Original research article

Study of evaluation of renal function in patients with subclinical and overt hypothyroidism and to correlate these values with the thyroid profile of the patients.

Alviya Nazneen[1], Farhan Usmani[2]

[1]Tutor, Department of Biochemistry, Patna Medical College and Hospital, Patna, Bihar, India.
[2]Associate Professor,Department of Biochemistry, Patna Medical College and Hospital, Patna, Bihar, India

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Abstract

Aim: to analyse the changes in biochemical markers of renal function in patients with subclinical and overt hypothyroidism and to correlate these values with the thyroid profile of the patients

Methods: The present analytical cross-sectional was conducted in the Department of Biochemistry, Patna. Medical College and Hospital, Patna, Bihar, India from April 2019 to November 2019. The study includes 100 subclinical hypothyroid patients and 100 overt hypothyroidism (OHT) cases, 200 euthyroid patients (ET). Thyroid function test, serum creatinine and eGFR were measured in all the three groups.

Results: There is no significance change in age group 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 ($p < 0.05$). Patients suffering from OHT have the highest percentage of increase in serum creatinine in comparison to other two groups. 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.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 ($p>0.05$). There is negative significant correlations of creatinine with Free T_4 ($p< 0.05$) and the positive correlations of eGFR with Free T4 ($p< 0.05$). There is poor correlation of creatinine and eGFR with Free T3 ($p>0.05$).

Conclusions: the 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.

Keywords: Overt hypothyroidism, Renal function tests, Subclinical hypothyroidism, Thyroid function tests

Introduction

Thyroid hormones affect 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. The direct renal effects are mediated by the effect of thyroid hormones on glomerular filtration rate (GFR). Thyroid dysfunction affects renal physiology and development; whereas kidney disease could result in thyroid dysfunction.[1]

**Correspondence*
Dr. Alviya Nazneen
Tutor, Department of Biochemistry, Patna Medical College and Hospital, Patna, Bihar, India.
E-mail: alviyanazeen1982@gmail.com

Subclinical hypothyroidism (SCH) is defined as an elevated serum thyroid-stimulating hormone (TSH) above the defined upper limit of the reference range, with a serum free thyroxine (fT4) within the reference range. SCH cases present with few or no symptoms or signs of thyroid dysfunction and thus by its very nature SCH is a laboratory diagnosis. The prevalence of SCH in the United States adult population is 4-8.5%.[2] Various epidemiological studies in India show a prevalence rate of SCH varying between 9% and 11.4%. The progression to overt hypothyroidism (OHT) is approximately 2-5% per year. Due to its asymptomatic nature, the SCH cases are not detected clinically and also its relation to the kidney function is not well established.[3] There is paucity of data in Indian population. Patients with SCH report more symptoms

than Euthyroid individuals, but fewer symptoms than overtly hypothyroid participants. There is controversy in management of patients with a serum TSH level <10μIU/L. There is inadequate literature in this area and statements may often be an expert panel opinion rather than strictly evidence based. There is a well-known interaction between thyroid and kidney functions. Thyroid hormones are involved in the growth, development and physiology of the kidney.[4]

Serum creatinine is elevated and glomerular filtration rate (GFR) values are reversibly reduced in overt hypothyroid patients than in euthyroid subjects.[5-7] Long standing hypothyroidism can cause significant changes in renal function such as decrease in sodium re-absorption in the proximal tubules, impairment in the concentrating and diluting capacities of the distal tubules, a decrease in the urinary urate excretion and a decrease in the renal blood flow and glomerular filtration rate (GFR). These renal abnormalities occur because the deficiency of thyroid hormones (TH) reduces the cardiac output leading to generalized hypodynamic state of the circulatory system. Hypothyroidism also results in increased glomerular capillary permeability of proteins; the consequent proteinuria often precedes the reduction in GFR in hypothyroidism.[8]

Very few studies have reported the effect of hypothyroidism on renal function tests especially creatinine. Some studies have also reported hyperuricemia leading to gouts in hypothyroid subjects. Not much data is available on the impact of hypothyroidism on renal function tests in this region. This study was therefore planned to analyse the changes in biochemical markers of renal function in patients with subclinical and overt hypothyroidism and to correlate these values with the thyroid profile of the patients

Materials and Methods

The present analytical cross-sectional was conducted in the Department of Biochemistry, Patna Medical College and Hospital, Patna, Bihar, India from April 2019 to November 2019. The study includes 100 subclinical hypothyroid patients and 100 overt hypothyroidism (OHT) cases, 200 euthyroid patients (ET).

The study protocol was reviewed by the Ethical Committee of the Hospital and granted ethical clearance.

Inclusion criteria

20 to 50 years old subjects were enrolled in this study. The subjects were divided in three different groups after laboratory investigations:

Group 1: 100 patients include in subclinical hypothyroidism (SCH): Subjects with normal Free T_3 and Free $T_4$and increased TSH.

Group 2: 100 patients include in overt hypothyroid group (OHT): Subjects having low Free T_3 and low Free T_4andincreased TSH.

Group 3: 200 patients include in euthyroid group (ET): Subjects with normal TSH, Free T_3 and Free T_4

Exclusion criteria

- Participants with the following conditions were excluded:
- Subjects taking drugs which can alter thyroid hormones level.
- Patients with kidney diseases.
- Patients with liver diseases.
- Patients suffering from metabolic syndrome and chronic inflammatory diseases.
- Patients who refused to give consent for the study.

Methodology

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.

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. Serum creatinine was analyzed by the Enzymatic Kinase method in Erba 200 fully automated analyzer in Central Clinical Biochemistry Laboratory.

eGFR was calculated by Modification of Diet in Renal Disease(MDRD) formula.[9]

The laboratory reference range of TSH, Free T_3, FreeT_4, serum creatinine and eGFR were as below:

- TSH - 0.55-4.78 micro IU/ml. 2. Free T_3- 2.3-4.2 pg/ml.
- Free T_4 -0.89-1.76 ng/dl.
- Serum. Creatinine- 0.6-1.3 mg/dl in women and 0.7-
- 1.4 mg/dl in men.
- eGFR –90-120 ml/min

Statistical analysis

The recorded data was compiled entered in a spreadsheet computer program (Microsoft Excel 2010) and then exported to data editor page of SPSS version 20 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics included computation of percentages, means and standard deviations.

Results

Table 1: Comparison of demographic variables among the three groups

Variables	Euthyroid group (Mean+SD) N=200	SCH group (Mean+ SD) N=100	OHT group (Mean+ SD) N=100
Age (Yrs)	34.21+6.45	32.85+6.88	31.70+6.71
Male	125	55	54
Female	75	45	46

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)	2.45+ 1.51	16.89+7.92	26.22+14.86	<0.05
Free T3 (pg/mL)	3.16+ 1.26	3.31+0.41	1.18+0.69	<0.05
Free T4 (ng/dL)	1.47+0.20	1.52+0.19	0.39+0.28	<0.05
Creatinine (mg/dl)	0.81+0.19*	0.93+0.21*	1.11+0.25*	<0.05
eGFR (ml/min/m^2)	99.95+16.32*	86.87+13.75*	74.80+15.78*	<0.05

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

Serum Creatinine	Euthyroid group	SCH group	OHT group
Normal range*	182(91%)	88 (88%)	75 (75%)
Higher range	18 (9%)	12(12%)	25 (25%)
Total	**200**	**100**	**100**

Table 4: Comparison of eGFR among the three groups

eGFR	Euthyroid group	SCH group	OHT group
90-120(ml/min/m^2)	140(70%)	64(64%)	30(28%)
< 90 (ml/min/m^2)	60 (30%)	36(36%)	70(70%)
Total	**200**	**100**	**100**

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

Serum Creatinine Parameter	r value	"p" value	Parameter	eGFR r value	"p" value
TSH	0.31	0.011*	TSH	-0.33	0.007*
Free T 3	-0.19	0.15	Free T3	0.15	0.24
Free T 4	0.04	0.32	Free T4	0.11	0.88

Table 6: Correlation of serum creatinine and eGFR with Thyroid profile in the OHT group:

Serum Creatinine Parameter	r value	"p" value	Parameter	eGFR r value	"p" value
TSH	0.44	0.003*	TSH	-0.41	<0.0005*
Free T 3	-0.04	0.916	Free T3	0.16	0.36
Free T 4	-0.31	0.01	Free T4	0.29	0.02*

Discussion

Our study showed that there was no significant change in the age among the three groups (p=0.31) [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 13% higher than SCH group and mean eGFR of OHT group was 11% 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.[5] observed that OHT and SCH patients showed significant raise in serum creatinine as compared to the control group. Jia D et al.[10] also suggested that a higher level of serum creatinine was found in OHT group as compared to SCHm group and control group. Meenakshi G[11] 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.[12–17] 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 et al.[18] 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.

Our Study revealed the highest percentage of patients having high serum creatinine level(25%) and low eGFR (70%) 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]. 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),[19] Norway (n = 29480)[20] and Korea (n = 2284)[21] which are similar findings with our study. Woodward A. et al.[22] concluded that eGFR of the hypothyroid, euthyroid patients were 64 mL/min/1.73m^{2}and 77 mL/min/1.73m^2 respectively.

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.

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