creatinine	$r = 0.4162$ $p = 0.0242$	$r = -0.1794$ $p = 0.2748$	$r = -0.0624$ $p = 0.8421$
Uric acid	$r = 0.4452$ $p = 0.0281$	$r = -0.1582$ $p = 0.4126$	$r = -0.0762$ $p = 0.7912$

$p < 0.05$ was considered to be significant

Significant negative correlation was observed between T4 and urea. A positive correlation was seen in TSH and serum creatinine levels. Among serum uric acid and TSH values also a positive significant correlation was observed.

TABLE IV: Comparison of laboratory parameters in subclinical hypothyroids (G III) before and after levothyroxine replacement therapy for 3 months

Biochemical parameters	Subclinical hypothyroids (n=38) before levothyroxine therapy	Sub clinical hypothyroids (n=32) after levothyroxine therapy	p value
TSH(μ IU/ml)	12.32 ± 3.32	3.66 ± 0.46	<0.0001
T3(ng/ml)	1.12 ± 0.12	1.23 ± 0.18	$=0.135$
T4(μ g/dl)	8.82 ± 1.96	11.18 ± 1.24	<0.05
Urea(mg/dl)	21.98 ± 4.58	20.97 ± 4.46	$=0.986$
Creatinine(mg/dl)	0.89 ± 0.25	0.67 ± 0.12	<0.05
Uric acid(mg/dl)	5.42 ± 1.08	3.48 ± 0.72	<0.001

There was a significant decrease in mean TSH level after treatment ($12.32 \pm 3.32 \mu\text{IU/ml}$ vs $3.66 \pm 0.46 \mu\text{IU/ml}$, p value < 0.0001). No significant difference was observed in pre-treatment and post treatment values of T3. There was a statistically increase in T4 values after levothyroxine therapy ($8.82 \pm 1.96 \mu\text{g/dl}$ vs $11.18 \pm 1.24 \mu\text{g/dl}$, p value <0.05).

There was no significant change in urea level after treatment ($21.98 \pm 4.58 \text{mg/dl}$ vs $20.97 \pm 4.46 \text{mg/dl}$, p value $=0.986$). A statistically significant decrease in s. creatinine level was observed after treatment ($0.89 \pm 0.25 \text{mg/dl}$ vs $0.67 \pm 0.12 \text{mg/dl}$, p value <0.05). There was a significant decrease in mean uric acid from pre-treatment values of $5.42 \pm 1.08 \text{mg/dl}$ to $3.48 \pm 0.72 \text{mg/dl}$, (p value < 0.001).

Table V: Comparison of lab values in overt hypothyroids (G II) before and after levothyroxine replacement therapy for 3 months

Biochemical parameters	Overt hypothyroids(n=45) pre treatment	Overt hypothyroids (n=45) post therapy	P value
TSH (μ IU/ml)	46.58 ± 3.93	4.45 ± 3.04	<0.0001
T3 (ng/ml)	0.68 ± 0.34	1.02 ± 0.05	<0.001
T4 (μ g/dl)	3.92 ± 1.58	8.82 ± 1.86	<0.0001
Urea (mg/dl)	23.16 ± 6.62	21.49 ± 7.98	$=0.246$
Creatinine (mg/dl)	1.24 ± 0.32	0.81 ± 0.16	<0.001
Uric acid (mg/dl)	7.11 ± 2.11	4.53 ± 2.29	<0.001

There was a significant decrease in TSH from pre-treatment mean values of $46.58 \pm 3.93 \mu\text{IU/ml}$ to $4.45 \pm 2.04 \mu\text{IU/ml}$ (p value < 0.0001). There was a significant increase in T3 after treatment ($0.68 \pm 0.34 \text{ng/ml}$ vs $1.02 \pm 0.05 \text{ng/ml}$, p value < 0.001). There was a significant increase in T4 mean values from $3.92 \pm 1.58 \mu\text{g/dl}$ to $8.82 \pm 1.86 \mu\text{g/dl}$, p value < 0.0001 .

No significant changes in urea levels was observed treatment ($23.16 \pm 6.62 \text{mg/dl}$ vs $21.49 \pm 7.98 \text{mg/dl}$, p value $= 0.246$). A significant decrease in creatinine values after treatment from $1.24 \pm 0.32 \text{mg/dl}$ to $0.81 \pm 0.16 \text{mg/dl}$ (p value < 0.001). There was a significant decrease in uric acid levels

from $7.11 \pm 2.11 \text{mg/dl}$ to $4.53 \pm 2.29 \text{mg/dl}$ (p value < 0.001).

DISCUSSION

In the present study around 80 % patients of hypothyroidism were females in mean 45.20 ± 11.74 years age, which suggests that hypothyroidism is much more prevalent in middle aged females. Similar findings were also reported by many workers. (23-27) In contrast Rehman SU et al, (28) Khaira JS et al (29) observed hypothyroidism is more prevalent in elderly over 60 years of age.

The sub clinical hypothyroid patients in this study showed increased mean levels

of serum creatinine and uric acid. Furthermore, the increments of serum creatinine as well as uric acid values were significantly higher in OH patients as compared to SCH. In present study as well as other studies including those of Nagarajapa KJ et al⁽³⁰⁾ and Kreisman SH et al⁽³¹⁾ demonstrated the progressive elevation of serum creatinine values in hypothyroidism which might be due to direct or indirect effects of thyroid hormones on renal hemodynamics.⁽³²⁾ Hollander den et al reported that thyroid deficiency reduces myocardial contractility and cardiac output.⁽¹⁰⁾ Moreover an impaired endothelial mediated vasodilatation in hypothyroidism leads to increased peripheral and renal vascular resistance. These effects reduces GFR and thus a low creatinine clearance and a high serum creatinine.^(6,7,9,14) Altay et al in their study reported that associated myopathy in hypothyroids may contribute to increased serum creatinine levels.⁽³³⁾

This study also demonstrated the progressive rise of uric acid values. This finding is agreed with other investigators Giordano et al⁽³⁴⁾ and many case studies which reported the changes in renal hemodynamics leading to reduced clearance of uric acid may attribute to hyperuricemia.⁽³⁵⁻³⁹⁾ Thus our findings confirm the data in literature concerning high prevalence of hyperuricemia and gout in hypothyroids.⁽³⁵⁻⁴⁰⁾

This results of serum urea values in present study showed no significant changes .Our study further supports the findings of other studies including Montenegro et al.⁽⁸⁾ who also reported a negative correlation of blood urea and serumT4 levels.

Various experimental studies have documented that hypothyroidism is associated with reduction of renal blood flow and GFR,^(4-7,11,22) so replacement of thyroid hormones with levothyroxine can improve renal functions.^(21-23,31,41,42) Similarly, in this study, the selected hypothyroid patients who were given levothyroxine replacement therapy showed

the normalization of thyroid levels and restoration of renal functions test parameters; serum creatinine and uric acid.

CONCLUSIONS

The present study demonstrated the deterioration of renal functions with the progression of hypothyroidism. These changes though subtle but significant even in patients of mild or subclinical hypothyroidism. Furthermore when thyroid levels of these patients were restored with levothyroxine therapy, the reversal of decline in kidney function tests parameters were observed. Thus, the study might be helpful for physicians to advice kidney and thyroid function tests together in screening as well as in treatment of hypothyroid patients.

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