

# Study of Serum Creatinine and Serum Uric Acid in Subclinical and Overt Hypothyroid Patients

M. S. Yamini<sup>1</sup>, Simant Baliar Singh<sup>2</sup>

<sup>1</sup>III Year Post Graduate, Department of Biochemistry, ESIC MC & PGIMSR, Bengaluru-10, Karnataka, India

<sup>2</sup>Professor, Department of Biochemistry, ESIC MC & PGIMSR, Bengaluru-10, Karnataka, India  
Email: msy.mini[at]gmail.com

**Abstract:** **Background:** The relationship between hypothyroidism and kidney dysfunction is complex. The paucity of Indian data highlighting the effect of inadequate thyroid hormones on renal function led us to study in order to examine potential mechanistic links between thyroid and kidney disease in this sub-population. To study Serum creatinine and Serum Uric acid and correlate with TSH, FT3, FT4 in subclinical and overt hypothyroid patients. **Material and Methods:** A Cross-Sectional Study was conducted on patients who are diagnosed with hypothyroidism in OPD of the Department of General Medicine of ESIC MC, Rajajinagar Bangalore-10. Study was conducted on 96 Hypothyroid patients. Serum TSH, FT3, FT4 were analysed by using chemiluminescence immunoassay from Beckman coulter. Serum Creatinine by modified Jaffe's method, Serum Uric acid by uricase method were analysed using COBAS INTEGRA 400 PLUS. **Results:** In our study there is statistically significant, positive correlation between S.Creatinine and TSH in hypothyroid groups ( $R=0.60$ ,  $p<0.0001$ ). There is positive correlation between S.uric acid and TSH which is statistically significant ( $r=0.36$ ,  $P=0.0002$ ) and there is negative correlation between FT4 and S.uric acid and statistically significant ( $r=-0.25$ ,  $P=0.01$ ). We found that with increase in Serum TSH level, decrease in FT3 and FT4 there is increase in Serum creatinine level. We also found Serum Uric acid level increased with increase in Serum TSH level. **Conclusion:** There is increased serum creatinine and Serum uric acid with increased Serum TSH level in hypothyroid patients. This points toward possible role of these renal parameters in the etiopathogenesis of kidney disorders. Hence, Serum creatinine, Serum Uric acid might be used as additional parameters in hypothyroid patients to prevent kidney related disorders.

**Keywords:** Hypothyroidism, Creatinine, Uric acid

## 1. Introduction

According to a projection from various studies on thyroid disease, it has been estimated that about 42 million people in India suffer from thyroid diseases.<sup>1</sup> Derangement of Renal function is also another common disease condition in the general population - Chronic Kidney Disease (CKD) has a high estimated global prevalence of between 11 to 13%.

Hypothyroidism is defined as deficient production of thyroid hormone. The term primary hypothyroidism indicates decreased thyroidal secretion of thyroid hormone, an increased secretion of TSH resulting in elevated serum TSH concentrations. Decreased thyroidal secretion of thyroid hormone can also be caused by insufficient stimulation of the thyroid gland by TSH, due to factors directly interfering with pituitary TSH release (secondary hypothyroidism) or indirectly by diminishing hypothalamic TRH release (tertiary hypothyroidism)<sup>2</sup>

In clinical practice it is not always possible to discriminate between secondary and tertiary hypothyroidism, which are consequently often referred to as central hypothyroidism

Thyroid hormones influence renal development, kidney hemodynamics, glomerular filtration rate and sodium and water homeostasis.<sup>3</sup>

Various studies have demonstrated a higher prevalence of hypothyroidism with increasing severity of kidney dysfunction via several suggested pathways like iodine retention, metabolic acidosis, heavy protein losses, changes in hypothalamus-pituitary-thyroid axis.<sup>5</sup> Conversely, it has

also been suggested that hypothyroidism leads to kidney dysfunction through several potential mechanisms, including decreased cardiac output, altered intra-renal hemodynamics (i.e., intra-renal vasoconstriction resulting from decreased vasodilator synthesis and activity), reduced renin-angiotensin-aldosterone production and activity, and decreased tubulo-glomerular feedback due to alterations in chloride channel and expression.<sup>4</sup>

### Objectives of the study:

To study Serum creatinine and Serum Uric acid in subclinical and overt hypothyroid patients.

## 2. Literature Survey

Rhee CM et al. (2015) conducted a cross sectional study of 461,607 US veterans who underwent repeated measures of serum TSH and creatinine testing at identical time points, each 10 ml/min/1.73m<sup>2</sup> decrement in eGFR was associated with an 18% higher risk of hypothyroidism, independent of socio-demographics and comorbidities.<sup>5</sup>

Kreisman SH & Hennessey JV (1999) in a study of 24 patients reported that elevation of levels of serum creatinine can occur within as little as 2 weeks of significant hypothyroidism. These levels typically normalize rapidly with thyroid hormone replacement after short periods of hypothyroidism, but slower and incomplete recovery has been noted with more prolonged periods of severe hypothyroidism.<sup>6</sup>

## 3. Material and Methods

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Patients who are diagnosed with hypothyroidism in IPD and OPD of the Department of General Medicine of ESIC Model Hospital Rajajinagar Bangalore-10 are included in the study. It is an Observational, Cross-Sectional Study. The study carried out for a period of 18 months from February 2021 to July 2022 in ESIC-MC & PGIMSR

**Sample size:** For the sample size calculation the population of hypothyroid cases whose eGFR is less than 90 is found to be 55% based on previous literature.<sup>7</sup> The sample size is calculated with 95% confidence interval, 80% power and relative precision of 10%. The sample size for the study is found to be 96. The Sample size calculation was performed using [www.openepi.com](http://www.openepi.com)

**Inclusion Criteria:**

- 1) Patient willing to give informed consent
- 2) Patients aged 20-50 years of either sex who are diagnosed with hypothyroidism are included in the study.

**Exclusion criteria:**

- 1) Cases with established kidney disorders, chronic liver disease, Ischaemic heart disease.
- 2) Cases with hypertension.
- 3) Cases with Diabetes Mellitus.
- 4) Patients on prolonged use of NSAIDs, Diuretics, Aminoglycosides, 1<sup>st</sup> generation Cephalosporins, Vancomycin
- 5) Cases with Gout.
- 6) Pregnant women

**Method of Collection of Data**

**Collection of blood samples:** After taking informed consent, under aseptic precautions 5ml of venous blood sample drawn, and then transferred to plain sterile vacutainer tubes, blood is allowed to clot at 37°C, and then centrifuged at 3000rpm for 10 minutes to separate the serum, the sera thus separated will be transferred to plain bullet vials and used for analysis of serum creatinine, blood urea, serum uric acid and serum TSH, FT3, FT4 in the Clinical Biochemistry Laboratory of ESICMC & PGIMSR Hospital, Bangalore.

**Analysis of samples:** serum separated is analysed for serum TSH, FT4, FT3 level by Beckmann coulter serum creatinine,

blood urea, serum uric acid by fully automated analyser Cobas Integra 400 plus by Roche diagnostics, for which Internal and External Quality Assurance Programmes are maintained.

**Statistical Analysis**

The quantitative variables analysed for descriptive statistics like proportion, mean, inter-quartile range and standard deviation. The data analysed using student's unpaired 't' test and statistical package SPSS24 version. Karl Pearson's correlation coefficient test performed to measure the strength of relationship between Serum creatinine, Serum Uric acid levels with the TSH, FT3, FT4 levels. The P value of < 0.05 considered as statistically significant.

**4. Results**

A total of 96 hypothyroid subjects were taken in the study, among them 71 are subclinical and 25 are overt hypothyroid cases. Mean age in the hypothyroid group 38.47 years with a standard deviation of 7.47 years with female preponderance. As shown in Table 1, the mean TSH is 9.83 microIU/ml with standard deviation of 5.17 microIU/ml, mean of FT3 is 3.17pg/ml with standard deviation of 0.51 pg/ml and mean of FT4 is 0.80 ng/dl with standard deviation of 0.36 ng/dl in the hypothyroids of the study group. 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.<sup>8</sup>The mean serum creatinine levels in hypothyroid subjects are 0.74 mg/dl with standard deviation of 0.19mg/dl. The mean serum uric acid levels in hypothyroid subjects are 4.58 mg/dl with standard deviation of 1.44 mg/dl.

**Table 1: Biochemical Parameters of Hypothyroid Subjects**

| Biochemical parameters | Mean +/- SD   | Minimum Value | Maximum value |
|------------------------|---------------|---------------|---------------|
| TSH                    | 9.83 +/- 5.17 | 5.63          | 29.9          |
| FT3                    | 3.1 +/- 0.51  | 1.57          | 4.81          |
| FT4                    | 0.8 +/- 0.36  | 0.31          | 1.11          |
| Serum Creatinine       | 0.74 +/- 0.19 | 0.4           | 1.5           |
| Serum Uric acid        | 4.58 +/- 1.44 | 1.3           | 9.3           |

**Table 2: Comparison Biochemical Parameters in Subclinical and Overt Hypothyroid Groups**

| Biochemical parameters | Mean +/- SD    |               |               | P value |
|------------------------|----------------|---------------|---------------|---------|
|                        | Total          | Subclinical   | Overt         |         |
| Age                    | 38.47 +/- 7.47 | 39.5 +/- 6.87 | 35.4 +/- 8.4  | 0.01    |
| TSH                    | 9.83 +/- 5.17  | 7.39 +/- 1.2  | 16.7 +/- 5.8  | 0.0001  |
| FT3                    | 3.1 +/- 0.51   | 3.28 +/- 0.48 | 2.8 +/- 0.4   | 0.0003  |
| FT4                    | 0.8 +/- 0.36   | 0.85 +/- 0.39 | 0.65 +/- 0.1  | 0.0001  |
| Serum Creatinine       | 0.74 +/- 0.19  | 0.68 +/- 0.14 | 0.92 +/- 0.20 | 0.0001  |
| Serum Uric acid        | 4.58 +/- 1.44  | 4.37 +/- 1.35 | 5.24 +/- 1.59 | 0.01    |

**Table 3: Correlation between Thyroid Profile and Serum Creatinine in Hypothyroid Subjects**

| S.Creatinine              | Group              | TSH                  |                | FT3             |         | FT4          |         |
|---------------------------|--------------------|----------------------|----------------|-----------------|---------|--------------|---------|
|                           |                    | R value              | P value        | Rvalue          | P value | Rvalue       | P value |
|                           | <b>Subclinical</b> | 0.34                 | <b>0.003**</b> | -0.21           | 0.06    | 0.04         | 0.73    |
| <b>Overt</b>              | 0.43               | <b>0.02*</b>         | -0.20          | 0.31            | -0.07   | 0.73         |         |
| <b>Total hypothyroids</b> | 0.60               | <b>&lt;0.0001***</b> | -0.36          | <b>0.0003**</b> | -0.24   | <b>0.01*</b> |         |

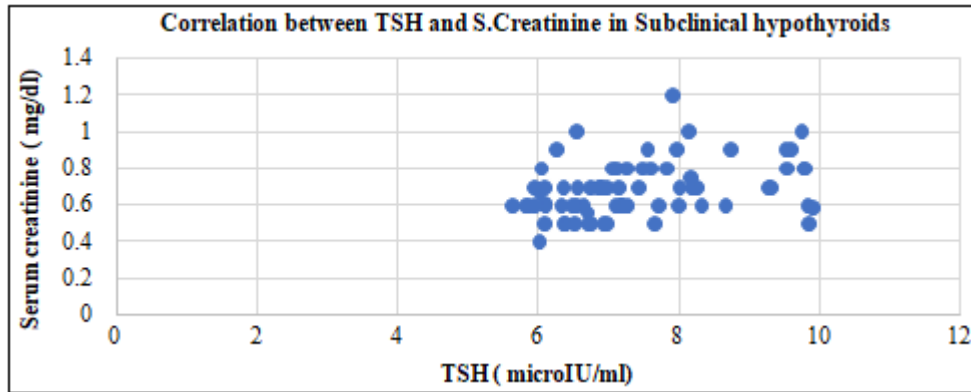
\*P <0.05

\*\* P<0.01

\*\*\*P< 0.0001

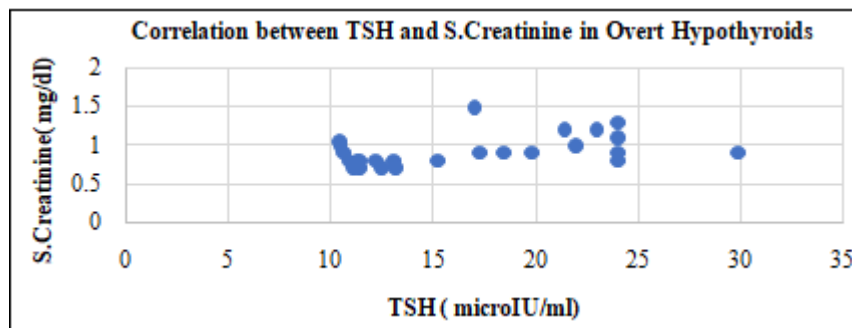
n=96

There is statistically significant, positive correlation between S.Creatinine and TSH in hypothyroid groups and there is negative correlation between FT3, FT4 and S.creatinine which is statistically significant.



**Graph 1:** Correlation of TSH with S.Creatinine in Subclinical Hypothyroid subjects

There is correlation between TSH and S.Creatinine in subclinical hypothyroid group and statistically significant ( $r = 0.34$ ,  $p = 0.003$ )



**Graph 2:** Correlation of TSH with S.Creatinine in Overt Hypothyroid subjects

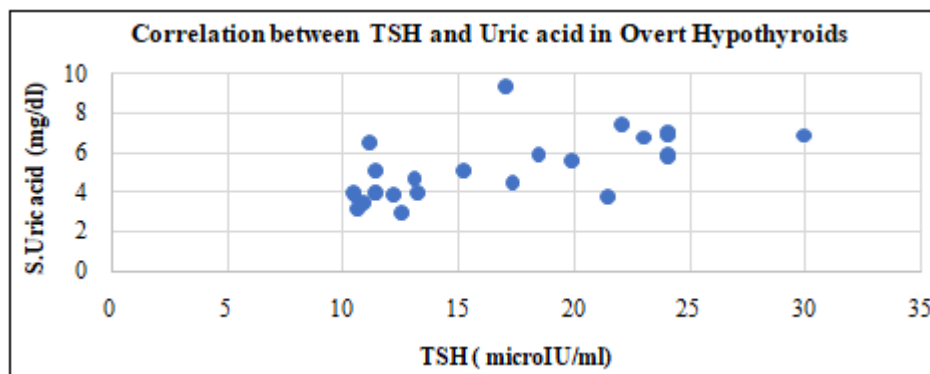
There is correlation between TSH and Serum creatinine in Overt Hypothyroid group and statistically significant ( $r = 0.43$ ,  $p = 0.02$ )

**Table 4:** Correlation between Thyroid Profile and Serum Uric Acid in Hypothyroid Subjects

| S. Uric acid | Group              | TSH     |          | FT3     |         | FT4     |         |
|--------------|--------------------|---------|----------|---------|---------|---------|---------|
|              |                    | R value | P value  | R value | P value | R value | P value |
|              | Subclinical        | 0.03    | 0.76     | 0.10    | 0.36    | -0.13   | 0.27    |
|              | Overt              | 0.63    | 0.0007** | -0.003  | 0.98    | -0.33   | 0.10    |
|              | Total hypothyroids | 0.36    | 0.0002** | -0.02   | 0.81    | -0.25   | 0.01**  |

\* $P < 0.05$       \*\*  $P < 0.01$       \*\*\* $P < 0.0001$        $n = 96$

There is positive correlation between S.uric acid and TSH which is statistically significant and there is negative correlation between FT4 and S.uric acid and statistically significant.



**Graph 3:** Correlation of TSH with S.Uric acid in overt Hypothyroid subjects

There is correlation between TSH and S.Uric acid in overall hypothyroid subjects and statistically significant ( $r = 0.36$ ,  $P = 0.0002$ ).

## 5. Discussion

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 shows effect on electrolyte and fluid metabolism and also in cardiovascular functions.<sup>9,10</sup>

Impairment in kidney function may lead to changes in the synthesis, secretion and elimination of thyroid hormones.<sup>11</sup> The most common renal dysfunction in hypothyroid patients is decreased renal blood flow, increased serum creatinine level, impaired free water excretion, and hyponatremia.<sup>12</sup>

As a mild thyroid failure, SCH is a widespread condition that often progresses to OHT. Concerning the high prevalence of the disorder, the outcomes of our study showed higher SCH prevalence rates in women, which is in agreement with the results of previous researches in China and other countries.<sup>13</sup>

Decreased GFR has been described as secondary to the generalized hypodynamic circulation in hypothyroid patients.<sup>13,15</sup> After a reduction in the level of GFR, the flow rate of renal plasma decreased and serum creatinine increased.<sup>14</sup>

In our study it showed increase in the serum creatinine levels with increase in TSH level which is significant could be explained by the study done by Patil VP, Shilpasree AS et al in 2018 which concluded that the TSH values may be used to predict the lower kidney function (higher creatinine values) among the SCH group<sup>15</sup>

Similarly, the relationship between kidney function and SCH was evaluated by Kaur et al. between participants of age 20–70 years. They stated that SCH had a significant association with increased levels of serum creatinine ( $P < 0.001$ )<sup>16</sup> Similarly, we found a significant and positive correlation between TSH and the level of serum creatinine and significant negative correlation between FT3, FT4 and Serum creatinine.

On the contrary, Tayal et al. stated that there was a significant positive correlation between the serum level of creatinine in the overt hypothyroid group and TSH, but could not find such a correlation in the SCH group<sup>17</sup>

Alternatively, regulating various metabolic pathways in the body is the mainstay of thyroid hormones function. Purine metabolism involves the de novo purine salvage pathway, purine biosynthetic pathway, and degradation can be affected by thyroid hormones. Alteration in these pathways can end in uric acid production and impair its degradation.<sup>16,18</sup>

Hyperuricemia may occur secondary to renal plasma flow reduction and impaired GFR<sup>18</sup>. In our study there is significant correlation between TSH, FT4 and Serum Uric acid levels. Kaur et al. did not report any considerable increases in the level of serum uric acid.<sup>15</sup> Moreover, in a study performed by Liang et al., no significant increase was found in the serum uric acid of patients with SCH but they did not study the serum creatinine between participants<sup>20</sup>.

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.<sup>21</sup> In our study, similar to the studies mentioned above, creatinine values were found to be significantly higher in patients with hypothyroidism.

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.<sup>21</sup> Giardano et al. proved that gout due to hyperuricemia is more common in hypothyroid patients.<sup>19</sup>

In this study, serum uric acid is significantly correlated with TSH and negatively correlated with FT4 which is not significant. In an epidemiological study in northern Finland in 1969, hyperuricemia was found in rural, urban and hospital admitted hypothyroid patients<sup>22</sup> As TSH level increases serum uric acid is increased and FT4 is decreased. The elevation of uric acid in patients with overt hypothyroidism was found to be significant ( $p = 0.001$ ). 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.<sup>23</sup>

## 6. Conclusion

Hypothyroidism is a common condition results from thyroid hormone deficiency or disease/defect in hypothalamo pituitary axis which is readily diagnosed and managed by preventing progression to overt hypothyroid state and if untreated potentially fatal. In our study, we found that high levels of TSH and low-normal levels of FT3 were modestly associated with an increased serum creatinine levels which is a risk of incident CKD. Hypothyroidism results in a reversible elevation in serum creatinine due to the reduction in GFR as well as possible myopathy and rhabdomyolysis.

In our study, Hypothyroid patients have increase in the Serum Uric acid level with raise in their TSH level. Hyperuricemia can consequently lead to gout. This condition can be prevented by regular screening and monitoring for the renal function in the patients of thyroid disorder.

Serum creatinine and uric acid level in SCH and overt hypothyroidism increases as the degree of hypothyroidism increases may suggest that these values should be used in renal monitoring in daily practice in hypothyroid patients

It can be concluded that all the hypothyroid patients might be investigated for renal function tests like Serum creatinine,



Serum Uric acid which could prevent complications in kidney function by detecting earlier.

## 7. Future Scope

Our study shows increased serum creatinine and serum uric acid levels in hypothyroid patients. It can be considered measuring serum creatinine and serum uric acid as a routine analysis especially in overt hypothyroids to prevent renal impairment. Limitation of our study is sample size of overt hypothyroid cases could be improved.

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## Author Profile



**Dr. M. S. Yamini**, III Year Post Graduate, Department of Biochemistry, ESIC MC & PGIMSR, Bengaluru-10, Karnataka, India.



**Dr. Simant Baliarsingh** is Professor in Department of Biochemistry, ESIC MC & PGIMSR, Bengaluru-10, Karnataka, India.