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## Original Work

# Dynamic Changes in Biochemical Markers of Renal Function with Thyroid Status – A Study in Indian Population

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**ABSTRACT:** Thyroid dysfunction is known to cause significant changes in glomerular filtration rate. The present cross-sectional study was performed to evaluate the changes in biochemical markers of renal function in hypothyroid subjects before and after treatment. Thyroid function tests ($T_3$, $T_4$ and TSH levels) were assayed in 385 subjects. Based on TSH levels, subjects were classified as euthyroid (n=198), sub-clinical hypothyroid (n=98; TSH 6.1 to 19.9 µIU/ml) and overt hypothyroid (n=89; TSH ≥ 20 µIU/ml, abnormally low $T_4$ levels). Forty-eight hypothyroid patients were re-evaluated after 3 months of thyroxine replacement therapy. Renal function tests were carried out in all subjects and statistically analyzed. Serum creatinine was significantly increased in sub-clinical and overt hypothyroid groups as compared to euthyroid subjects. Serum creatinine showed a significant negative correlation with $T_3$ &$T_4$ levels in overt group(r = -0.372 and r = - 0.371), whereas a positive correlation was observed with TSH (r=0.283). Uric acid levels were significantly increased in the overt group as compared to euthyroid subjects. Uric acid levels showed a significant negative correlation with $T_3$ levels in the overt group (r= -0.298). After 3 months of thyroxine replacement therapy, creatinine and uric acids levels decreased significantly and were comparable to euthyroid levels. Hypothyroidism leads to reversible changes in renal function.

**KEY WORDS:** Renal functions; Thyroid functions: Biochemical markers

## INTRODUCTION

Long-standing hypothyroidism can cause significant reversible changes in renal function such as a decrease in sodium resorption in the proximal tubules, impairment in the concentrating and diluting capacities of the distal tubules, a decrease in urinary urate excretion, and a decrease in renal blood flow and glomerular filtration rate (GFR)[1,2]. In experimental animals, surgical or drug-induced hypothyroidism of a few weeks' duration has been shown to result in a decrease in GFR[3,4]. However, the effect of hypothyroidism on serum urea, creatinine and uric acid levels in humans has not been well documented in Indian population.

Minor degree of hypothyroidism leads to adverse effects in various tissues, even though clinically the patients are euthyroid. The present cross-sectional study was performed to determine whether thyroid dysfunction, sub-clinical and overt, has deleterious effects on renal function .For this, serum urea, creatinine and uric acid levels were measured in patients who presented with hypothyroidism. The study

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was further extended to observe the effects of thyroxine treatment on renal function in hypothyroid patients. Although renal function is profoundly influenced by thyroid status, this has not been studied in detail in human subjects. The purpose of the present study was therefore to determine the relationship between renal function and thyroid status before and after treatment for hypothyroidism.

## METHODOLOGY

The study was conducted on 385 subjects of age group 15 to 55 years visiting thyroid clinic. Patients were clinically evaluated to rule out hypertension, diabetes mellitus or any other medical condition, which may affect the renal function. 5 ml of fasting blood sample (in non-additive vacutainer) was collected for each patient. Serum was divided into two aliquots- one aliquot was used for thyroid function tests and the other was immediately analyzed for routine biochemical tests including renal function.

### Thyroid function tests

Serum TSH, $T_4$ and $T_3$ were assayed using ELISA kits obtained from Ranbaxy, India. Serum $T_3$ and $T_4$ were performed using competitive ELISA technique and serum TSH was performed using sandwich ELISA technique. The normal ranges for TSH, $T_4$ and $T_3$ values were 0.39-6.16μIU/ml, 4.4-10.8μg/dl, and 0.52-1.85ng/ml respectively. The intra- and inter-assay coefficients of variation (CV) for TSH, $T_4$ and $T_3$ were 5 and 6, 3 and 3.7, 5.4 and 6 respectively.

### Renal function tests

Serum urea, creatinine and uric acid levels were determined on Olympus AU 400 autoanalyser using standard kits. Serum urea was measured by kinetic UV test, creatinine by Jaffe method (kinetic) without deproteinization and uric acid by enzymatic end-point method. The intra- and inter-assay CV for creatinine, urea and urate were 3.5 and 3.6, 2.8 and 3.6, and 2.1 and 2.5 respectively.

After conducting thyroid function tests, subjects having euthyroid state (n=198, TSH≤ 6.0, normal $T_3$ and $T_4$ levels) were taken as controls. Hypothyroid patients (n=187) constituted the study group. These patients were further divided into sub clinical hypothyroid (n=98; TSH- 6.1 to19.9μIU/ml with normal $T_4$ and $T_3$ levels) and overt hypothyroid (n=89) with TSH ≥ 20 μIU/ml and/ or abnormally low $T_4$ and $T_3$ levels). Forty- eight hypothyroid patients were re-evaluated after 3 months of thyroxine replacement therapy.

### Statistical analysis

Statistical analysis was carried out using SPSS for windows 10.0 software (SPSS Inc.,Chicago, IL, USA) and Microsoft Excel. Values were reported as mean ± standard error of mean. The difference between groups was compared by Wilcoxon test or Mann- Whitney test for continuous variables and by Chi-Square tests for categorical variables. Pearson's correlation was applied to test for association between continuous variables. A two-tailed p value<0.05 was considered statistically significant.

## RESULTS

The study group and the control group were age and sex matched. The age group of patients in the study group was 43.4 ± 2.67 years and in the control group was 44.1 ± 3.2 years. The study group comprised of 150 women and 37 men and in control group 153 women and 45 men were enrolled.

The values of thyroid hormones and biochemical markers of renal function are presented in **table 1**. T3 and T4 values were significantly lower and TSH levels were higher in the sub-clinical and overt hypothyroid group as compared to the euthyroid group (p<0.001).

Mean serum urea levels in all the patients varied from 18 mg/dl to 34 mg/dl and no significant difference was observed between any of the groups. Mean serum creatinine concentrations were significantly increased in both patient groups i.e. sub-clinical and overt hypothyroid as compared to euthyroid subjects, the values being 0.87 ± 0.07 mg/dl (p=0.001), 0.85 ± 0.03 mg/dl (p=0.000) respectively as compared to euthyroid group 0.69 ±0.01 mg/dl. 96.6% of patients included in overt hypothyroid group were found to have hyperuricemia, whereas only 10.2% patients in the sub-clinical hypothyroid group had mild hyperuricemia. Uric acid levels were significantly increased only in the overt hypothyroid group (6.73 ± 0.19mg/dl; p=0.02) as compared to euthyroid subjects (5.87 ± 0.18 mg/dl). Serum uric acid levels in the sub-clinical hypothyroid group (5.93 ±0.50 mg/dl) were not significantly different from the euthyroid group.

The correlations of biochemical markers of renal function with the different components of thyroid function tests were evaluated. A significant negative correlation was observed

between serum creatinine and serum $T_3$ & $T_4$ levels only in overt group (r = -0.372 and r= -0.371 respectively). A significant positive correlation of serum creatinine values was noted with TSH levels (r = 0.283). Uric acid levels showed a significant negative correlation only with T3 levels in overt hypothyroid group (r = 0.298, p= 0.023) (**Table 2)**.

**Table 1: Levels of different biochemical parameters in euthyroid, sub-clinical hypothyroid and overt hypothyroid patients**

| Parameters | Euthyroid (n=198) (Mean ± SEM) | Sub-clinical Hypothyroid (n=98) (Mean ± SEM) | Overt Hpothyroid (n=89) (Mean± SEM) |
|---|---|---|---|
| $T_3$ (ng/ml) | 1.04 ± 0.01 | 0.92 ±0.01** | 0.52 ±0.02** |
| $T_4$ (µg/dl) | 8.66 ± 0.05 | 7.16 ± 0.08** | 4.13 ± 0.15** |
| TSH (µIU/ml) | 2.48 ± 0.09 | 11.9 ± 0.50** | 41.46 ± 1.04** |
| Urea (mg/dl) | 23.01 ± 0.54 | 24.05 ± 0.89 | 23.59 ± 0.69 |
| Creatinine (mg/dl) | 0.69 ± 0.01 | 0.87 ± 0.07** | 0.85 ± 0.03** |
| Uric acid (mg/dl) | 5.87 ± 0.18 | 5.93 ±0.50 | 6.73 ± 0.19* |

* p<0.05, ** p<0.01 when compared with euthyroid subjects

**Table 2: Correlation of various parameters in different states of thyroid function**

| Parameters | | Urea (mg/dl) | Creatinine (mg/dl) | Uric acid (mg/dl) |
|---|---|---|---|---|
| **$T_3$ (ng/ml)** | Euthyroid | r = 0.05 | r = 0.044 | r = 0.024 |
| | Sub-clinical Hypothyroid | r = -0.035 | r = -0.01 | r = 0.006 |
| | Overt Hypothyroid | r = -0.15 | r = -0.372** | r = -0.298* |
| **$T_4$ (µg/dl)** | Euthyroid | r = -0.018 | r = -0.044 | r = 0.038 |
| | Sub-clinical Hypothyroid | r = -0.137 | r = 0.077 | r = 0.185 |
| | Overt Hypothyroid | r = -0.169 | r = -0.371** | r = -0.189 |
| **TSH (µ IU/ml)** | Euthyroid | r = 0.009 | r= -0.056 | r= -0.027 |
| | Sub-clinical Hypothyroid | r= -0.03 | r= -0.03 | r= -0.291 |
| | Overt Hypothyroid | r= 0.184 | r= 0.283** | r= 0.235 |

* P=<0.05 ** P<0.01

48 patients were re-evaluated 3 months after starting thyroxine replacement therapy. After 3 months of thyroxine replacement (in accordance with their initial hypothyroid state) all the 48 patients were euthyroid-symptomatically as well as on laboratory evaluation. **Table 3** presents the comparative data of these patients before and after thyroxine replacement. The values of T3, T4 and TSH were in the normal range and showed a highly significant change as compared to initial values (p<0.001). The values of serum creatinine and serum uric acid also decreased significantly (p<0.001) and were comparable to euthyroid levels.

**Table 3: Comparison of hypothyroid patients before and after thyroxine replacement therapy**

| Parameter | Before Treatment (n=48) (Mean ± SEM) | After Treatment (n=48) (Mean ± SEM) | p –Value |
|---|---|---|---|
| $T_3$ (ng/ml) | 0.68 ± 0.27 | 1.06 ± 0.06 | 0.000 |
| $T_4$ (µg/dl) | 4.95 ± 2.01 | 8.61± 0.87 | 0.000 |
| TSH (µIU/ml) | 36.44 ± 15.48 | 3.45 ± 2.27 | 0.000 |
| Urea (mg/dl) | 24.01 ± 8.6 | 25.51 ± 6.29 | 0.351 |
| Creatinine (mg/dl) | 0.85 ± 0.29 | 0.68 ±0.17 | 0.000 |
| Uric acid (mg/dl) | 6.76 ± 1.49 | 5.61± 1.10 | 0.000 |

## DISCUSSION

The present case-control hospital based study evaluated the biochemical markers of renal function in hypothyroid subjects and compared the results with those of euthyroid subjects as well as 48 subjects who attained a euthyroid state after thyroxine treatment. This study shows that there is significant increase in creatinine and uric acid levels in hypothyroid patients as compared to euthyroid subjects, though the effects of hypothyroidism on uric acid can be seen only in the overt hypothyroid group. Similar changes in serum creatinine with hypothyroidism have been reported in isolated case studies and few other studies involving lesser number of hypothyroid subjects[5-7]. Even infants with congenital hypothyroidism have shown higher serum creatinine levels in proportion to the severity of hypothyroidism, though no effects were observed on serum urea levels[8]. The consistency of elevation of creatinine in the present study with other studies[5,6,8] argues against the previously held notion of practically unchanged serum creatinine value due to a balance between decrease in renal clearance and decreased generation[9].

Hyperuricemia leading to gout has been reported in hypothyroid subjects in a few studies done around the world[10,11]. In the present study no case of gout was reported despite the presence of hyperuricemia in 96.6% overtly hypothyroid cases. The increase in uric acid in hypothyroid state may result from either increased production due to myopathy associated with hypothyroidism or due to decreased renal clearance of uric acid[12]. Though the observed decrease in renal function was not so severe in our study, a recent case report illustrated how hypothyroid –induced renal dysfunction may lead to adverse clinical consequences especially in patients taking medications cleared by the kidneys[13].

In overt hypothyroid group, serum creatinine levels showed a significant negative correlation with $T_3$ levels (r = -0.372) and $T_4$ levels (r = -0.371) and a positive correlation with TSH levels (r = 0.283). Similarly uric acid had a negative correlation with $T_3$ levels (r = -0.298) only in overt hypothyroid cases. Though there are a few scattered case reports on how hypothyroidism can affect creatinine and uric acid levels, literature search did not show any formal studies reporting such correlations. Based on our findings, this study clearly suggests that serum creatinine is influenced by a decrease in $T_3$ and/or $T_4$ or an increase in TSH levels but uric acid levels are mainly influenced by $T_3$ or the active thyroid fraction.

With thyroxine replacement therapy a significant decrease in both creatinine and uric acid levels was observed. Other scattered studies and case reports also demonstrate an improvement in renal status of patients with treatment for hypothyroidism.[5,7,14,15]. In the present study, 95.65% patients showed a decrease in serum creatinine and 93.47% patients showed a decrease in uric acid after treatment for hypothyroidism. A 20% decrease in serum creatinine and 17% decrease in serum uric acid levels were observed after 3 months of thyroxine replacement. Another study reported 41.3% decrease in serum creatinine levels after 2 months of L-thyroxine substitution[8]. This observation clearly indicates that the changes in renal function were due to hypothyroid state and were not merely co-existent with hypothyroidism.

Histological changes in nephrons, especially basement membrane thickening have been demonstrated in both hypothyroid rats[3] and humans[16]. Physiological effects include

changes in water and electrolyte metabolism, notably hyponatremia, and reliable alterations of renal hemodynamics[17,18], including decrements in renal blood flow, renal plasma flow, glomerular filtration rate (GFR), and single nephron GFR. The cause of the decreased renal plasma flow and GFR observed is believed to be principally due to the generalized hypodynamic state of the circulatory system in hypothyroidism[9]. GFR values in myxedematous patients are on average one-third lower than the values in euthyroid individuals[2,19]. This decrement in GFR is readily reversible upon correction of thyroid hormone deficiency[20]. However, a recent study in the pediatric age group has demonstrated that GFR and effective renal plasma flow continue to be decreased in hypothyroid children even 1-5 years after thyroxine therapy[21].

Another possible mechanism of action of thyroid hormone on renal function could be explained by its influence on maturation of the renin-angiotensin system (RAAS). Plasma renin activity and plasma levels of angiotensinogen, angiotensin II and aldosterone are directly related to plasma levels of thyroid hormones[22]. Hypothyroidism is associated with low plasma renin[23]. In contrast, hyperthyroidism is accompanied by hyperactivity of the RAAS[24]. Moreover, it has been shown that T3 treatment increases angiotensin receptor density in the kidney, liver and both cardiac ventricles[25,26]. Thyroid hormone (T3) also induces relaxation of blood vessel resulting in a reduction in vascular resistance and increases serum levels of renin activity and angiotensinogen concentration[27].

This study confirms that the hypothyroid state is associated with a consistent elevation in the serum creatinine and uric acid levels, presumably due to a decrease in the GFR or alteration in RAAS. Although clinically a severe impairment of renal function in humans is unusual, it should be stressed that most of the described abnormalities improve after administration of thyroid hormone. Knowledge of reversible association between hypothyroidism and elevated serum creatinine and uric acid is important for a clinician. This information would avoid unnecessary investigations, treatment cost and worry in patients presenting with either increased creatinine or gout with undetermined thyroid status. The assessment of thyroid function should be routinely carried out for evaluation of patients presenting with deranged renal function.

## REFERENCES


1. Leeper RD, Benua RS, Brener JL, et al. Hyperuricemia in myxedema. J Clin Endocrinol Metab 1960 Nov;20:1457-66.
2. Allon M, Harrow A, Pasque CB, et al. Renal sodium and water handling in hypothyroid patients: the role of renal insufficiency. J Am Soc Nephrol. 1990 Aug;1(2):205-10.
3. Davis RG, Madsen KM, Fregly MJ, et al. Kidney structure in hypothyroidism. Am J Pathol. 1983 Oct;113(1):41-9.
4. Zimmerman RS, Ryan J, Edwards BS. et al. Cardiorenal endocrine dynamics during volume expansion in hypothyroid dogs. Am J Physiol. 1988 Jul;255(1 pt 2):R61-6.
5. del-Río Camacho G, Tapia Ceballos L, Picazo Angelín B, et al. Renal failure and acquired hypothyroidism. Pediatr Nephrol. 2003 Mar;18(3):290-2.
6. den Hollander JG, Wulkan RW, Mantel MJ, et al. Correlation between severity of thyroid dysfunction and renal function. Clin Endocrinol (Oxf). 2005 Apr;62(4): 423- 7.
7. Nakahama H, Sakaguchi K, Horita Y, et al. Treatment of severe hypothyroidism reduced serum creatinine levels in two chronic renal failure patients. *Nephron*. 2001 Jul;88(3):264-7.
8. Asami T, Uchiyama M. Elevated serum creatinine levels in infants with congenital hypothyroidism: reflection of decreased renal function? *Acta Paediatr*. 2000 Dec; 89(12):1431-4.
9. Kaptein EM. The kidneys and the electrolyte metabolism in hypothyroidism. In: Braverman LE, Utiger RD, eds. Werner and Ingbar's The Thyroid. 9th Edition, Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:792-3.
10. Dariyerli N, Andican G, Catakoglu AB, et al. Hyperuricemia in Hypothyroidism: Is It Associated with Post-Insulin Infusion Glycemic Response? *Tohoku J Exp Med*. 2003 Feb;199(2):59-68.
11. Giordano N, Santacroce C, Mattii G, et al. Hyperuricemia and gout in thyroid endocrine disorders. *Clin Exp Rheumatol*. 2001 Nov-Dec;19(6):661-5.
12. Yokogoshi Y, Saito S. Abnormal serum uric acid level in endocrine disorders. *Nippon Rinsho*. 1996 Dec;54(12):3360-3.
13. Phillips BD, Gopalakrishnan G, Gohh R, et al. Lithium toxicity precipitated by profound hypothyroidism. *Thyroid*. 2008 Jun;18(6):651-4.

14. van Welsem ME, Lobatto S. Treatment of severe hypothyroidism in a patient with progressive renal failure leads to significant improvement of renal function. *Clin Nephrol*. 2007 Jan;67(6):391-3.
15. Mooraki A, Bastani B. Reversible renal insufficiency, hyperuricemia and gouty arthritis in a case of hypothyroidism. *Clin Nephrol*. 1998 Jan;49(1):59-61.
16. Capasso G, De Santo NG, Kinne R. Thyroid hormones and renal transport: Cellular and biochemical aspects. *Kidney Int*. 1987 Oct;32(4):443-51.
17. Montenegro J, Gonzalez O, Saracho R, et al. Changes in renal function in primary hypothyroidism. *Am J Kidney Dis*. 1996 Feb;27(2):195-8.
18. Gillum DM, Falk SA, Hammond WS, et al. Glomerular dynamics in the hypothyroid rat and the role of the renin-angiotensin system. *Am J Physiol*. 1987 Jul;253(1 Pt 2):F170-9.
19. Katz AI, Emmanuel DS, Lindheimer MD. Thyroid hormone and the kidney. *Nephron*.1975;15(3-5):223-49.
20. Balldin J, Berqgren U, Svennerholm L, et al. Reduced glomerular filtration rate in a lithium-treated bipolar patient with primary hypothyroidism-reversal by levothyroxine. *Clin Nephrol*. 1988; 29 (3): 160-61.
21. Elgadi A, Verbovszki P, Marcus C, et al. Long-term effects of primary hypothyroidism on renal function in children. *J Pediatr*. 2008 Jan;152(6):860-4.
22. Vargas F, Moreno JM, Rodríguez-Gómez I, et al. Vascular and renal function in experimental thyroid disorders. *Eur J Endocrinol*. 2006 Feb;154 (2):197-212.
23. Bouhnik J, Galen FX, Clauser E, et al. The renin-angiotensin system in thyroidectomized rats. *Endocrinology*. 1981 Feb;108(2):647–50.
24. Ichihara A, Kobori H, Miyashita Y, et al. Differential effects of thyroid hormone on renin secretion, content and mRNA in juxtaglomerular cells. *Am J Physiol*. 1998 Feb;274(2 Pt 1):E224-E31.
25. Marchant C, Brown L, Sernia C. Renin-angiotensin system in thyroid dysfunction in rats. *J Cardiovasc Pharmacol*. 1993 Sep;22 (3):449–55.
26. Chen K, Carey LC, Valego NK, et al. Thyroid hormone replacement normalizes renal renin and angiotensin receptor expression in thyroidectomized fetal sheep *Am J Physiol Regul Integr Comp Physiol*. 2007 Aug;293(2): R701-R6.
27. Toshihiro I, Kenji S. Thyroid Hormone and the Renin Angiotensin System. *Myakkangaku (Article in Japanese)*. 2006; 46(5):661-5.