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Correlation of Serum Creatinine with TSH in Overt Hypothyroidism Patients

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Abstract: ***In this study, we aim to determine the correlation between serum creatinine and TSH values in overt hypothyroidism patients. This cross - sectional descriptive study was conducted from October 2022 to April 2024 in the Department of General Medicine and Endocrinology at Justice K. S Hegde Charitable Hospital, a constituent unit of Nitte (Deemed to be University). A total of 62 hypothyroid patients were selected using convenience sampling. Clinical data, including serum TSH, creatinine was collected along with patient demographics and medical histories. Statistical analysis was performed using SPSS version26.0, employing descriptive statistics, spearman correlation coefficients and Mann - Whitney tests. The study included 62 patients (females 82.3%, males 17.7%) with a mean age of 43.56 years. The mean TSH, creatinine of the patients in the present study were 19.05 uIU/ml, 0.87 mg/dl. There was no significant correlation between TSH and creatinine. We conclude that among the overt hypothyroidism patients, TSH was positively correlated with creatinine. However, the differentials were not statistically significant. We recommend conducting further studies to estimate the effect of various thyroid factors on kidney function tests and the long - term impact of hypothyroidism treatment on kidney health.***

Keywords: Overt hypothyroidism, serum TSH, serum creatinine, correlation.

1. Introduction

One of the body's largest endocrine glands, the thyroid secretes triiodothyronine (T3) and thyroxine (T4). The brain and pituitary gland control the thyroid gland's synthesis of T4 and T3.

A reduction in thyroid hormone production brought on by a malfunction in any component of the hypothalamic - pituitary - thyroid axis is known as hypothyroidism. (1) High TSH, low T4 and T3 are found in the laboratory. Hormones produced by the thyroid gland affect kidney function both in the developing kidney and in the mature kidney. It might be influenced to some extent by changes in cardiovascular function caused by thyroid hormone, or it could be directly affected by the functioning of the glomerulus, tubular secretory and absorptive capacities, and the balance of electrolytes and water. (2)

It is well known that the thyroid and kidneys interact, and that thyroid illness may drastically change kidney function, especially by influencing GFR. (3) A range of kidney function tests are utilized in everyday clinical practice; blood creatinine and eGFR are the most commonly used biomarkers. The kidney's physiology, growth, and development are influenced by thyroid hormones. Significant disruption in the biochemical markers of renal function is linked to hypothyroidism. Compared to euthyroid individuals, overt hypothyroid patients had higher serum creatinine and reversibly lower glomerular filtration rate (GFR) values. (4)

Muscle produces creatinine from creatine phosphate by irreversible, nonenzymatic phosphate loss and degradation. The high - energy buffer found in the brain and skeletal muscles is creatine phosphate. By providing a high energy phosphate that is easily accessible and can be utilized to rebuild ATP from ADP, creatinine phosphate slows down the pace at which ATP is depleted. (5) Serum creatinine and uric acid levels are raised in instances of hypothyroidism, both overt and subclinical. Since these criteria are clinically relevant in hypothyroidism, it is important to accurately estimate these biochemical indicators in order to treat patients. Renal impairment brought on by hypothyroidism may be lessened by early detection and treatment of the condition. It is thus essential to regularly evaluate thyroid function. (6)

Nevertheless, there are few clinical trials including hypothyroid participants, and little information is known about the effects of hypothyroidism on human renal function. The objective of this research is to examine if there is a notable alteration in the biochemical renal function parameters that are often used in our everyday medical procedures for both subclinical hypothyroidism and overt hypothyroidism. Additionally, we will explore whether these values are associated with the thyroid hormone profile.

2. Literature Survey

In an observational cross - sectional study, the mean values of serum creatinine, urea, and ACR were significantly increased among untreated patients with primary hypothyroidism, with the decrease in the eGFR, in comparison to healthy control group ($p<0.001$), whereas patients on treatment for hypothyroidism show fall in serum creatinine, serum urea, and ACR level, with increase in eGFR values compared with drug naïve primary hypothyroid patients. ($p<0.0001$). . In addition, the results of eGFR and ACR are significantly correlated with thyroid - stimulating hormone (TSH) values (7).

In a cross - sectional retrospective study, thyroid and kidney function tests were analyzed in 201 patients of whom 120 were subclinical hypothyroidism and 81 patients were overt hypothyroidism. These were compared with 203 age - and sex - matched euthyroid control group. Overt hypothyroid subjects showed significantly raised serum urea, creatinine and uric acid levels as compared to controls but subclinical hypothyroid patients did not showed significant increased levels of serum urea, uric acid and creatinine levels (8)

Thyroid and kidney function tests were analyzed in 47 patients with overt and 77 patients with subclinical hypothyroidism in a cross - sectional study.

These were compared with 120 age - and sex - matched euthyroid controls. The overt hypothyroid subjects showed significantly raised serum urea, creatinine and uric acid levels as compared to controls whereas subclinical hypothyroid patients showed significant increased levels of serum urea and creatinine levels. TSH showed significant positive correlation with creatinine and uric acid values and, fT4 had a negative correlation with uric acid in overt hypothyroidism (9).

The HUNT study conducted by Åsvold et al observed that hypothyroidism, even in its subclinical form, is associated with reduced GFR. They found that mean eGFR was lower in people with subclinical (79.3 mL/ min per 1.73 m2, $p < 0.001$) or overt hypothyroidism (76.5 mL/min per 1.73 m2, $p < 0.001$) compared with people with TSH values in the lower third of the reference range (0.50–1.4 µIU/mL; 83 mL/min per 1.73 m2) (10).

In a hospital - based study conducted by Arora et al, 29 significantly raised serum creatinine values have been reported among patients with hypothyroidism compared with euthyroid controls ($p<0.001$). They observed a group of overt hypothyroid patients ($n = 46$) for 6 weeks with uninterrupted thyroid hormonal replacement and found that posttreatment serum creatinine level lowered significantly compared with pretreatment status ($p = 0.005$) (11).

Montenegro et al observed significant alteration in serum creatinine level among pretreatment and posttreatment condition of hypothyroid patients (1.16 ± 0.04 vs 0.87 ± 0.02 mg/dL, $p<0.05$). This shows the reversible alteration of serum creatinine in primary hypothyroidism (12).

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 indirect effects through paracrine or endocrine mediators, such as insulin - like growth factor type 1 (IGF - 1) and vascular endothelial growth factor (13).

The hypothyroidism - associated rise in serum creatinine may also be of relevance in patients with thyroid carcinoma in which the withdrawal of levothyroxine treatment for total body scan preparation can lead to accumulation of drugs whose metabolism and elimination are primarily renal. (14)

The purpose of our study is to investigate whether there is a significant change in the biochemical renal function parameters that we use in daily practice in subclinical hypothyroidism and overt hypothyroidism and whether these values are correlated with the thyroid hormone profile

3. Methodology

Study design: Descriptive Study

Study setting: Patients attending Justice K. S. Hegde Charitable Hospital, a unit of K. S. Hegde Medical Academy, affiliated to NITTE (Deemed to be University), Derlakatte, Mangaluru with primary hypothyroidism.

Study duration: 1 - 10 - 2022 to 30 - 04 - 2024

Sample size: 62

Sample size calculation: On the basis of study conducted by Saini et al, assuming 5% level of significance, standard deviation of creatinine as 0.04 (from overt hypothyroid group), with estimation error of 0.01, the sample size estimated for the study is 62.

Sample size is estimated using nMaster software version - 2.

Inclusion criteria:
Patients visiting general medicine and endocrinology OPD or admitted patients aged more than 18 years diagnosed with Overt Hypothyroidism at Justice K. S

Hegde Charitable Hospital, a unit of K. S. Hegde Medical Academy, affiliated to NITTE (Deemed to be University), Derlakatte, Mangaluru.

Exclusion criteria:
1) Patients are unable to provide informed consent to the study.
2) Previously diagnosed renal diseases like nephrotic or nephritic syndrome, nephropathy, urinary tract infection, renal stones, chronic kidney disease, acute kidney injury, etc.
3) Under treatment with those drugs that affect renal functions like angiotensin converting enzyme inhibitors/angiotensin receptor blockers, diuretics, NSAID's, allopurinol, steroids, etc.
4) Patients with diabetes, hypertension, known cardiovascular disorder.
5) Patients with acute/chronic infection or inflammation.
6) Patients with malignancy/pregnancy.
7) Patients with history of drugs affecting thyroid hormonal status, like Lithium, Amiodarone, Phenytoin, Carbamazepine, Salicylates, Beta Blockers, Rifampicin, Cytotoxic drugs, etc.
8) Patients with chronic diseases like Tuberculosis, Leprosy, AIDS.

Method of Data Collection:
Patients aged above 18 years visiting general medicine and endocrinology OPD and admitted patients under medicine and endocrinology diagnosed with overt Hypothyroidism at Justice K. S Hegde Charitable Hospital, a unit of K. S. Hegde Medical Academy, affiliated to NITTE (Deemed to be University), Derlakatte, Mangaluru will be selected for the study. After taking informed consent, clinical details of the patients will be noted after thorough examination along with the serum creatinine and TSH values of the patient, which are done as a part of their routine follow up.

Outcome Measures:
1) Estimate Serum Creatinine
2) Estimate Serum TSH

3) Estimate Correlation between Serum Creatinine and Serum TSH.

Statistical Analysis:
Data will be analyzed using Karl Pearson coefficient of correlation.
P<0.05 will be considered as statistically significant
SPSS - statistical software will be used to analyze the data collected (version 20)

4. Results

Age

Table 3.1: Age distribution of patients

	Frequency	Percent
21 - 30 years	4	6.5
31 - 40 years	20	32.3
>40 years	38	61.3
Total	62	100

Most of the patients in the study belonged to more than 40 years (61.3%), while 32.3% of patients were in 31 to 40 years.

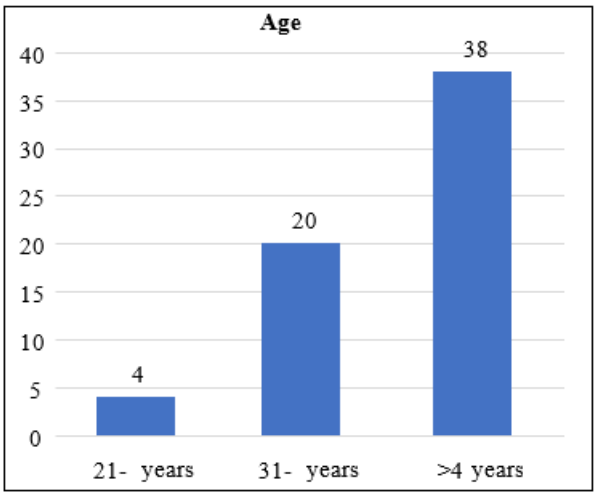

Figure 3.1: Age distribution of patients

The mean age of the patients in the current study was 43.56 years.

Sex

Table 3.3: Sex distribution of patients

	Frequency	Percent
Male	11	17.7
Female	51	82.3
Total	62	100

Most of the patients were females in the study (82.3%)

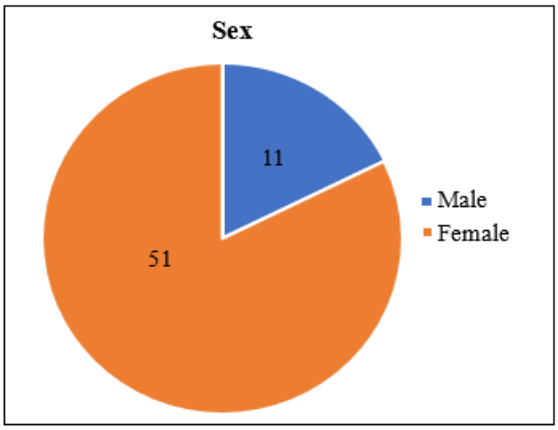

Figure 3.3: Sex distribution of patients

Clinical features

Table 3.4: Distribution of patients as per clinical features

	Frequency	Percent
Diffuse thyroid swelling+	7	11.3
Multiple nodular thyroid swellings+	1	1.6
Nodular swelling in both thyroid+	1	1.6
Nodular swelling in right thyroid+	1	1.6
Nothing significant	52	83.9
Total	62	100

Diffuse thyroid swelling was the most common clinical feature (11.3%)

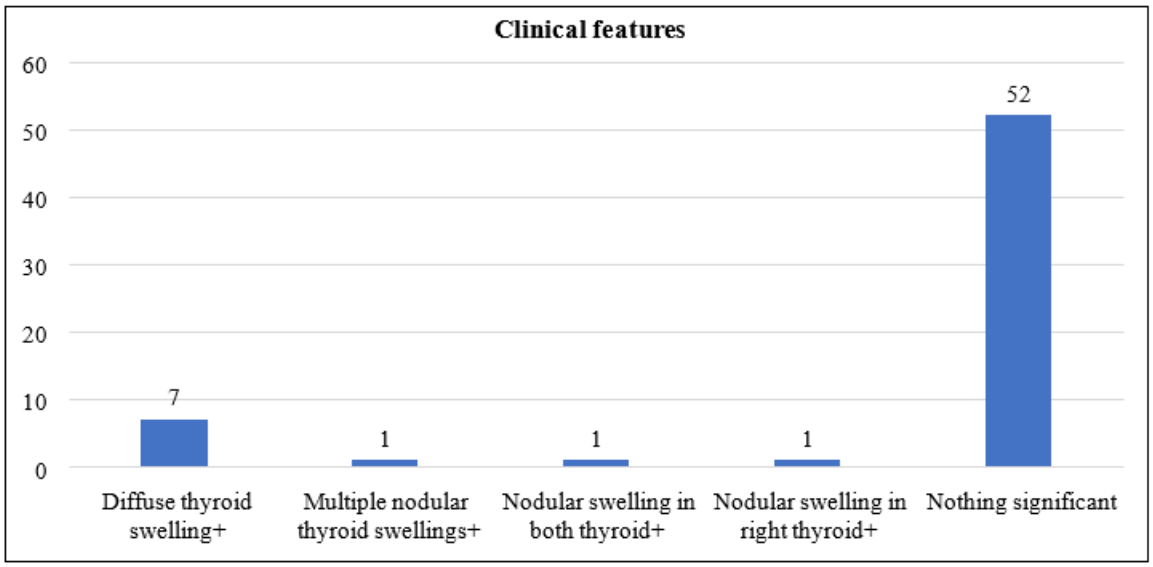

Figure 3.4: Distribution of patients as per clinical features

On/off treatment

Table 3.6: Distribution of patients as per treatment status

	Frequency	Percent
On	37	59.7
Off	25	40.3
Total	62	100

59.7% of the patients were on treatment in the study

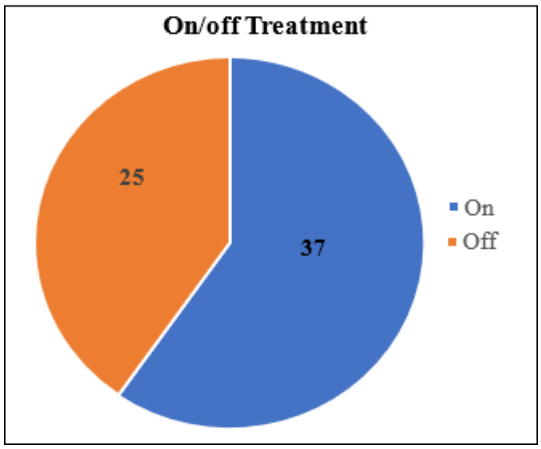

Figure 3.6: Distribution of patients as per treatment status

Biochemical Parameters

Table 3.7: Descriptive statistics of the TSH and kidney functions among the patients

	Mean	Median	Std. Deviation	IQR
TSH (uIU/ml)	9.05	5.92	11.69	4.1725, 8.6925
Creatinine (mg/dl)	0.87	0.9	0.2	0.7, 1
eGFR (ml/min/1.73m2)	85.55	86.5	29.2	59.75, 111.50

The mean TSH, creatinine and eGFR of the patients in the present study were 9.05 uIU/ml, 0.87 mg/dl and 85.55 ml/min/1.73m2.

Overall Correlation between TSH and creatinine and eGFR

Table 3.11: Correlation between TSH and creatinine and eGFR among the patients

	Rho (correlation coefficient)	P value
Creatinine	0.041	0.754
eGFR	0.007	0.957

There was no significant correlation between TSH and creatinine and eGFR

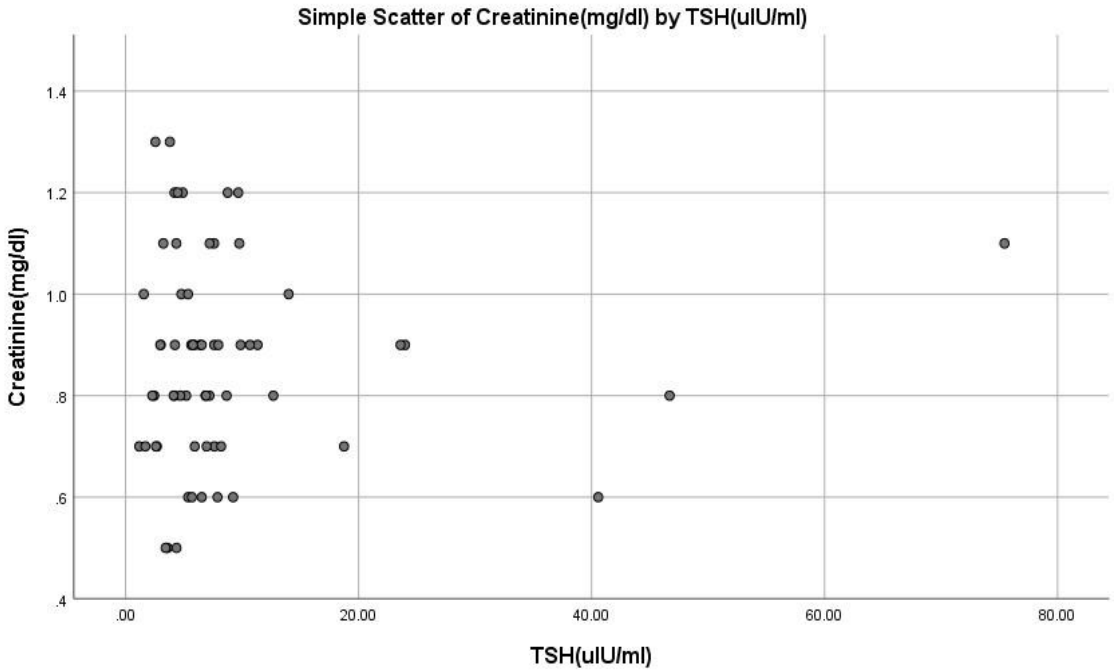

Figure 3.10: Scatter plot between creatinine and TSH

Most values of creatinine in the scatter plot were normal and no correlation with TSH.

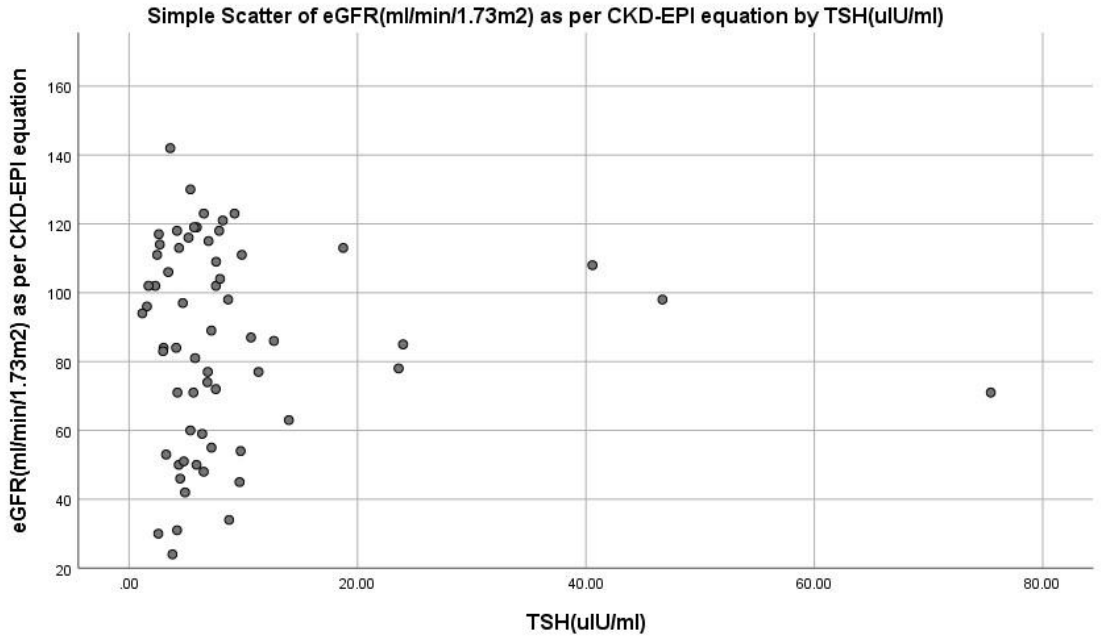

Figure 3.11: Scatter plot between eGFR and TSH Treatment (thyroxin supplementation)

Table 3.14: Correlation between TSH and creatinine and eGFR among the patients according to treatment status

	Rho (correlation coefficient)	P value
On		
Creatinine	0.203	0.227
eGFR	-0.297	0.074
Off		
Creatinine	-0.06	0.775
eGFR	0.004	0.984

As per thyroxin supplementation, there was no significant correlation between TSH and creatinine and eGFR

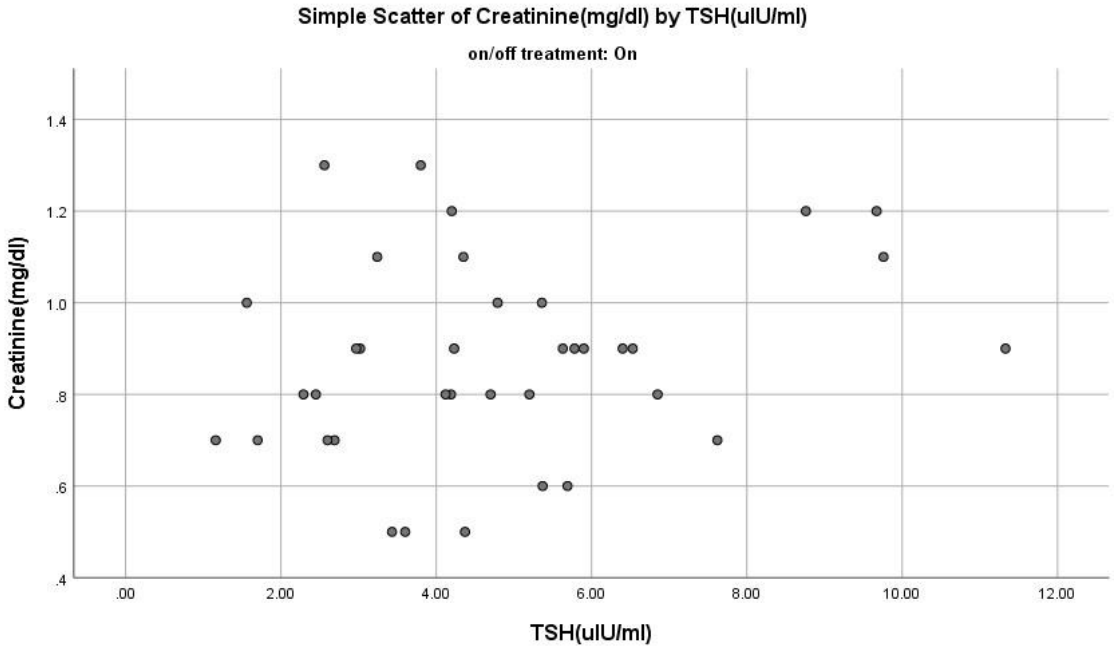

Figure 3.24: Scatter plot between creatinine and TSH among patients who are on treatment.

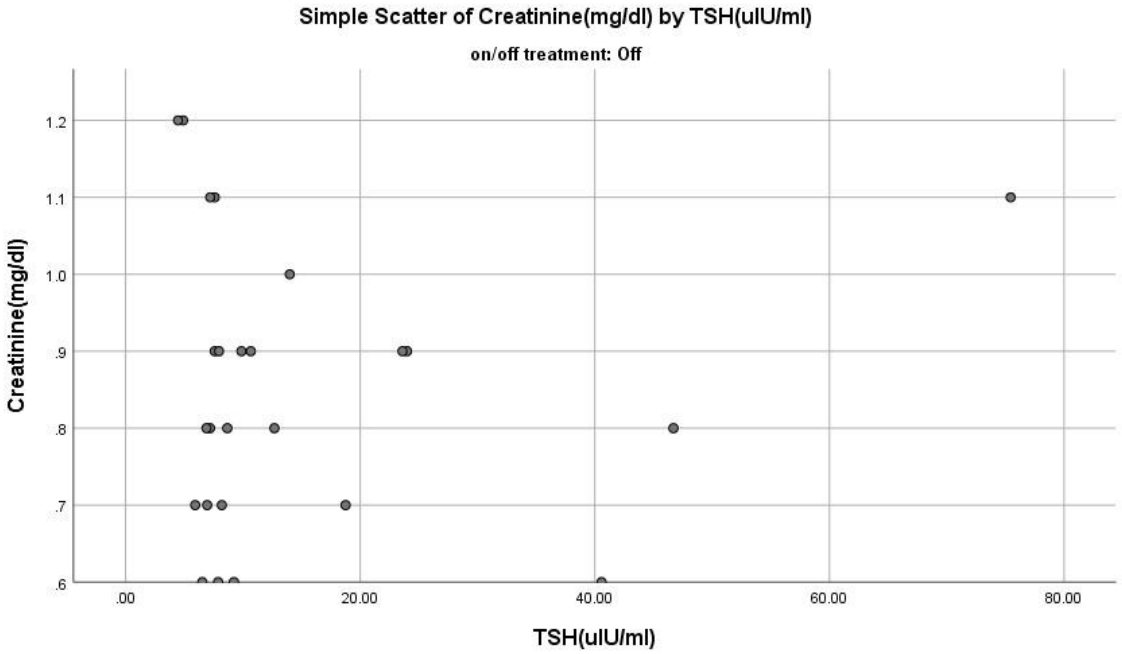

Figure 3.25: Scatter plot between creatinine and TSH among patients who are off treatment

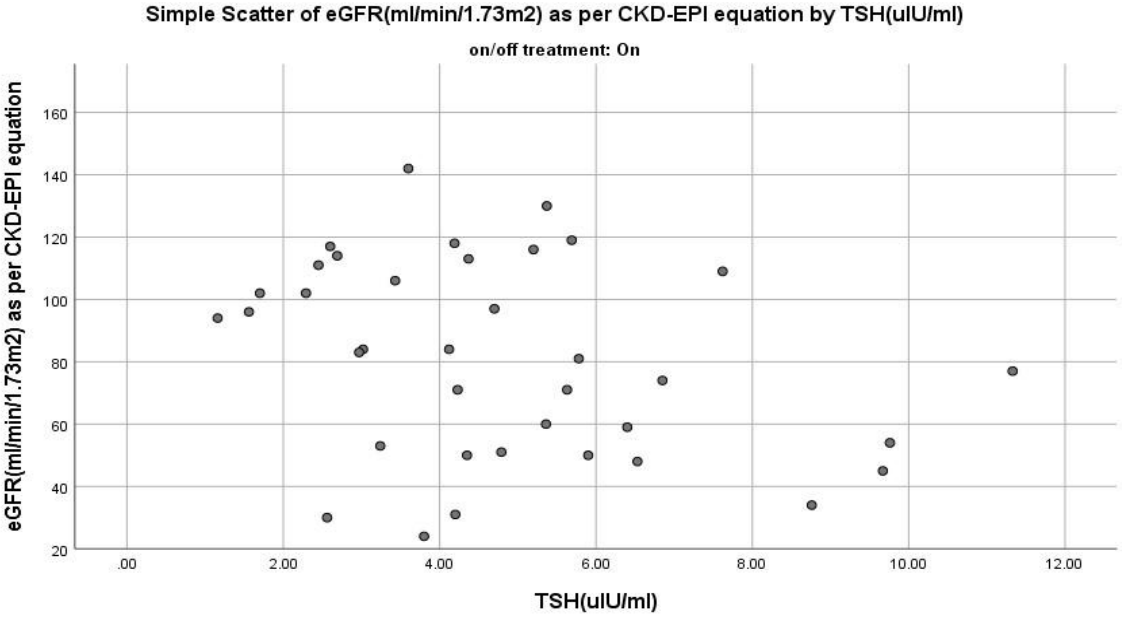

Figure 3.26: Scatter plot between eGFR and TSH among patients who are on treatment

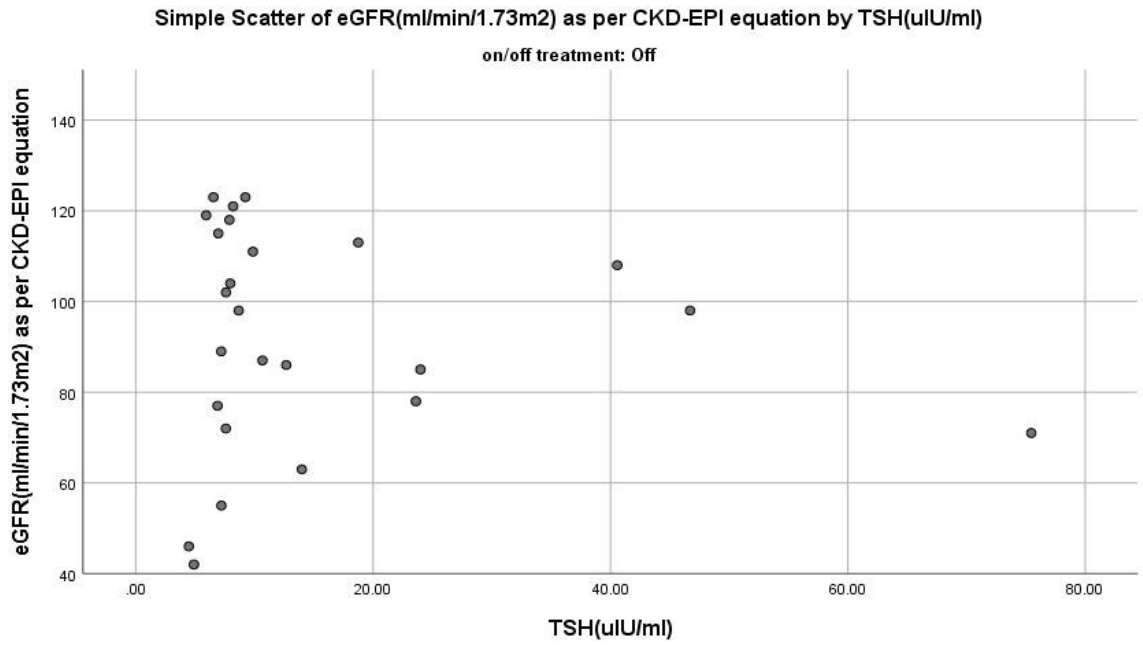

Figure 3.27: Scatter plot between creatinine and eGFR among patients who are off treatment

Sex

Table 3.15: Correlation between TSH and creatinine and eGFR among the patients according to sex

	Rho (correlation coefficient)	P value
Male		
Creatinine	0.065	0.851
eGFR	-0.228	0.501
Female		
Creatinine	0.038	0.789
eGFR	0.042	0.77

As per sex, there was no significant correlation between TSH and creatinine and eGFR

5. Discussion

The present descriptive study determined the effect of TSH on the kidneys by estimating serum creatinine levels. Also, we determined the correlation between serum creatinine and TSH values in overt hypothyroidism.
patients.

Demography:
The current study included those visiting general medicine and endocrinology OPD or admitted patients aged more than 18 years diagnosed with Overt Hypothyroidism in a tertiary referral care hospital in India. We excluded those with renal diseases and those taking the known drugs affecting renal function. The average (in years) was around 40 years.

In a cross - sectional study by **Jaiswal et al.**[57] investigated the serum creatinine values in the patients hypothyroid who enrolled 100 patients in the hypothyroid (50) and euthyroid groups (50). The average age (in years) in both groups was 34.14 and 30. In similar comparative cross - sectional studies, the average age was around 30 - 40 years in **Shrivastava et al.7 (100 patients), Saini et al.**[62] **(244 patients)** and **Eranhikkal et al.**[8] **(140 patients).** In **Nagarajappa K et al.**[63] with a similar study design compared the 40 non - treated hypothyroid patients with 40 controls. The average age (in years) in case and control groups were 35.4 and 37.3. **Marwah et al.**[1] the study comprised 108 patients with an average age (in years) of 44.57. Similarly, **Patil et al.**[6] **(**608 patients), **Hollander et al.**[64] (37 patients with untreated primary hypothyroidism) and **M Kimmel et al.**[65] (9 hypothyroid) included patients with an average age above 40 years. **Saha et al.**[60] included 88 hypothyroid patients and 44 controls. They were between 25 and 55 years.

In case - control studies of **Arora et al.**[58] **(**176 patients) and **P Torkian et al.**[66] (239 patients) the average age (in years) was 40 - 50 years. **Sayari et al.**[67] performed a case - control study on children between 2 and 14 years. This study included 107 children. The average age (in years) was 7.49 and 6.69 in the SCH and ET groups.

Naguib et al.[61] involved 41 untreated hypothyroid patients. Patients in this prospective cohort study have an average age (in years) of 38.

In the current study, over 80% were females. Over 90% of patients were females in **Jaiswal et al.**[57] and **Shrivatsava et al.**[7]. **Naguib et al.**[61] study has majority of females with 80.4%. **Hollander et al.**[64]study has females over 73%. In **Saha et al.**[60] and **Patil et al.6** study females were above 60%. Above 50% females were present in **Marwah et al.**[1] and **Eranhikkal et al.**[8] study. In **Nagarajappa K et al.**[63] study, females were 80% in the hypothyroid group and 75% in the euthyroid group. **Arora et al.**[58] study have 72.5% females in the hypothyroid group and 68.7% in the euthyroid group. In **P Torkian et al.**[66] analysis female population in SCH and ET groups were 52% and 50.4%, respectively. **Akagunduz et al.5**[9] evaluated that 85.5% of females in both hypothyroid and euthyroid groups. In **Saini et al.**[62] study, females were 80.22% in the hypothyroid group and 78% in the euthyroid group. In contrast, **M Kimmel et al.**[65] study has majority of males with 66.6%. In **Sayari et al.**[67] study, males were 52% in SCH group and 58% in healthy group. *Except for* **M Kimmel et al.6**[5] **and Sayari et al.**[67], gender distribution was similar.

Treatment pattern:

Around 60% of patients in our study were on hypothyroidism treatment. In **Arora et al.**[58] study, 57.5% of patients took thyroxine replacement treatment. In **Saha et al.**[60] investigation, the number of hypothyroid patients under management was 40 over 2 months. In **Naguib et al.**[61] study treatment was performed on all hypothyroid patients. In **M Kimmel et al.**[65] evaluation, all 9 patients underwent Ltriiodothyronine replacement treatment. In **Hollander et al.6**[4] analysis treatment was given for all hypothyroid patients.

Parameters measured:

The mean TSH, Cr, and eGFR among the patients in our study were 9, 0.87, and 85.5.

In **Jaiswal et al.**[57] study the average creatinine in hypothyroid and ET groups were 0.92 and 0.79. In hypothyroid and healthy groups of **Marwah et al.1** showed the average TSH was 8.00 and 2.20. While the creatinine in hypothyroid group was higher than the control group (1.52 vs 0.62). In **Shrivatsava et al.**[7] study the average TSH values of hypothyroid and healthy groups **(**32.02 vs 2.25). **Eranhikkal et al.8** study revealed that an average TSH was higher in hypothyroid group than normal group (8.83 vs 1.87). Likewise average creatinine was also higher in hypothyroid group than control group (2.16 vs 0.75). In **A H Khan et al.**[68] investigation the average serum creatinine in OHT group was higher than ET group (1.38 vs 1.01). In **Nagarajappa K et al.**[63] analysis the average value of TSH in hypothyroid group of was higher than (28.58 vs 2.39) healthy group. The average of creatinine in hypothyroid group was higher than healthy group (1.8 vs 0.86). **Sayari et al.**[67] study shows that average value of TSH was higher in OHT group when related to ET group (8.94 vs 3.0). The average creatinine shows small variation in OHT and ET group (0.79 vs 0.63). In **Arora et al.**[58] analysis the average TSH of hypothyroid group was higher than euthyroid group (36.44 vs 2.57). The average creatinine of hypothyroid and euthyroid groups were 0.85 and 0.71 respectively. After treatment the TSH reduced to 3.45 and also the creatinine was 0.69. In **P Torkian et al.**[66] study the average TSH was 5.4 in SCH group which was higher than ET group of 1.4.

Likewise, creatinine was also higher in the OHT group than the ET group (1.20 vs.0.98). In **Akagunduz et al.**[59] study the average values of creatinine in healthy group was lesser than OHT group (0.7 vs 0.8). Meanwhile, the SCH group has 0.7 with no notable difference. The average TSH in the OHT group was higher than the ET group (7.81 vs 2.52). In **Saha et al.**[60] investigation, the average TSH and creatinine in primary hypothyroid patients on drug naïve were 18.74 and 1.18, and in patients under treatment, were 3.76 and 0.89. The normal group's TSH and creatinine average values were 1.54 and 0.79, respectively. In **Naguib et al.**[61] study before and after the treatment, the average TSH was 11.1 and 4.3 and creatinine was 2.3 and 0.97, and eGFR was 67 and 79, respectively. After treatment, creatinine was decreased, and eGFR was increased. **Saini et al.**[62] analysis have an average creatinine value of 0.85 in the control group; it was higher in both SCH (1.07) and OHT groups (1.11). The average TSH in control group was 2.42. While it was higher in SCH group (7.61) and highest in OHT group (42.30). Average TSH shows the highest value in the OHT group (88.84) of the Patil et al. (7) study when related to the SCH group (8.26) and control group (2.51). The average creatinine in the OHT group was (1.05), slightly higher than the SCH group (0.91) and control groups (0.85). The average eGFR was lesser in the OHT group than the other two groups. In **M Kimmel et al.**[65] evaluation, the average TSH in hypothyroid patients before treatment and after treatment was (39.5 vs 0.24). The creatinine average value decreased from 1.2 to 0.9. On the other hand, eGFR was increased from 68 to 93. In **Hollander et al.**[64] analysis the average TSH and creatinine were decreased after the treatment (99.1 vs 4.6) and (90 vs 77). While the eGFR increased after treatment (70 vs 83).

In **Jaiswal et al.**[57] study, the TSH shows a positive correlation with creatinine (r= 0.16). In **Marwah et al.**[1] analysis the creatinine level (r = 0.082) did not significantly correlate with hypothyroidism. In **Shrivatsava et al.**[7] shows a positive correlation with creatinine (r= 0.16). While TSH shows a negative correlation with eGFR values (r= - 0.15), which was also not statistically relevant. Correlation result of **Eranhikkal et al.**[8] study with TSH and creatinine was positive (r=0.45). In **Sayari et al.**[67] analysis, the creatinine (r= 0.048) shows a positive correlation with TSH in the OHT group, but it was weak. **Arora et al.**[58] study showed positive correlation of TSH with creatinine (r= 0.076). With TSH and creatinine **P Torkian et al.6**[6] study shows positive correlation in OHT group (r= 0.302). Analysis by **Akagunduz et al.**[59] on TSH with creatinine revealed negative correlation (r= - 0.041) in OHT group and positive correlation (r= 0.115) in SCH group. **Saha et al.**[60] investigation on normal and primary hypothyroid patients revealed that TSH has positively correlated with serum creatinine (r= 0.21 and r= 0.65) and negative correlation with CKD - EPI e - GFR (r= –0.11 and r= –0.66). Correlation with TSH in **Naguib et al.**[61] study showed positive with creatinine and negative with eGFR. **Saini et al.**[62] study shows positive correlation of TSH with creatinine in SCH group (r= 0.042) and in OHT group (r=0.342). In **Patil et al.**[6] study the OHT group shows positive correlation of serum creatinine (r=0.54) with TSH. Whereas the correlation was inverse among e - GFR and TSH.

The pattern of variation i. e. TSH positively correlated with creatinine in hypothyroidism is similar across the studies. However, there was no significant correlation between TSH and creatinine and eGFR observed in our study.

6. Limitations

- Since the current study was cross - sectional, the causality of the derangement in kidney function parameters was not established.
- This study has over three - fourth of patients as females, hence the generalizability of results to male hypothyroidism is limited.
- Since the present study was done in a single referral setting, generalizability to others is limited.
- The pattern of change in parameters before and after initiation of treatment longitudinally is not estimated

7. Conclusion

In the present study, around 10% had diffuse thyroid swelling, 61% had Primary, 23% had subclinical, and 16% with overt hypothyroidism. We concluded that among the hypothyroidism patients, TSH was positively correlated with creatinine. However, the differentials were not significant. Similar non- significance was estimated with eGFR. The findings aids in providing insights into how the thyroid gland and kidney interact, demonstrating the impact of hypothyroidism on the kidneys' ability to function. We recommend conducting further studies to estimate the effect of various thyroid factors on kidney function tests and the long - term impact of hypothyroidism treatment on kidney health.

8. Future Scope

1) Longitudinal Analysis: The current study appears to be cross - sectional. Future studies could track changes in TSH, creatinine, and eGFR over time in patients with different types of hypothyroidism.
2) Diverse Populations: Expand the study to include a more diverse demographic, especially given the predominance of female patients in this study.
3) Intervention Studies: Explore how different interventions, such as varying dosages of thyroxin or other treatments, affect kidney function markers.
4) Additional Biomarkers: Investigate other potential biomarkers that might correlate with thyroid function and kidney health.
5) Mechanistic Studies: Research the underlying mechanisms linking thyroid function to kidney health, especially given the lack of significant correlation found in this study.

These areas could provide more comprehensive insights into the relationship between hypothyroidism and renal function.

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