

## Evaluation of Renal Functions in Hypothyroidism

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**Abstract:** *The structure and function of the thyroid change in different stages of the sexual cycle in females. Its function is slightly increased during pregnancy and lactation and is decreased during menopause. Thyroid hormones are essential for an adequate growth and development of the kidney. Hypothyroidism is accompanied by a decrease in glomerular filtration, hyponatremia, and an alteration of the ability for water excretion. The most common kidney derangements associated to hypothyroidism are: elevation of serum creatinine levels, reduction in GFR and renal plasma flow, disruption of the capacity to excrete free water and hyponatremia. These alterations may be absent in patients with central hypothyroidism due to the fact that this kind of thyroid hypofunction is often accompanied by other pituitary hormone deficiencies. Patient sample collected for TFT was utilized for study. 5ml of blood is collected before treatment. 60 patients sample selected for study age ranging between 25±10 of which 30 were hypothyroid. They were compared with 30 healthy control subjects. If the tests are to be used for monitoring the level of proteinuria in established renal disease, they can then be used as surrogates for 24hr measurements. There are various mechanisms of interaction between kidney and thyroid functions in the disease states of each other organ. There are not only functional alterations but also structural correlates of these interactions. TSH elevations are common in Chronic kidney diseases and do not always reflect hypothyroidisms.*

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### I. Introduction

Thyroid is one of the largest endocrine gland in the body. The thyroid gland, so named by Thomas Wharton in 1965. It is larger in females than in males. The structure and function of the thyroid change in different stages of the sexual cycle in females. Its function is slightly increased during pregnancy and lactation and is decreased during menopause<sup>1</sup>. The thyroid gland is located in the neck, anterior to the trachea, between the cricoids cartilage and the supra-sternal notch. The thyroid consists of two lobes being connected together by a thin band of tissue called isthmus. It is normally 20 to 40 g in size, highly vascular, and soft in consistency. Four parathyroid glands, which produce parathyroid hormone, are located in the posterior region of each pole of the thyroid. The recurrent laryngeal nerves traverse the lateral borders of the thyroid gland. The thyroid hormones are the only iodine-containing compounds with established physiologic significance in vertebrates<sup>2</sup> such as Tetra iodothyronine (T4) and Triiodothyronine (T3). There are many types of thyroid diseases. However, the main conditions present in most thyroid illness are HYPOTHYROIDISM (thyroid under activity) and HYPERTHYROIDISM (thyroid over activity).<sup>3</sup> Thyroid hormones (TH) are essential for an adequate growth and development of the kidney.

Conversely, the kidney is not only an organ for metabolism and elimination of TH, but also a target organ of some of the iodothyronines' actions. Thyroid dysfunction causes remarkable changes in glomerular and tubular functions and electrolyte and water homeostasis. Hypothyroidism is accompanied by a decrease in glomerular filtration, hyponatremia, and an alteration of the ability for water excretion. Excessive levels of TH generate an increase in glomerular filtration rate and renal plasma flow. Renal disease, in turn, leads to significant changes in thyroid function.

The most common kidney derangements associated to hypothyroidism are: elevation of serum creatinine levels, reduction in GFR and renal plasma flow (RPF), disruption of the capacity to excrete free water and hyponatremia. These alterations may be absent in patients with central hypothyroidism due to the fact that this kind of thyroid hypofunction is often accompanied by other pituitary hormone deficiencies that might affect directly or indirectly the kidney function<sup>4</sup>. Primary hypothyroidism is associated with a reversible elevation of serum creatinine in both adults<sup>5,6</sup> and children<sup>7,8</sup>. This increase is observed in more than half (w55%) of adults with hypothyroidism<sup>9</sup>. Moreover, Capasso G et al (1999), Den Hollander JG, et al (2005) have reported an elevation of serum creatinine associated with subclinical hypothyroidism<sup>10</sup>.

Primary hypothyroidism is associated with a reduction of GFR and RPF that are normalized following levothyroxine administration<sup>11,12,13,14,15,16,17</sup>. Similarly, normalization of circulating TH concentrations with replacement therapy in hypothyroid patients with chronic kidney disease (CKD) can significantly improve GFR<sup>18</sup>. However, it has recently been reported that kidney function recovers slowly in hypothyroid children, and sometimes partially, after the introduction of replacement with levothyroxine<sup>19</sup>.

The long-term clinical implications of these findings are unknown. Hypothyroidism-associated kidney dysfunction seems to be more related with the decline in thyroid hormone levels rather than with thyroid autoimmunity<sup>20</sup>. Among the mechanisms involved in hypothyroidism-associated kidney derangements are direct effects of TH on the cardiovascular system (increased peripheral resistance and reduction of myocardial contractility and stroke volume) and metabolism (hyperlipidemia), and indirect effects through paracrine or endocrine mediators, such as insulin-like growth factor type 1 (IGF-1) and vascular endothelial growth factor<sup>21,22,23</sup>.

Hyponatremia is the commonest electrolyte derangement in hypothyroid patients. Hyponatremia appears in 45% of hypothyroid patients who have elevated serum creatinine, but in less than a quarter (21%) of those with normal creatinine levels. It is mainly due to a reduction in GFR causing diminished water delivery to the distal tubular segments. This becomes evident after water load, although ADH may be appropriately suppressed. Other possible mechanism of hypothyroidism induced hyponatremia is an inappropriate ADH secretion syndrome (SIADH)-like disorder<sup>24,25</sup>.

## II. Aim & Objectives:

The present study was conducted in order to test the usefulness of estimating Renal function in patients with hypothyroidism to identify the renal involvement as early as at the time of diagnosis of thyroid disorders.

1. To evaluate the Serum fT3, fT4 and TSH – estimated by ELISA method in hypothyroidism patients and normal healthy controls.
2. To examine the ability of protein to Creatinine ratio to predict urinary 24hour protein loss in patients with chronic kidney disease.
3. To study the Creatinine clearance levels.

## III. Materials & Methods

The study was conducted on Patients attending the Meenakshi Medical College Hospital &RI Kanchipuram. During the period of 2011-2013. Patient sample collected for TFT was utilized for study. Approximately 5ml of blood is collected before treatment. Serum was separated immediately by centrifugation at 3000rpm for 10 minutes at 4°C. 60 patients sample selected for study age ranging between 45±10 of which 30 were hypothyroid. They were compared with 30 healthy control subjects.

### Statistical analysis

All quantitative estimation was made on 30 patients in each group. The values were expressed as mean ± SD and statistical analysis was done by students ‘T’ test and ‘P’ values were arrived to assess the statistical significance of changed observed. P values less than 0.005 was considered significant. All data were analyzed by SPSS software version 17 for windows [SPSS Inc., Chicago, USA].

### Study variables:-

The following parameters were done on the patients’ sample.

- 1) Serum fT3, fT4 and TSH – estimated by ELISA method
- 2) Urine protein:- estimated by turbido metric method.
- 3) Urine Creatinine :- estimated by kinetic Jaffe’s method
- 4) Serum Creatinine:- estimated by kinetic Jaffe’s method
- 5) Creatinine clearance: - By using the Cockcroft & Gault formula.

### Apparatus and glassware

All glassware used for the experiments were thoroughly washed initially detergent solution and then washed with double distilled deionized water three times and dried before used.

All precautionary measures were taken to prevent contamination during all stages of procedure.

All colorimetric readings were taken using colorimeter.

### Thyroid hormone testing

The blood samples of all the participants were collected after an overnight fast and all following parameters were estimated on the day of collection.

1. Free T3 assay
2. Free T4 assay
3. TSH assay

The present study comprises of 30 clinically diagnosed cases of chronic kidney disease with hypothyroidism. The age group ranges from 20-70 years, out of these, 9 patients were males (30%) and 21 patients were females (70%). Statistical analysis on the data were performed using “Excel”.

**IV. Result:**

The present study comprises of 30 clinically diagnosed cases of chronic kidney disease with hypothyroidism . The age group ranges from 20-70 years, out of these, 9 patients were males (30%) and 21 patients were females (70%). Statistical analysis on the data were performed using “Excel”.

Table 1 show that the serum thyroid profile in hypothyroid patients and in normal subjects. Serum fT3 levels (P<0.001) and fT4 levels (P<0.001) were significantly decreased but the serum TSH levels (P<0.000) increased significantly in hypothyroid patients when compared with normal subject.

Particulars	Control (30)	Hypothyroidism (30)
fT3 (ng/mL)	2.6 ± 0.65	1.62 ± 0.82*
fT4 (pg/dL)	1.2 ± 0.15	2.99 ± 1.14*
TSH(μIU/mL)	0.62 ± 0.26	18.8 ± 2.97*

Each value is expressed as mean ± SD for thirty patients in each group.

a: as compared with control

Statistical significance: \* p<0.001; @ p<0.01; # p<0.05.

**Renal Function in hypothyroidism:-**

Median age for all patients was 51.5 ±14.2175. For all patients, median 24hr urinary protein loss was 2089.5 ± 580.192 mg/24hr and median urine volumes was 1.35± 0.43333 L/24hr.

Table.2 Data summary showing patient’s median (standard deviation) age, 24hr urine volumes, urinary protein output and creatinine clearance.

	N	Age (years)	Urine volume (L/24hr)	Urine protein (mg/24hr)	Creatinine clearance (ml/min)
All patients	30	51.5 ± 14.2175	1.35 ± 0.4333	2089.5 ± 580.192	10.4602 ± 0.53743
Male	9	52 ± 12.20064	1.34 ± 0.3975	2089.5 ± 485.7697	10.4775 ± 0.52218
Female	21	49.5 ± 12.6026	1.41 ± 0.4841	2077 ± 553.3312	10.387 ± 0.56858

**Protein: Creatinine Ratio Versus 24 hrs Urine Proteins**

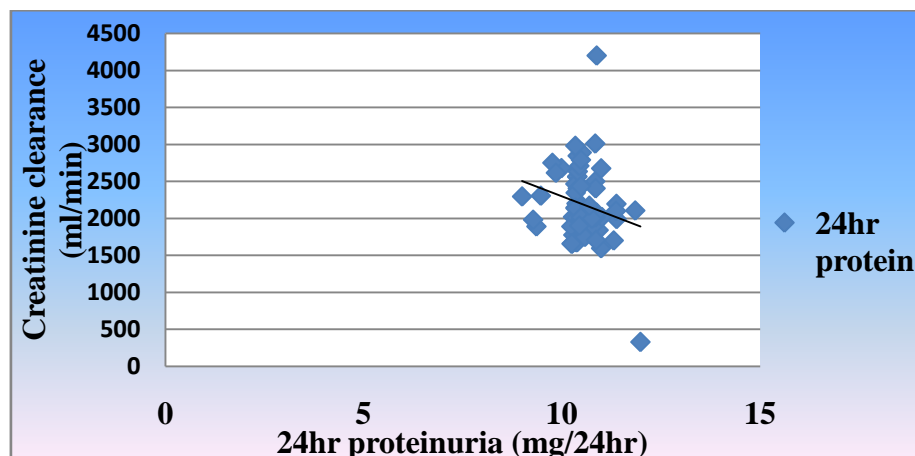
The present study shows a very good correlation between 24hr urine protein loss and protein to creatinine ratio (PCR) in early morning urine. PCR to be a good predictor of both abnormal urine protein loss and clinically significant urine protein loss.

**Correlation between PCR in early morning urine and 24hr urinary protein loss.**

There is a good correlation between 24hr urinary protein loss and PCR in first void urine. The correlation coefficient between them is 0.69184. .

**Creatinine clearance**

There is a negative correlation between 24hr urinary protein loss and creatinine clearance, it means that if the creatinine clearance decreases the protein loss increases. That is, the creatinine clearance and 24hr urinary protein are inversely proportional to each other. The correlation coefficient between is -0.2167. The graphical representation of this is shown in diagram.3.



Creatinine clearance compared with 24hr urine protein loss. Correlation coefficient is 0.2167.

## V. Discussion

The thyroid gland and thyroid hormones play central role in human development. Animal and human studies indicate thyroid hormones play important role in cardiovascular, nervous, immune, and reproductive system development and function

### Thyroid hormones in hypothyroidism:-

In the present study, the serum thyroid hormones levels of fT3, fT4 and TSH were observed in both control and hypothyroidism groups. The levels of fT3 and fT4 were found to be significantly decreased and TSH levels also significantly increased in hypothyroidism groups compared to normal control groups.

There are three categories of thyroid dysfunction that have been characterized in adult humans: subclinical hypothyroidism, overt hypothyroidism, and hyperthyroidism. Subclinical hypothyroidism is defined as a slightly elevated TSH concentration and normal serum free T3 and T4 concentration associated with few or no symptoms

Overt hypothyroidism or under active thyroid gland is the most common clinical disorder of thyroid function. It is best defined as high serum TSH concentration and a low free T4 serum concentration. Insufficient iodine level or low Iodine intake are a major cause of overt hypothyroidism. However, in areas where iodine intake is adequate, the most common cause of hypothyroidism is Hashimoto's thyroiditis, an autoimmune disease caused by autoantibodies to TPO. Other autoimmune and radiation also are causes of hypothyroidism. Overall, women are most susceptible to autoimmune disease than men suggesting they may be more susceptible to the development of hypothyroidism.

Hypothyroidism is one of the most common chronic disorders in western populations. In the United Kingdom, the annual incidence of primary hypothyroidism in women is 3.5 per 1000 and 0.6 per 1000.

Pridep kumar saha et al 2010 have been reported as primary hypothyroidism is confirmed by an increased serum thyroid stimulating hormone (TSH) concentration (>7.0mIU/L) above the upper limit of reference range. Our results also correlate with them (>18.8mIU/L)

Subclinical primary hypothyroidism has been recognized in several studies to be associated with markers of cardiovascular risk and cardiac impairment. Even minor deviations from serum TSH normal range might accelerate the development of atherosclerosis and have adverse effects on cardiovascular performance in the general population. Moreover, subclinical primary hypothyroidism has been identified as a strong predictor of all-cause mortality in chronic dialysis patients and as a risk factor for nephropathy and cardiovascular events in type 2 diabetic patients<sup>24,25,26</sup>. There is, however, limited quantitative evidence regarding the prevalence of subclinical primary hypothyroidism in large samples of individuals, including large non-U.S. cohorts at different levels of estimated glomerular filtration rate (GFR). To explore this question, we have performed a cross-sectional analysis using a large database from a Clinical Chemistry Laboratory, with the purpose of estimating the prevalence of subclinical primary hypothyroidism at different levels of kidney function.

The thyroid hormones increase the metabolic activities of almost all the tissues of body. The basal metabolic rate can increase to 60% to 100% above normal when large quantities of the hormones are secreted. One of the primary functions of the thyroid hormones is to control protein synthesis and nitrogen balance.

### Renal Function in hypothyroidism

In the present study shows good correlation between 24hr urinary protein loss and PCR in first void urine. The correlation coefficient between them is 0.69184 and negative correlation between 24hr urinary protein loss and creatinine clearance. The correlation coefficient between is -0.2167 Because creatinine is

endogenously produced and released into body fluids at a constant rate, its clearance has been measured as an indicator of GFR

The kidney normally plays an important role in the metabolism, degradation, and excretion of several thyroid hormones. It is not surprising therefore that impairment in kidney function leads to disturbed thyroid physiology, all levels of the hypothalamic-pituitary-thyroid axis may be involved, including alterations in hormone production, distribution, and excretion, epidemiologic data suggests that predialysis patients with chronic kidney disease have an increased risk of hypothyroidism; many cases are sub clinical.

Thyroid function has been extensively evaluated in patients with chronic kidney disease, however the result are variable, an increased incidence of goiter in those patients has been reported in studies conducted in China and Turkey, while other centers such as United States, Canada, Great Britain and Australia found the reverse .

The GFR is reversibly reduced (by about 40%) in more than 55% of adults with hypothyroidism due to several reasons. There is decreased sensitivity to  $\beta$ -adrenergic stimulus and decreased renin release along with decreased angiotensin II and impaired RAAS activity, resulting in loss of GFR. There is a structural constraint imposed by limited glomerular surface area for filtration due to renal parenchymal growth retardation in hypothyroidism. There is a reduced proximal tubular absorption of sodium, chloride, and water. In addition, the renal basolateral chloride channel expression is reduced. Thus, reduced chloride reabsorption increases the distal chloride delivery, triggering the macula densa mediated tubuloglomerular feedback which reduces the RAAS activity. Consequently, the GFR falls.

There is a reversible reduction in the kidney to body weight ratio in hypothyroidism, where the renal mass almost doubles with treatment. Hypothyroidism results in a reversible elevation in serum creatinine due to the reduction in GFR as well as possible myopathy and rhabdomyolysis.

## VI. Conclusion

In hypothyroid patients when compared with normal subjects following difference was noticed

- Thyroid hormone  $ft_3$  and  $ft_4$  levels were significantly decreased and also TSH levels were increased in hypothyroidism patients
- Measurement of Creatinine clearance test is a cost – effective tool for screening and risk stratification of chronic renal failure.

In summary this study has shown that, in hypothyroidism patients with kidney disease, urine protein to creatinine ratio accurately predict proteinuria. PCR is to be used as first line screening test for evidence of renal disease. If the tests are to be used for monitoring the level of proteinuria in established renal disease, they can then be used as surrogates for 24hr measurements. There are various mechanisms of interaction between kidney and thyroid functions in the disease states of each other organ. There are not only functional alterations but also structural correlates of these interactions. TSH elevations are common in Chronic kidney diseases and do not always reflect hypothyroidism.

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