Evaluation of Serum Creatinine, Uric Acid Levels and Urinary Albumin Creatinine Ratio in Patients of Primary Hypothyroidism

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ABSTRACT
Background: Primary hypothyroidism is a clinical condition due to deficiency of thyroid hormones. Thyroid hormones have profound effect on renal development, renal hemodynamics, glomerular filtration rate, electrolytes and water homeostasis. The aim of this case control prospective study is to evaluate the effect of primary hypothyroidism on renal functions.

Methods: Serum creatinine, blood urea nitrogen, uric acid, urinary albumin creatinine ratio and eGFR levels were estimated in 75 newly diagnosed and untreated patients of primary hypothyroidism in the age group of 20 to 60 years of either sex (Study group) and 75 healthy, age and sex matched individuals with normal thyroid profile (Control group). Follow up of patients in study group was done after 8 weeks of thyroxine replacement and serum creatinine, uric acid, urinary albumin creatinine ratio and eGFR levels were estimated.

Results: The mean eGFR level in study group at baseline was lower and mean serum creatinine, blood urea nitrogen, serum uric acid and urinary albumin creatinine ratio (UACR) levels were higher than control group. After 8 weeks of thyroxine replacement; the mean serum creatinine, uric acid, blood urea nitrogen levels were decreased and eGFR levels were increased. Also serum TSH shows positive correlation with serum creatinine, blood urea nitrogen, uric acid and urinary albumin creatinine ratio but negative correlation with eGFR.

Conclusion: Primary hypothyroidism is associated with significant alteration in renal function which is reversible on thyroxine replacement.

Keywords: Blood Urea Nitrogen, Creatinine, Primary hypothyroidism, Uric acid, Urinary Albumin Creatinine Ratio.

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INTRODUCTION
Primary hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone. The prevalence of hypothyroidism in developed countries is about 5%, whereas in India, it is reported to be around 10.95%.¹ In India hypothyroidism is the commonest thyroid disease, affecting 1 out of 10 persons.² Hypothyroidism is more common in women than men.³ The relationship of kidney and thyroid function is known for many years.⁴ Thyroid hormones play a vital role in renal development and physiology.⁵ Thyroid hormones influence 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.

Thyroid hormones have direct effects on kidney and affect the functioning renal mass (measured as the kidney to body mass ratio), with hypothyroidism reducing this ratio.⁶ Besides there are intrinsic renal effects by which thyroid hormone influences the tubular secretory and re-absorptive processes. Thyroid hormone affects renal clearance of water load by their effects on the GFR.⁷ Thyroid hormones influence sodium reabsorption at the proximal convoluted tubule primarily by increasing the activity of the Na/K ATPase, tubular potassium permeability and tubular reabsorption of calcium.⁸ Thyroid hormones regulate the adrenergic receptors and dopaminergic activation of the renal tubular cells.⁹ Thyroid hormones also affect the renin–angiotensin–aldosterone axis by adrenergic regulation, renin release, as well as influencing the angiotensinase activity.¹⁰ As a consequence, the renal blood flow is reduced which affect glomerular filtration rate. Also there is increase in glomerular capillary permeability to proteins in hypothyroidism.¹¹ The urinary albumin creatinine ratio is a sensitive indicator of renal functions.

Uric acid is an end product of purine metabolism which is affected by disturbance in thyroid hormones leading to alteration in the uric acid levels and subsequently causing gout. In comparison to the prevalence reported in the general population, a significant increase of both hyperuricemia and gout was found in the
hypothyroid patients. So renal system is adversely affected by hypothyroid state of body. In the light of above facts this study was undertaken to evaluate the effect of primary hypothyroidism on renal function.

**MATERIALS AND METHODS**

After taking approval from ethical committee; this case control prospective study was undertaken in Department of Medicine, Sri Guru Ramdas Institute of Medical Sciences and Research, Amritsar on 150 subjects divided into two groups.

**Study Group:** comprised of 75 newly diagnosed and untreated patients of primary hypothyroidism in age group of 20-60 years.

**Control Group:** comprised of 75 healthy, age and sex matched subjects with normal thyroid profile.

**Inclusion Criteria**

1. 75 newly diagnosed and untreated patients of primary hypothyroidism in age group of 20-60 years

**Exclusion Criteria**

1. Pregnancy
3. Chronic liver disease
4. Diabetes, hypertension or systemic illness like collagen vascular disorders.
5. Patients on thyroxine, antihypertensive and steroid.
6. Patients having malignancy and on chemotherapy.
7. Drugs affecting thyroid function like lithium, iodide, amiodarone, metformin, dopamine agonist, interferon, somatostatin analogue.

Written informed consent was taken from all the enrolled subjects. Detailed medical history and relevant clinical examination was carried out. The weight and height of all the enrolled subjects were recorded and Body Mass Index (BMI) was calculated. Blood and random urine samples were taken and analysed for thyroid profile, blood urea nitrogen, serum creatinine, uric acid and urinary albumin creatinine ratio. To segregate patients of primary hypothyroidism, patients with high serum TSH levels (TSH > 4.68mIU/L) were labeled as hypothyroids. Further patients with high TSH and low FreeT4 and T3 level were labeled as Overt hypothyroidism and patients with high TSH and normal Free T4 and T3 levels were labeled as subclinical hypothyroidism.

The normal range taken for FreeT3:
- For age 20-39 yrs = 2.32-6.09 pg/ml,
- For age 40-59 yrs = 2.71-6.16 pg/ml
- For age 60-79 yrs = 2.45-5.93 pg/ml

Free T4 = 0.78-2.19 ng/dl
Serum TSH= 0.46-4.68 mIU/L.
Serum Creatinine= 0.6-1.3 mg/dl
Serum uric acid =2.6-7.2 mg/dl
Blood urea nitrogen= 7-18 mg/dl

Urinary albumin creatinine ratio < 30 mg/g.

Estimation of serum creatinine was done by alkaline picrate kinetic method, serum uric acid by uricase method; blood urea nitrogen by urease calorimetric method on RXL fully automated analyzer by Siemens. The Free Thyroid Profile was estimated by Chemiluminescence. Random urine sample of about 5 ml of enrolled subjects were taken in a sterile container and processed in Siemens Dimensions RXL fully automatic analyzer for urinary albumin creatinine ratio. The estimated GFR was calculated by using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation. Patients enrolled in study group were given thyroxine replacement and follow up was done after eight weeks. On follow up blood sample were taken from enrolled patients and serum creatinine, uric acid, blood urea nitrogen and eGFR levels were estimated.

**Statistical Analysis**

The recorded data was processed and analysed with the help of statistical software statistical package for the social sciences (version 20) and Microsoft Office Excel 2010. The statistical test applied for analysis were student t test and pearson correlation. For all test p value of <0.05 was considered to be statistically significant.

**Table I:** Comparison of thyroid profile, eGFR, serum creatinine, uric acid, blood urea nitrogen and UACR at baseline in Study and Control group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Group Mean±SD</th>
<th>Control Group Mean±SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free T3 (pg/ml)</td>
<td>2.51±0.66</td>
<td>2.96±0.52</td>
<td>0.000</td>
</tr>
<tr>
<td>Free T4 (ng/dl)</td>
<td>0.61±0.18</td>
<td>1.05±1.05</td>
<td>0.000</td>
</tr>
<tr>
<td>Serum TSH (mIU/L)</td>
<td>37.68±52.8</td>
<td>2.45±0.80</td>
<td>0.000</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>79.01±18.66</td>
<td>106.16±14.76</td>
<td>0.008</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.03±0.20</td>
<td>0.71±0.10</td>
<td>0.029</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>15.21±4.14</td>
<td>9.41±1.91</td>
<td>0.018</td>
</tr>
<tr>
<td>Serum uric acid (mg/dl)</td>
<td>5.31±1.32</td>
<td>3.55±0.76</td>
<td>0.047</td>
</tr>
<tr>
<td>UACR (mg/g)</td>
<td>9.69±4.52</td>
<td>6.73±3.59</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**Table II:** Comparison of eGFR, serum creatinine, blood urea nitrogen, serum uric acid in study group at baseline and after 8 weeks of treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>At Baseline Mean±SD</th>
<th>After Treatment Mean±SD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR</td>
<td>78.94±18.78</td>
<td>91.21±25.32</td>
<td>0.000</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.03±0.20</td>
<td>0.90±0.22</td>
<td>0.050</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>15.21±4.14</td>
<td>13.30±3.75</td>
<td>0.037</td>
</tr>
<tr>
<td>Serum uric acid</td>
<td>5.31±1.32</td>
<td>4.33±1.33</td>
<td>0.046</td>
</tr>
</tbody>
</table>
RESULTS
In the present study both the groups were age and sex matched. The mean age of study group was 41.8±11.26 years and of control group was 39.6±12.64 years. In study group, 14 (18.6%) were males and 61 (81.3%) were females. In control group 17 (22.6%) were males and 58 (77.3%) were females. It was observed that patients enrolled in the study group showed female preponderance. Comparison of thyroid profile, eGFR, serum creatinine, uric acid, blood urea nitrogen and UACR at baseline was done in Study and Control group as depicted in table no I. Comparison of eGFR, serum creatinine, blood urea nitrogen, serum uric acid in study group was done at baseline and after 8 weeks of treatment as depicted in table no II. Correlation of serum TSH with eGFR, serum creatinine, uric acid, blood urea nitrogen and UACR at baseline was seen as depicted in table no III. In the present study the mean serum TSH level in the study group at baseline was significantly higher than control group with p value 0.000. The mean Free T3 and mean Free T4 level in the study group at baseline was significantly lower as compared to control group with p=0.000 and p=0.000 respectively. All the patients enrolled in the study group were found to be having overt hypothyroidism. The mean eGFR level in study group was significantly lower and mean serum creatinine, blood urea nitrogen, uric acid and urinary albumin creatinine ratio levels were significantly higher in study group at baseline as compared to control group. After 8 weeks of treatment the mean eGFR level was significantly increased and mean serum creatinine, blood urea nitrogen, serum uric acid levels were significantly decreased in study group. TSH shows positive correlation with serum creatinine, blood urea nitrogen, serum uric acid and negative correlation with eGFR.

DISCUSSION
Primary hypothyroidism is a clinical syndrome resulting from deficiency of thyroid hormones which, in turn, results in a generalised slowing down of metabolic processes. Thyroid hormones have effect on nearly every organ system of the human body, for kidney it is no exception. Hypothyroidism affects renal blood flow, glomerular filtration rate, tubular function, electrolyte homeostasis, and kidney structure. The present study was undertaken to study the effect of primary hypothyroidism on renal functions. In the present study both the groups were age and sex matched. The mean age of study group was 41.8±11.26 years and of control group was 39.6±12.64 years. In study group 14 (18.6%) were males and 61 (81.3%) were females. In control group 17 (22.6%) were males and 58 (77.3%) were females. It was observed that patients with primary hypothyroidism enrolled in the study group showed female preponderance. A study conducted by Tayal et al on 385 subjects observed mean age of 43.4±2.67 years in the study group and 44.1±3.2 years in the control group. There were 150 females and 37 males in the study group and 153 females and 45 males in the control group. The demographic profile of our study is in concordance with this study as in both the studies, there were more females in the study group.12

It was observed that the mean BMI in study group (23.96±2.07kg/m²) at baseline was significantly higher than that in control group (21.45±2.10kg/m²) with p value 0.014. This is in accordance with study done by Chaudhury HS et al. who observed higher BMI in hypothyroid cases (study group) as compared to control group. This alteration in BMI could be explained with decreased basal metabolic rate and TSH directly stimulate preadipocyte differentiation and result in adipogenesis.13 In the present study the mean serum TSH level in the study group (37.68±52.23mIU/L) at baseline was significantly higher than control group (2.45±0.80mIU/L) with p value 0.000. The mean Free T4 level in the study group (0.61±0.18ng/dl) at baseline was significantly lower as compared to control group (1.05±1.05ng/dl) with p value 0.000. The mean Free T3 level in the study group (2.51±0.66pg/ml) at baseline was also significantly lower as compared to control group (2.96±0.52pg/ml) with p value 0.000. All the patients enrolled in the study group were found to be having overt hypothyroidism. A similar study conducted by Nagarajappa K et al. included 40 cases and 40 controls and observed significantly high mean serum TSH and significantly low mean Free T3 and T4 among cases as compared to controls.14

In the present study the mean eGFR in study group (79.01±18.66ml/min/1.73m²) at baseline was lower as compared to control group (106.16±14.76ml/min/1.73m²) and the difference was statistically significant (p=0.008). This is in accordance with study conducted by Patil VP et al. who observed significant reduction in eGFR among hypothyroid patients (p=0.05).15 The eGFR is an important yardstick for assessment of renal function and the reason for above finding could be: 1. Hypothyroidism is associated with negative inotropic and chronotropic effect on heart leading to decrease in cardiac output and renal blood flow, impaired activity of renin-angiotensin-aldosterone system and decrease in atrial natriuretic factor level, which could lead to decreased renal perfusion. 2. The glomerular surface area can be decreased by growth retardation in renal parenchyma. 3. A filtrate overload caused by deficient sodium and water reabsorption in the proximal tubule could lead to an adaptive parglomerular vasoconstriction. 4. Hypothyroidism causes decrease in renal vasodilators such as insulin like growth factor 1 and vascular endothelial growth factor.

## Table III: Correlation of serum TSH with eGFR, serum creatinine, uric acid, blood urea nitrogen and UACR at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>r value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH vs eGFR</td>
<td>-0.20</td>
<td>0.000</td>
</tr>
<tr>
<td>TSH vs Blood Urea Nitrogen</td>
<td>0.49</td>
<td>0.000</td>
</tr>
<tr>
<td>TSH vs Serum Creatinine</td>
<td>0.53</td>
<td>0.000</td>
</tr>
<tr>
<td>TSH vs Serum Uric acid</td>
<td>0.46</td>
<td>0.040</td>
</tr>
<tr>
<td>TSH vs UACR</td>
<td>0.52</td>
<td>0.000</td>
</tr>
</tbody>
</table>

(Pearson correlation)
thereby decreases the relaxing capacity of renal vasculature and further affecting renal blood flow and glomerular filtration rate. In our study we found a higher mean serum creatinine level in both the groups compared to the normal biological reference range. The mean serum creatinine level was higher in study group (1.03±0.20mg/dl) as compared to control group (0.71±0.10mg/dl) and the difference was statistically significant (p<0.02). The result of our study is in concordance with study conducted by Kumbary B et al on 70 subjects and another study conducted by Saini V et al which showed a significant positive correlation of TSH with serum creatinine, uric acid and UACR levels in patients of overt hypothyroidism (p<0.05).

In present study though the mean blood urea nitrogen in both the groups were within normal biological reference range but it was significantly higher in study group (15.21±4.14mg/dl) as compared to control group (9.41±1.91mg/dl) with p value 0.01. The result of our study is in concordance with study conducted by Kumbary B et al. who observed significant rise in mean blood urea nitrogen in study group as compared to control group but the mean blood urea level was within normal range in both the groups (p<0.05). The statistically significant (p<0.05) alteration in mean blood urea nitrogen and serum creatinine level in study group as compared to control group can be explained by decrease in glomerular filtration rate associated with hypothyroidism. Serum creatinine level in study group may also be increased due to hypothyroidism induced myopathy.

In our study we found the mean serum uric acid level was within normal biological reference range in both the groups but the mean serum uric acid level was higher in study group (5.31±1.32mg/dl) as compared to control group (3.55±0.76mg/dl) and the difference was statistically significant (p<0.04). The study conducted by Giordano et al support result of our study and showed 33.3% prevalence of hyperuricemia in patients with primary hypothyroidism.

The reason of statistically significant rise in mean serum uric acid level in study group as compared to control group is presumably due to decreased renal clearance of uric acid associated with reduction in renal blood flow and alteration in glomerular filtration rate. The other cause may be altered purine metabolism and hypothyroidism induced myopathy.

In present study the mean urinary albumin creatinine ratio (UACR) levels in both the groups were within the normal biological reference range but the mean UACR level in study group (9.69±4.52mg/g) at baseline was significantly higher as compared to control group (6.73±3.59mg/g) with p value 0.000 (p<0.05). The study conducted by Saha S et al. support result of our study and showed significant rise in mean urinary albumin creatinine ratio level among 48 newly diagnosed drug naive primary hypothyroidism patients (p<0.05).

Urinary albumin creatinine ratio is a sensitive marker of renal function. Our study showed the mean urinary albumin creatinine ratio level within normal biological reference range in both the groups but significantly higher in study group as compared to control group (p<0.05) and this significant alteration in mean UACR level in study group can be explained by endothelial dysfunction due to deposition of immune complexes especially antithyroid peroxidase antibody (anti TPO) in the renal glomeruli. In our study there might be some patients enrolled in study group with anti TPO antibody positive due to which the results showed mean UACR level significantly on higher side in study group as compared to control group.

In present study it was observed that with rise in serum TSH level in study group at baseline the eGFR level was increased and the difference was statistically significant (p=0.00). On the contrary the blood urea nitrogen, serum creatinine, uric acid and UACR levels were significantly increased with rise in serum TSH level with p=0.000, p=0.000, p=0.004, p=0.000 respectively. This showed a negative correlation between serum TSH and eGFR levels but a positive correlation between serum TSH and blood urea nitrogen, serum creatinine, uric acid and UACR levels in study group. This is in concordance with study conducted by Saini V et al. which showed a significant positive correlation of TSH with serum creatinine and uric acid levels in patients of overt hypothyroidism (p<0.05).

In our study it was observed that the mean eGFR level in study group at baseline (78.94±18.87ml/min/1.73m²) was increased after eight weeks of treatment (91.21±25.32ml/min/1.73m²) and the difference was statistically significant (p=0.00). This was in concordance with study conducted by Saha S et al. who observed significant increase in eGFR level in patients who were under treatment for hypothyroidism. The decline of eGFR is reversible which gets corrected after thyroxine replacement.

In our study the mean blood urea nitrogen level in study group at baseline (15.21±4.14mg/dl) was significantly lowered after eight weeks of treatment (13.30±3.75mg/dl) with p value 0.037. The mean serum creatinine in study group at baseline (1.03±0.20mg/dl) was also significantly lowered after eight weeks of treatment (0.90±0.22mg/dl) with p value 0.05. Significant reduction in mean serum uric acid levels were also observed in study group after eight weeks of treatment (4.33±1.33mg/dl) as compared to mean serum uric acid level at baseline (5.31±1.32mg/dl) and the difference was statistically significant (p=0.04). This is in concordance with study conducted by Saha S et al. who observed statistically significant decrease in mean blood urea, serum creatinine and uric acid levels in hypothyroid patients on treatment (p<0.05). Significant alteration in blood urea level in primary hypothyroid patients (p<0.05) was also observed by Montenegro et al. while comparing the patients pretreatment and posttreatment status.

CONCLUSION

In the present case control prospective study there was significant decrease in mean eGFR level and significant increase in mean serum creatinine, blood urea nitrogen, uric acid and urinary albumin creatinine ratio levels in the study group at baseline compared to control group. After 8 weeks of thyroxine replacement the mean eGFR level was increased and mean serum creatinine, blood urea nitrogen, serum uric acid levels were decreased in study group as compared to control group. The alteration in renal function was found to be reversible after eight weeks of treatment. The present study indicates the profound influence of Primary Hypothyroidism on renal functions and findings of study suggest that regular monitoring of renal functions should be done in patients of Primary hypothyroidism and patients with unexplained abnormal renal functions should be screened for thyroid disorders. The timely detection of altered renal functions...
due to primary hypothyroidism and management of primary hypothyroidism can prevent renal damage. This will also prevent unnecessary investigations among patients who presented with raised serum creatinine and uric acid with undetermined thyroid status.

REFERENCES


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Conflict of Interest: None Declared.

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