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# Study of evaluation of renal function in subclinical hypothyroid patients

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ABSTRACT

Subclinical hypothyroidism (SCH) is evaluated as an increased serum thyroid-stimulating hormone (TSH) above the given upper limit of the reference range, with free thyroxine (free $T_4$) and free triiodothyronine (free $T_3$) within the reference range. Thyroid hormones play major role in the growth, development and physiology of the renal system. The study was performed to evaluate renal functions in SCH cases. The study was conducted at Smt SMS Multispecialty hospital. 50 SCH and 50 overt hypothyroidism (OHT) cases, 100 euthyroid patients (ET) were enrolled in the study. Thyroid function test, serum creatinine and eGFR were measured in all the three groups. The result shows that there was a definitive trend of increased serum creatinine from euthyroid group to SCH group and finally to OHT group and definitive trend of decreased eGFR from euthyroid group to SCH group and finally to OHT group. Among the three groups, there are higher percentage of patients having high serum creatinine and low eGFR belongs to SCH and OHT group in comparison to ET group. Our result showed a significant positive correlation of TSH with serum creatinine in cases of SCH and OHT and significant negative correlation of TSH with eGFR in cases of SCH and OHT. Finding of our study suggests that renal function and thyroid function are interrelated with each other in SCH cases. SCH patients should be monitored for renal parameters regularly to prevent long term complications. Early diagnosis and early treatment of the disease and can increase the quality of life.



## 1. Introduction

Subclinical hypothyroidism (SCH) is evaluated as an increased serum thyroid-stimulating hormone (TSH) above the given upper limit of the reference range, with free thyroxine (free$T_4$) and free triiodothyronine (free $T_3$) within the reference range. Virtually, SCH patients present with minimal or no sign and symptoms of thyroid dysfunction at all, thus making it solely laboratory diagnosis by nature.

The prevalence of Hypothyroidism in the Indian population is 12% and out of that, 3% has Overt Hypothyroidism (OHT) and 9% has Subclinical hypothyroidism.[1] Several epidemiological studies in India expressed a prevalence rate of SCH, varying between 9% and 11.4%. Out of that, 2-5% of cases per year advance to OHT. Due to the asymptomatic status of SCH, the majority of cases go undiagnosed. SCH patients express more symptoms than Euthyroid (ET) individuals, but lesser symptoms than OHT participants.

Hypothyroidism is associated with decreased glomerular filtration rate (GFR) and hyperthyroidism results in increased GFR as well as increased renin–angiotensin–aldosterone activation. There is an established association between thyroid hormone and renal functions. Thyroid hormones play an important role in the growth, development and physiology of the renal system.[2] Conversely, the kidney is an organ for metabolism and as well as elimination of free $T_3$ and free $T_4$, Thyroid abnormalities can cause significant changes in renal functions and water-electrolyte homeostasis. Hypothyroidism is associated with low GFR, hyponatremia. Excessive level of TSH lowers the glomerular filtration rate and renal blood flow, overall significantly altering the kidney functions.

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Hypothyroidism is associated with significant alteration in biochemical parameters of kidney function.[3,4] Increased serum creatinine is inversely associated with glomerular filtration rate (GFR) values in overt hypothyroid patients.[2,5–7] We hypothesize that SCH might be responsible for a decrease in GFR.

Effects of Thyroid Hormones on Renal Physiology:

Thyroid hormones affect renal physiology by indirect pre-renal changes and direct renal changes as well.

1. Indirect change in renal function is caused because of the effect of thyroid hormone on the cardiovascular system and renal blood flow.
2. The direct renal effects are mediated by the effect of thyroid hormones on[8]
   a. Glomerular filtration rate (GFR)
   b. Tubular secretary and reabsorptive processes
   c. Hormonal influences on renal tubular physiology

Renal dysfunction can be assumed as the reflection of hypothyroidism. There is lack of literature to support an association between SCH and its systemic effects. Following cross sectional study investigation will help us to find out whether SCH manifests in the organ dysfunction, i.e., kidney function. It would guide us to make treatment plans for SCH and its associated co morbidities.

To our knowledge, this study is first of its kind to investigate changes in renal function in patients with subclinical hypothyroidism at Smt. SMS Multispecialty Hospital, Ahmedabad.

Hence, the study was performed to evaluate renal functions by estimating serum creatinine and estimated GFR (eGFR) in SCH cases with the following objectives:

1. To find out the effect of SCH on kidney function
2. To investigate the association between thyroid profile and renal function test in cases of SCH.

## 2. Materials and Methods

Type of study- Observational cross-sectional Study.

In the following study, 50 cases for subclinical hypothyroidism, overt hypothyroidism, and 100 cases for euthyroid patients who attended medicine OPD or admitted under the jurisdiction of the department of medicine at Smt SMS Multispecialty Hospital, Ahmedabad from June 2019 to December 2019 were enrolled. Detailed personal history, basic information and clinical history were collected from the patients after their consent.

### *2.1. Participants' recruitment procedure*

In total 200 patients were enrolled in this study.

### *2.2. Inclusion criteria*

18 to 45 years old subjects were enrolled in this study. The subjects were divided in three different groups after laboratory investigations:

**Group 1:** Subclinical hypothyroidism (SCH): Subjects with normal Free $T_3$ and Free $T_4$and increased TSH.

**Group 2:** Overt hypothyroid group (OHT): Subjects having low Free $T_3$ and low Free $T_4$andincreased TSH.

**Group 3:** Euthyroid group (ET): Subjects with normal TSH, Free $T_3$ and Free $T_4$

### *2.3. Exclusion criteria*

Participants with the following conditions were excluded:

1. Subjects taking drugs which can alter thyroid hormones level.
2. Patients with kidney diseases.
3. Patients with liver diseases.
4. Patients suffering from metabolic syndrome and chronic inflammatory diseases.
5. Patients who refused to give consent for the study.

5 ml blood sample from each patient was drawn in a plain bulb to separate serum by centrifugation at 3000 rpm for 10 minutes and separated serum (not hemolysed) was transferred to properly labeled aliquots and biochemical analysis was performed.

Ethical clearance has been obtained from the Institutional Ethical Clearance Committee of Dr. M K Shah Medical College& Research Centre.

Free $T_3$, Free T4 and Thyroid Stimulating Hormone [TSH] were analyzed by two-site immunoenzymometric assay method in TOSOH Immunoassay Hormone Analyzer in Central Clinical Biochemistry Laboratory.

1. Serum creatinine was analyzed by the Enzymatic Kinase method in Erba 200 fully automated analyzer in Central Clinical Biochemistry Laboratory.
2. eGFR was calculated by Modification of Diet in Renal Disease(MDRD) formula.[9]

$$eGFR = 186 \times (S\ Cr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

The laboratory reference range of TSH, Free $T_3$, Free$T_4$, serum creatinine and eGFR were as below:

1. TSH - 0.55-4.78 micro IU/ml.
2. Free $T_3$- 2.3-4.2 pg/ml.
3. Free $T_4$ -0.89-1.76 ng/dl.
4. Serum. Creatinine- 0.6-1.3 mg/dl in women and 0.7-1.4 mg/dl in men.
5. eGFR –90-120 ml/min/$m^2$[11]

### *2.4. Statistical analysis*

The results were documented, entered and analyzed through Excel 2007 and SPSS for windows version 10.0 software. Results were reported as the mean + standard deviation. The differences in Thyroid profile, Serum Creatinine and

eGFR among the groups were assessed using Analysis of variance (ANOVA). The correlation was calculated by using a regression model. "p" values< 0.05 was acknowledged statistically significant.

## 3. Results

Out of 200 patients, 100 are of Euthyroid group, 50 are of SCH and 50 are of OHT. Table 1 shows variables among the three groups. There is no significance change in age group among the three groups. Table 2 shows comparison of TSH, Free $T_3$. Free $T_4$, Serum creatinine and eGFR among the three groups. We found significant difference in the mean of TSH, free $T_3$. Free $T_4$, serum creatinine and eGFR among the three groups ($p < 0.05$). Table 3 and Figure 1explain the distribution of serum creatinine among the three groups. Patients suffering from OHT have the highest percentage of increase in serum creatinine in comparison to other two groups. Table 4 and Figure 2 shows the distribution of eGFR among the three groups which shows the maximum percentage of patients having decreased GFR(<90 mg/ml/$m^2$) belongs to the group of patients with OHT and the maximum percentage of patients having normal eGFR belongs to the group of patients with euthyroid condition. Table 5 shows the correlation of creatinine and eGFR with TSH, Free $T_3$ and Free $T_4$ in the SCH group. It shows that the positive significant correlations of Creatinine with TSH ($p<0.05$) and the negative significant correlations of eGFR with TSH ($p<0.05$). There is a poor correlation of creatinine and eGFR with thyroid hormones ($p>0.05$). Table 6 shows the correlation of Creatinine and eGFR with TSH, Free $T_3$ and Free $T_4$ in the OHT group. It shows that the positive significant correlations of creatinine with TSH ($p<0.05$) and the negative significant correlations of eGFR with TSH ($p<0.05$). There is negative significant correlations of creatinine with Free $T_4$ ($p< 0.05$) and the positive significant correlations of eGFR with Free $T_4$ ($p< 0.05$). There is poor correlation of creatinine and eGFR with Free $T_3$ ($p>0.05$).

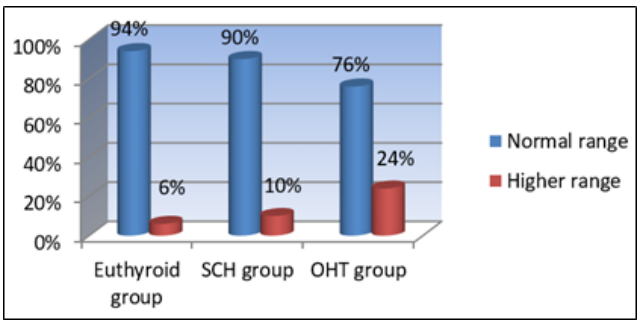


**Fig. 1:** Comparison of Serum creatinine among the three groups

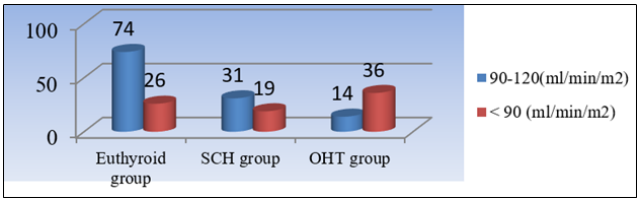


**Fig. 2:** Comparison of eGFR among the three groups

## 4. Discussion

Our study showed that there was no significant change in the age among the three groups (p=0.38) [Table 1]. TSH was normal in ET group, but a significant increase in SCH group and OHT group was observed. Free $T_3$ and Free $T_4$ were normal in SCH group and ET group, but a significant decrease was noticed in OHT group [Table 2].

The serum creatinine values were within the normal reference range in all the three groups. Serum creatinine was higher in the SCH group in compare to the euthyroid group. Patients from OHT group had much higher value of serum creatinine when compared to the other 2 groups ($p <0.05$). A constant increase in serum creatinine levels in comparison of ET group of patients to SCH group and OHT group was observed. In comparison to ET group, eGFR was on lower side in OHT and SCH group of patients. eGFR was lowest in the OHT cases and borderline decreased in the SCH cases when compared among the three groups ($p <0.05$) [Table 2]. Mean eGFR of ET group was on average 14% higher than SCH group and mean eGFR of OHT group was 12% higher than SCH group. It showed that there was a definitive trend of decrease eGFR from the euthyroid group to the SCH group and finally to the OHT group [Table 2]. Saini V et al[10] observed that OHT and SCH patients showed significant raise in serum creatinine as compared to the control group. Jia D et al.[11] also suggested that a higher level of serum creatinine was found in OHT group as compared to SCH group and control group. Meenakshi G[12] concluded that there was an increased serum creatinine (1.71 mg/dl) in the hypothyroidism group as compared to the control group (0.92mg/dl) which is similar to our study.

The possible mechanism of elevated creatinine and decreased eGFR in hypothyroidism is decreased cardiac output, increased peripheral vascular resistance and increased myopathy which results in reduced renal blood flow, reduced GFR, decreased creatinine clearance and increased serum Creatinine.[13–18] In addition, thyroid hormones have effect on renal tubular transport too. In hypothyroidism, there is diminished tubular secretion of creatinine which results in decreased eGFR and increased serum creatinine. Sellitti DF[19] et al. observed the expression of TSH receptors in extra-thyroidal tissues including the kidney. Thus it is possible that TSH may affect renal function independently of Free $T_3$ or Free $T_4$.

**Table 1:** Comparison of demographic variables among the three groups

| Variables | Euthyroid group(Mean+ SD) | SCH group(Mean+ SD) | OHT group(Mean+ SD) |
|---|---|---|---|
| **Age (Yrs)** | 32.47+7.22 | 31.04+7.22 | 30.94+7.27 |
| **n (total participants)** | 100 | 50 | 50 |
| **Male** | 58 | 25 | 26 |
| **Female** | 42 | 25 | 24 |

**Table 2:** Comparison of various parameters among the three groups by ANOVA

| Parameter | Euthyroid group(Mean+ SD) | SCH group(Mean+ SD) | OHT group(Mean+ SD) | 'p' value |
|---|---|---|---|---|
| **TSH (micro lU/ml)** | 2.59+ 1.35 | 17.69+7.92 | 26.22+14.86 | <0.05 |
| **Free $T_3$ (pg/mL)** | 3.26+ 1.35 | 3.06+0.57 | 1.18+0.69 | <0.05 |
| **Free $T_4$ (ng/dL)** | 1.33+0.24 | 1.23+0.27 | 0.39+0.28 | <0.05 |
| **Creatinine (mg/dl)** | 0.86+0.15* | 0.95+0.15* | 1.11+0.25* | <0.05 |
| **eGFR (ml/min/$m^2$ )** | 100.75+17.56* | 88.18+14.59* | 75.60+16.15* | <0.05 |

**Table 3:** Comparison of Serum Creatinine among the three groups:

| Serum Creatinine | Euthyroid group | SCH group | OHT group |
|---|---|---|---|
| **Normal range*** | 94 (94%) | 45 (90%) | 38 (76%) |
| **Higher range** | 6 (6%) | 5 (10%) | 12 (24%) |
| **Total** | **100** | **50** | **50** |

*Normal range of creatinine is (in female= 0.6-1.3 mg/dl, in male = 0.7-1.4 mg/dl).

**Table 4:** Comparison of eGFR among the three groups:-

| eGFR | Euthyroid group | SCH group | OHT group |
|---|---|---|---|
| **90-120(ml/min/$m^2$ )** | 74 (74%) | 31(62%) | 14(28%) |
| **< 90 (ml/min/$m^2$ )** | 26 (26%) | 19 (38%) | 36(72%) |
| **Total** | **100** | **50** | **50** |

**Table 5:** Correlation of serum creatinine and eGFR with thyroid profile in the SCHgroup:

| Serum Creatinine | | | eGFR | | |
|---|---|---|---|---|---|
| **Parameter** | **r value** | **"p" value** | **Parameter** | **r value** | **"p" value** |
| **TSH** | 0.35 | 0.008* | TSH | -0.37 | 0.009* |
| **Free $T_3$** | -0.17 | 0.18 | Free $T_3$ | 0.13 | 0.28 |
| **Free $T_4$** | 0.02 | 0.38 | Free $T_4$ | 0.08 | 0.91 |

**Table 6:** Correlation of serum creatinine and eGFR with Thyroid profilein the OHT group:

| Serum Creatinine | | | eGFR | | |
|---|---|---|---|---|---|
| **Parameter** | **r value** | **"p" value** | **Parameter** | **r value** | **"p" value** |
| **TSH** | 0.40 | 0.004* | TSH | -0.47 | <0.0005* |
| **Free $T_3$** | -0.03 | 0.934 | Free $T_3$ | 0.18 | 0.32 |
| **Free $T_4$** | -0.35 | 0.01 | Free $T_4$ | 0.31 | 0.03* |

Our Study revealed the highest percentage of patients having high serum creatinine level(24%) and low eGFR (36%) was seen in OHT group patients in comparison to SCH group and Euthyroid group respectively, which are statistically significant ($p < 0.05$) [Tables 3 and 4 and Figures 1 and 2]. As per this study, the deterioration of kidney function is more commonly seen in cases of SCH and OHT as compared to the ET group and the reason behind it may be the pathophysiological changes in the kidney due to hypothyroidism.

There was a significant positive correlation of TSH with creatinine in OHT and SCH groups and significant negative correlation of TSH with eGFR in OHT and SCH groups [Tables 5 and 6]. In the OHT group, there was a significant negative correlation of Free $T_4$ with creatinine and significant positive correlation of Free $T_4$ with creatinine clearance [Table 6]. In the SCH group, there was a poor correlation between Free $T_3$ and Free $T_4$ with

creatinine and eGFR [Table 5]. An inverse association between TSH levels and eGFR in OHT group was also found in studies in Italy (n = 9888),[20] Norway (n = 29 480)[21] and Korea (n = 2284)[22] which are similar findings with our study. Woodward A. et al.[23] concluded that eGFR of the hypothyroid, euthyroid patients were 64 mL/min/1.73 $m^2$and 77 mL/min/1.73 $m^2$ respectively.

## 5. Conclusion

To conclude, the findings of our study suggest that renal function and thyroid function are interrelated with each other in patients with SCH. Even though the association between thyroid hormones and renal profile was modest, it may have important clinical implications. It suggests that patients of SCH group should be monitored for their renal parameters regularly to prevent long term complications. Early diagnosis of renal disorders, help to initiate early treatment of the disease and can increase the quality of life. Multisystem involvement should be considered in patients with SCH and treat them based on symptoms and laboratory findings accordingly.

## 6. Acknowledgment

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## 7. Source of Funding

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## 8. Conflict of Interest

None.

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