10.5005/jp-journals-10054-0046

ORIGINAL ARTICLE

A Study on Renal Function Status of Patients with Hypothyroidism attending a Tertiary Care Hospital in North Bengal

[1]Shubhrajit Saha, [2]Indrajit Nath, [3]Mita S Das, [4]Samarpita Mukherjee

ABSTRACT

Introduction: Thyroid hormones influence renal development, renal hemodynamics, glomerular filtration rate (GFR), electrolytes, and water homeostasis. The location of the present study is situated at Darjeeling district of West Bengal, which is a part of sub-Himalayan Terai regions with high prevalence of thyroid dysfunctions, especially hypothyroidism. The objective of this observational cross-sectional study is to substantiate the effects of thyroid hormonal status on kidney by estimating serum creatinine, serum urea, albumin-to-creatinine ratio (ACR), and estimated GFR (eGFR) among drug naïve primary hypothyroid patients, hypothyroid patients under treatment for more than 2 months, and age- and sex-matched control group.

Materials and methods: The study includes 48 patients with primary hypothyroidism in a drug naïve status, 40 hypothyroid patients under treatment, and 44 healthy control in the age group of 25 to 55 years. The collected blood and urine samples from the study population have been estimated for the study parameters. Both Chronic Kidney Disease Epidemiology (CKD-EPI) equation and four-variable Modification of Diet in Renal Disease (MDRD) Study equation were used to calculate eGFR.

Results: The mean values of serum creatinine, urea, and ACR are 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 ($p < 0.001$). In addition, the results of eGFR and ACR are significantly correlated with thyroid-stimulating hormone (TSH) values.

Conclusion: Statistically significant alteration in renal function parameters is associated with untreated primary hypothyroidism. Moreover, with the initiation of the treatment for the same can cause reversal of the altered status of renal function.

Keywords: Albumin-to-creatinine ratio, Estimated glomerular filtration rate, Hypothyroidism, Microalbumin, Renal function.

How to cite this article: Saha S, Nath I, Das MS, Mukherjee S. A Study on Renal Function Status of Patients with Hypothyroidism attending a Tertiary Care Hospital in North Bengal. Indian J Med Biochem 2018;22(1):10-17.

Source of support: Nil

Conflict of interest: None

[1,4]Resident, [2]Assistant Professor, [3]Professor

[1-4]Department of Biochemistry, North Bengal Medical College & Hospital, Siliguri, West Bengal, India

Corresponding Author: Indrajit Nath, Assistant Professor Department of Biochemistry, North Bengal Medical College & Hospital, Siliguri, West Bengal, India, Phone: +919474576468 e-mail: shubhrajit87@gmail.com

INTRODUCTION

The interplay between thyroid gland and the kidney in each other's functions is known for ages.[1] The hormones from thyroid gland influence the functions of kidney, both during embryonic development and in the mature condition. It can be directly affected by glomerular function, tubular secretory and absorptive capacities, electrolyte, and water homeostasis, or in partly mediated by thyroid hormone-induced cardiovascular changes. As a consequence, in both hypo- and hyperfunctioning thyroid gland, there are alterations in clinically important renal parameters, such as GFR, urinary ACR, and markers of tubular function.[2,3] Hypothyroidism is associated with reduction in GFR and increase in serum creatinine in more than half of the adults, even in subclinical hypothyroidism cases. There is also prominent hyponatremia. These changes normalize with onset of levothyroxine therapy.[4]

The prevalence and pattern of thyroid disorders depends on sex, age, ethnic, and geographical factors and especially on iodine intake.[5] Normally daily requirement of iodine is met by a well-balanced diet and drinking water except in hilly areas and Terai regions.[6] In such regions like sub-Himalayan Terai regions, for altered geographical scenario, even supplemented iodine may not be sufficient to fulfil the need of the residing population.[7,8] Thus the prevalence of thyroid dysfunctions, especially hypothyroidism, is very high here.[9]

In light of the above facts, the present study attempts to correlate the effects of thyroid hormones on renal functions more precisely in a population with greater risk of developing hypothyroidism, i.e., in Darjeeling District of West Bengal. In this institution-based observational study, an attempt has been made to explore the alterations in renal function parameters, namely, serum creatinine, serum urea, urinary ACR, and eGFR among drug naïve primary hypothyroid patients, hypothyroid patients under treatment for more than 2 months, and age- and

sex-matched control group, and also to correlate renal function parameters with serum TSH and serum-free thyroid (free T4) values among patients with primary hypothyroidism.

The observation of this study may help to take necessary steps in patients with thyroid dysfunction to prevent premature development of nephropathy and can also make the clinicians to think about thyroid dysfunction in patients with unexplained abnormal renal function.

STUDY METHODOLOGY

This institution-based observational study with mixed design[10] has been conducted over a period of 1 year (April 2015 to March 2016) at North Bengal Medical College and Hospital. Study population has been chosen from the patients referred to the laboratory of Department of Biochemistry for routine tests and thyroid profile. Apparently, healthy individuals of both male and female, without any previously known disease condition or drug history in the age group of 25 to 55 years have been selected for the study. In this process, patients having the following conditions have been excluded from the study.

Exclusion Criteria

- Hypertension
- Previously diagnosed cardiovascular disorder
- Frank diabetes and impaired glucose tolerance
- Acute or chronic infection and inflammation
- Previously diagnosed renal diseases like nephrotic or nephritic syndrome, nephropathy, urinary tract infection, renal stones, etc.
- Chronic diseases like tuberculosis, leprosy, acquired immunodeficiency syndrome
- Any autoimmune disorders like rheumatoid arthritis, systemic lupus erythematosus, etc.
- Other endocrine dysfunctions like Cushing syndrome, acromegaly, etc.
- Thyroid dysfunction arising secondary to pituitary or hypothalamus pathology, i.e., secondary hypothyroidism and hyperthyroidism
- Under treatment with those drugs that affect renal functions like angiotensin converting enzyme inhibitors/angiotensin receptor blockers, diuretics, allopurinol, steroids, etc.
- History of drugs affecting thyroid hormonal status, e.g., Li, amiodarone, phenytoin, carbamazepine, salicylates, beta blockers, rifampicin, cytotoxic drugs, etc.
- Malignancy
- Pregnancy

Within the period of 1 year, among 132 individuals included in this study, 44 individuals are considered as control and rest of the people are categorized into two groups:

1. Newly diagnosed drug naïve primary hypothyroid patients (n = 48)
2. Primary hypothyroid individuals under treatment for more than 2 months (n = 40)

For this purpose normal reference range of thyroid hormones has been considered as follows: free T4 0.8 to 2.5 ng/dL, TSH 0.4 to 4.2 μIU/mL. Individuals are considered as in hypothyroid state if TSH >4.2 μIU/mL.[11]

After having proper consent, using semi-structure questionnaires the particulars of participants, including height, weight, family history, etc., are taken along with blood and urine samples for the study. The values of the parameters under study, viz., thyroid hormonal status (serum TSH and free T4), serum creatinine, serum urea, and eGFR and ACR values have been collected and sorted. Estimated GFR has been calculated by four-variable MDRD study equation and the CKD-EPI equation. These equations are the most widely used IDMS traceable equations for estimating GFR in patients more than 18 years and over. Both the equations include variables for age, gender, and race and have been proven superior to Cockcroft Gault creatinine clearance equation.[12-14] Random urine samples are processed to measure urine microalbumin and urinary creatinine, to determine ACR.

Four-variable MDRD Study Equation[12]

$$\text{GFR} = 175 \times (\text{sCr} - 1.154) \times (\text{age} - 0.203) \times (0.742 \text{ if female})$$

where sCr is serum creatinine in mg/dL.

CKD-EPI eGFR Calculator[13]

$$\text{GFR} = 141 \times \min(\text{sCr}/\kappa, 1)\alpha \times \max(\text{sCr}/\kappa, 1) - 1.209 \times 0.993 \times \text{age} \times 1.018 \text{ (if female)} \times 1.159 \text{ (if black)}$$

where sCr is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of sCr/κ or 1, and max indicates the maximum of sCr/κ or 1.

RESULTS

Data collected from 132 individuals are processed and analyzed with the help of statistical software Statistical Package for the Social Sciences (version 20) and Microsoft Office Excel 2010. In the total study population, 25 to 34 years age group consists of 44.67% population, 30.67% fall into 35 to 44 years age group, and the rest into 45 to 55 years age group. About 34% of the studied individuals are males and 66% of them are females. Using chi-square test, it was found that the population with thyroid disorders (total 88 individuals out of 132) is having a significant female preponderance in the study ($p < 0.05$).

The control group is having TSH mean value in normal range, i.e., 1.54 ± 1.16 μIU/mL with the drug naïve primary hypothyroid patients having mean TSH 18.54 ± 9.29 μIU/mL and primary hypothyroid patients on treatment having 3.76 ± 1.61 μIU/mL. The descriptive statistical data of other study parameters are arranged in Table 1.

Using the one-way analysis of variance test, it has been seen that there are overall differences in mean values of study parameters, like serum creatinine, serum urea, ACR, and eGFR, in the chosen study groups. Further *post hoc* tests with Bonferroni correction has been done to isolate which group specifically differed from the others and how much significant is that, regarding a specific parameter (Table 2).

Attaining that there are alterations in renal function in various study groups, an attempt has been made to find possible association between serum TSH and free T4 values with renal function parameters among control group, patients with primary hypothyroidism and primary hyperthyroidism as a whole, and by Pearson's correlation analysis (Tables 3 and 4).

Table 1: Descriptive statistics of study parameters

	Control group (mean ± SD)	*Drug naïve primary hypothyroid patients (mean ± SD)*	*Primary hypothyroid patients on treatment (mean ± SD)*
No. of cases	44	48	40
TSH (μIU/mL)	1.54 ± 1.16	18.74 ± 9.29	3.76 ± 1.61
Free T4 (ng/dL)	1.29 ± 0.17	0.78 ± 0.23	1.25 ± 0.19
Serum creatinine (mg/dL)	0.79 ± 0.09	1.18 ± 0.13	0.89 ± 0.11
Serum urea (mg/dL)	18.31 ± 2.44	24.25 ± 6.79	16.66 ± 3.4
CKD-EPI eGFR (mL/min per 1.73 m^2 body surface area)	103.53 ± 5.29	66.06 ± 9.3	92.38 ± 11.62
MDRD eGFR (mL/min per 1.73 m^2 body surface area)	91.32 ± 4.83	60.29 ± 7.88	81.93 ± 10.74
ACR (mg/gm)	24.21 ± 3.43	115.9 ± 30.94	46.96 ± 17.24

SD: Standard deviation

Table 2: Significance (p-value) of various study parameters by *post hoc* analysis with Bonferroni correction

Post hoc test with Bonferroni correction	*Serum creatinine*	*Serum urea*	*CKD-EPI eGFR*	*MDRD eGFR*	*ACR*
Control ↔ drug naïve primary hypothyroid	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
Control ↔ primary hypothyroid on treatment	<0.001*	1	<0.001*	<0.001*	<0.001*
Drug naïve primary hypothyroid ↔ Primary hypothyroid on treatment	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

*Significance at the level of p < 0.001.

Table 3: Correlation analysis of serum TSH with renal function parameters

		Control group (n = 44)		*Patients with primary hypothyroidism (n = 88)*	
	Parameters correlated	*r-value*	*Pearson's correlation significance*	*r-value*	*Pearson's correlation significance*
Thyroid-stimulating hormone	Serum creatinine	0.211	0.23	0.655*	<0.001
	Serum urea	–0.272	0.12	0.487*	<0.001
	CKD-EPI eGFR	–0.118	0.51	–0.668*	<0.001
	MDRD eGFR	0.001	0.99	–0.648*	<0.001
	ACR	0.247	0.16	0.829*	<0.001

r: Pearson correlation coefficient; *Significance at the level of p < 0.001; **Significance at the level of p < 0.05

Table 4: Correlation analysis of serum free T4 with renal function parameters

		Control group (n = 44)		*Patients with primary hypothyroidism (n = 88)*	
	Parameters correlated	*r-value*	*Pearson's correlation significance*	*r-value*	*Pearson's correlation significance*
Free T4	Serum creatinine	–0.053	0.767	–0.620*	<0.001
	Serum urea	–0.059	0.741	–0.484*	<0.001
	CKD-EPI eGFR	–0.258	0.141	0.639*	<0.001
	MDRD eGFR	–0.146	0.41	0.621*	<0.001
	ACR	–0.7	0.7	–0.680*	<0.001

r: Pearson correlation coefficient; *Significance at the level of p < 0.001; **Significance at the level of p < 0.05

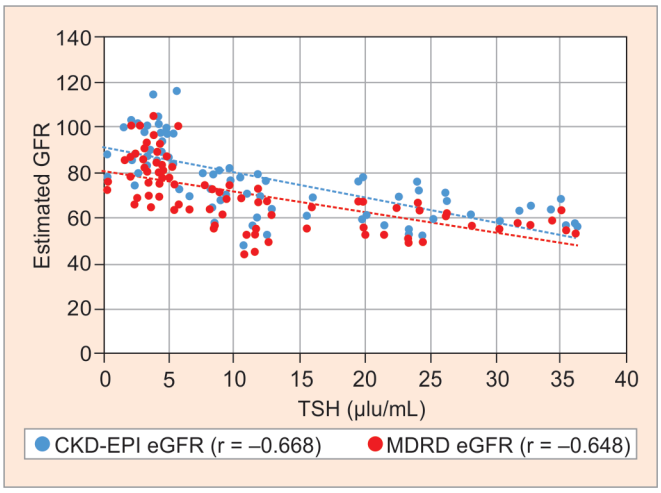
Pearson correlation analysis shows that serum creatinine, serum urea, and urinary ACR are positively correlated with serum TSH value among patients with primary hypothyroidism (n = 88) regardless of the treatment status. Moreover, eGFR values are negatively correlated with serum TSH values among them.

Regarding serum free T4 values, serum creatinine, serum urea, and ACR are negatively correlated with it, among patients with primary hypothyroidism (n = 88) regardless of the treatment status. Here the eGFR values are positively correlated with free T4 among them (Graphs 1 to 4).

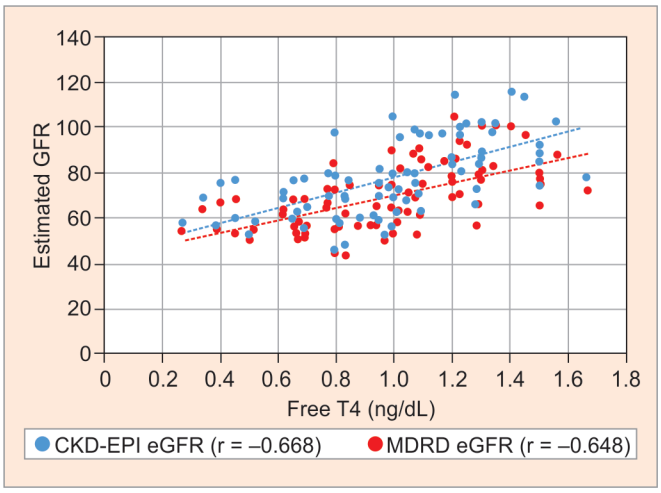
DISCUSSION

Thyroid hormones have effect on nearly every organ system of the human body, for kidney it is no exception. Since the period of embryogenesis, they are involved in general tissue growth as well as glomerular filtration, tubular functions, and electrolyte handling of kidney.[15,16] In the present study, the alteration in renal function has been observed among the patients with thyroid disorders with some prefixed inclusion and exclusion criteria at North Bengal Medical College & Hospital, which is having a catchment area with higher prevalence of thyroid disorders. The entire study population has been divided into three categories. Those are newly diagnosed drug naïve primary hypothyroid patients, patients under treatment for more than 2 months for primary hypothyroidism, and a healthy control group with euthyroid status. For this purpose parameters like serum creatinine, serum urea, urinary ACR, and eGFR are explored among them.

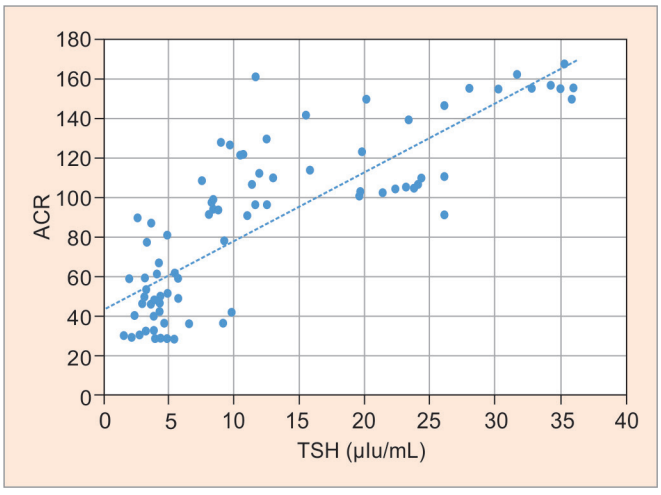
To segregate the population with thyroid disorders, serum TSH > 4.2 µIU/mL is considered as hypothyroidism.



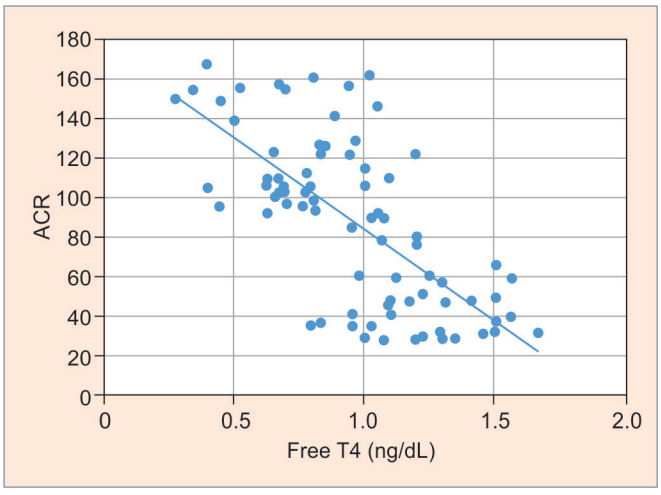
Graph 1: Linear regression line for eGFR values (in mL/min per 1.73 m^2 body surface area) with serum TSH among patients with primary hypothyroidism (r = Pearson correlation coefficient)



Graph 2: Linear regression line for eGFR values (in mL/min per 1.73 m^2 body surface area) with serum free T4 among patients with primary hypothyroidism (r = Pearson correlation coefficient)



Graph 3: Linear regression line for ACR (mg/gm) values with serum TSH among patients with primary hypothyroidism (r = Pearson correlation coefficient)

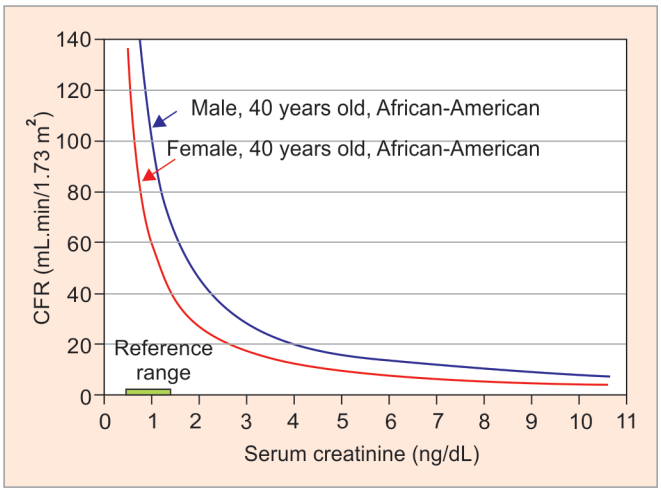


Graph 4: Linear regression line for ACR (mg/gm) with serum free T4 among patients with primary hypothyroidism (r = Pearson correlation coefficient)

It has been seen that the control group (n = 44) is having mean serum TSH (1.54 ± 1.16 µIU/mL) and serum free T4 (1.29 ± 0.17 ng/dL). Comparing patients with newly diagnosed drug naïve primary hypothyroidism and primary hypothyroidism patients on treatment, significant mean difference is observed for both serum TSH (18.74 ± 9.29 *vs* 3.76 ± 1.61 µIU/mL) and serum free T4 (0.78 ± 0.23 *vs* 1.25 ± 0.19 ng/dL), with a significance level of $p < 0.001$ for both the occasions.

A large decrease in GFR is associated with slight increases in the serum creatinine concentration within the typical reference range (0.6–1.2 mg/dL). A 60-year-old white woman with a serum creatinine level of 1 mg/dL, which is well within the typical reference range, has an eGFR of only 57 mL/min per 1.73 m^2, whereas the same creatinine concentration in a 20-year-old African-American male is consistent with normal renal function. Thus to better estimate the GFR, which is widely considered to be the most useful index of overall renal function, it has become customary to use equations that incorporate serum creatinine with other parameters. The most widely used of these equations in current practice is the four-parameter MDRD equation that incorporates serum creatinine, age, gender, and ethnic group (African American or not African American). The more recent CKD-EPI equation, which uses the same four parameters, is beginning to replace the MDRD equation. For clinical laboratory practice, it is recommended to report the eGFR along with creatinine measurements in adults (Graph 5). This addition provides more useful information than serum creatinine value alone.[17]

Elevation of serum creatinine levels along with the reduction in GFR and renal plasma flow is found to be associated with hypothyroidism. The GFR can be reduced up to 40% in hypothyroid humans[2,18,19] just as predicted as experiments on animal model.[20,21] This declining trend



Graph 5: Relation between GFR and serum creatinine

of GFR is corrected as soon as the hormone replacement for hypothyroidism has been started. This can only be possible if the changes in renal function do not cause permanent histological damage.[2,21]

The decrease in GFR has several causes:

- Hypothyroidism is associated with decreased cardiac output and circulating volume, impaired activity of the renin–angiotensin–aldosterone system, and a decreased atrial natriuretic factor level,[19,22] which could lead to decreased renal perfusion.[2]
- The glomerular surface area can be decreased by growth retardation in renal parenchyma.
- A filtrate overload caused by deficient sodium and water reabsorption in the proximal tubule could lead to an adaptive preglomerular vasoconstriction.
- Renal expression of the chloride channels is decreased in hypothyroid rats. So when there is increased chloride load, sensed in the distal tubules, the tubuloglomerular feedback mechanism decreases GFR.
- Finally, hypothyroidism causes a decrease in insulin-like growth factor 1 (IGF-1). However, in response to thyroxin replacement, the IGF-1 is increased, along with the vascular endothelial growth factor (VEGF). The IGF-1 is known to increase creatinine clearance in humans and VEGF increases the activity of nitric oxide synthase, thereby improving the relaxing capacity of the renal vasculature. Hence, both IGF-1 and VEGF could influence renal blood flow and GFR in hypothyroidism before and after thyroxin replacement.[15,23]

In the present study, eGFR is considered as an important yardstick for assessment of renal function. Estimated GFR has been calculated with the help of two different formulas using serum creatinine values, age, gender, and ethnic group, i.e., CKD-EPI eGFR and four-variable MDRD eGFR. As thyroid disorder alters metabolism of cystatin C, cystatin C-based equation has not been incorporated here.[24,25] Using both the equations, eGFR was observed to be significantly low ($p < 0.001$) in patients with newly diagnosed drug naïve primary hypothyroidism (CKD-EPI eGFR 66.06 ± 9.3 mL/min per 1.73 m^2, MDRD eGFR 60.29 ± 7.88 mL/min per 1.73 m^2) in comparison to the euthyroid control (CKD-EPI eGFR 103.53 ± 5.29 mL/min per 1.73 m^2, MDRD eGFR 91.32 ± 4.83 mL/min per 1.73 m^2). Patients under treatment for primary hypothyroidism more than 2 months showed increased eGFR (CKD-EPI eGFR 92.38 ± 11.62 mL/min per 1.73 m^2, MDRD eGFR 81.93 ± 10.74 mL/min per 1.73 m^2) from newly diagnosed drug naïve patients ($p < 0.001$). This is indicating reversibility of eGFR after initiation of levothyroxine replacement therapy. The HUNT study conducted by Åsvold et al[26] observed that the 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 m^2, $p < 0.001$) or overt hypothyroidism (76.5 mL/min per 1.73 m^2, $p < 0.001$) 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 m^2). On the contrary, both subclinical hyperthyroidism (mean 84.6 mL/min per 1.73 m^2, $p = 0.04$) and overt hyperthyroidism (104.9 mL/min per 1.73 m^2, $p < 0.001$) were associated with higher eGFR, compared with the reference group. Their data support the earlier findings by Adrees et al[27] and Woodward et al.[28] In primary hypothyroidism also, reversible increase in GFR was observed following thyroxine treatment.[2,4,16] The HUNT study used only four-variable MDRD study equation to estimate GFR.[26] In the present study, the findings are in harmony with the observations of Åsvold et al[26] and Den Hollander et al[2] and substantiated the fact by MDRD study equation along with more accurate CKD-EPI eGFR equation.

Values of serum creatinine differed significantly among patients with newly diagnosed primary hypothyroidism (1.18 ± 0.13 mg/dL) from control group (0.79 ± 0.09 mg/dL) and those on treatment for primary hypothyroidism for more than 2 months (0.89 ± 0.11 mg/dL) at a significance level of $p < 0.001$ on both the occasions. 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 ($p = 0.005$). In their longitudinal study on changes in renal function in primary hypothyroidism, Montenegro et al[21] 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. In the present study, the longitudinal follow-up was not done for primary hypothyroid patients. Still patients with primary hypothyroidism under treatment were found to have significantly low serum creatinine level compared with newly diagnosed drug naïve patients ($p < 0.001$). As the possible confounding factors have been eliminated beforehand, these data can be corroborated with the observations of Montenegro et al[21] and Arora et al.[29]

So far, creatinine-based equation has been used to evaluate GFR or eGFR in this study. But it can be argued that serum creatinine-based equations may not reflect the true GFR alteration in thyroid dysfunction, as the creatinine values in hypothyroidism patients are changing with the course of disease. Tsuda et al[30] in their recent study about intrarenal hemodynamic parameters demonstrated that the high serum TSH, even within higher normal range, was significantly correlated with reduction in GFR, renal plasma flow, and renal blood flow, by simultaneous measurements of plasma clearance of para-aminohippurate and inulin. So, alteration in serum creatinine, serum urea, and eGFR in patients with hypothyroidism before and after hormonal replacement is actually a reflection of alteration in GFR among them. Lippi et al studied on relationship between thyroid status and renal function in a general population of unselected outpatients (n = 13,383). They also found that when compared with euthyroid subjects, those with TSH < 0.2 μIU/mL and >2.5 μIU/mL had increased and decreased eGFR respectively.[31]

In all the studied groups, serum urea was found to be in the normal laboratory range. Still statistically significant alteration ($p < 0.001$) has been found while comparing newly diagnosed drug naïve primary hypothyroidism (24.25 ± 6.79 mg/dL) with control group (18.31 ± 2.44 mg/dL) and those are on treatment for primary hypothyroidism for more than 2 months (16.66 ± 3.4 mg/dL). This can be explained by the alteration in GFR in hypothyroidism which is reversible upon initiation of hormone replacement therapy.[2,4,26] Significant alteration in blood urea level in primary hypothyroid patients ($p < 0.05$) was also observed by Montenegro et al[21] while comparing the patients' pretreatment and posttreatment status (47 ± 4 *vs* 38 ± 2 mg/dL)[21] But Arora et al[29] found no significant alteration in serum urea levels among hypothyroid subjects in their hospital-based study.

Zhou et al[32] have explored the relationship between thyroid hormones and microalbuminuria in Chinese population (n = 3346). The prevalence of microalbuminuria decreased according to free T3 quartiles (p for trend = 0.0005). This study was the first to report an independent association between thyroid hormones concentration and microalbuminuria in a large population. In the present study, newly diagnosed drug naïve primary hypothyroid patients are having mean ACR 115.9 ± 30.94 mg/gm (in the range of microalbuminuria). It was observed that there is statistically significant decrease in ACR comparing primary hypothyroidism patients under treatment for more than 2 months with those are newly diagnosed (ACR 46.96 ± 17.24 *vs* 115.9 ± 30.94 mg/gm, $p < 0.001$). Even patients on treatment for hypothyroidism for more than 2 months are having microalbuminuria just above the normal range (46.96 ± 17.24 mg/gm for ACR), and that also statistically significant compared with euthyroid control ($p < 0.001$). So these data indicate microalbuminuria in primary hypothyroidism and suggest its reversibility on treatment.

It has been suggested that autoimmune thyroid disease may lead to endothelial dysfunction due to

deposition of immune-complexes [especially antithyroid peroxidase (TPO) antibody] in the renal glomeruli. So hypothyroidism associated with anti-TPO +ve status is more likely to develop microalbuminuria and is associated with reduced GFR.[4,33] But in the HUNT study, the association with eGFR was found to be roughly similar for hypothyroidism with and without TPO antibodies.[26] Also, the data provided by Zhou et al[32] showed that the link with microalbuminuria was roughly similar for thyroid hormones with or without anti-TPO antibody status ($p = 0.93$). This suggests that immunological damage to the kidney caused by autoimmunity is not a likely explanation for the association of thyroid hormonal status with reduced eGFR or microalbuminuria. The effects of thyroid hormones on alteration of renal functions might be independent of thyroid autoimmunity. However, this was beyond the scope of the present study to establish thyroid autoimmunity as an etiology for alteration in renal function, and further longitudinal studies are needed to establish that.

Åsvold et al[26] showed that TSH within the reference range was negatively associated with eGFR (p for trend <0.001). 1 µIU/mL higher TSH was associated with 1.9% lower eGFR, and there was no appreciable difference between women and men. Pearson correlation tests are performed to explore the correlation with serum TSH and free T4 with renal function parameters in the present study. It has been seen that among all the patients with hypothyroidism (n = 88), serum TSH is negatively correlated with eGFR measured both by MDRD formula and CKD-EPI formula ($p < 0.001$). Free T4 is positively correlated with eGFR ($p < 0.001$). On the contrary, serum creatinine, serum urea, and ACR are positively correlated with serum TSH ($p < 0.001$) and negatively with free T4 ($p < 0.001$). While conducting a cross-sectional study on Indian population, Saini et al[34] examined 47 patients with overt and 77 patients with subclinical hypothyroidism and found serum TSH is positively correlating with serum creatinine values among them ($p < 0.05$). In a study on "correlation of thyroid dysfunction with serum creatinine," Attaullah et al[35] observed that among hypothyroid subjects (n = 191) serum creatinine is positively correlating with TSH and negatively with serum T4 ($p < 0.001$ on both the occasions). They also observed that in hyperthyroid patients (n = 195) serum creatinine is negatively correlated with T4 ($p < 0.001$). Montenegro et al[21] failed to establish any correlation between renal function and serum concentrations of T4 or TSH in their study. They have dealt with relatively small sample size (n = 41), which could possibly be the reason behind such findings. In both simple and multivariate-adjusted linear regression analyses, free T3 levels were found to be negatively and significantly associated with ACR ($p < 0.05$), in the study by Zhou et al.[32]

Thus, it has been seen so far in the present study that both hypothyroidism and hyperthyroidism associate with significant alteration in kidney function. These effects are the results of direct renal actions, as well as systemic hemodynamic, metabolic, and cardiovascular effects, exerted by thyroid hormones. Fortunately, most of the renal manifestations of thyroid disorders, which are clinically more significant with hypothyroidism, are reversible with treatment. These could only be possible if the changes in renal function are not associated with any sort of permanent histological damage. However, it has recently been reported by Elgadi et al[36] that kidney function recovers slowly in hypothyroid children, and sometimes partially, after the introduction of replacement with levothyroxine. The long-term clinical implications of these findings are still unknown.

CONCLUSION

In the present institution-based observational study, most of the renal manifestations are found to be significant for drug naïve primary hypothyroid patients. It has been seen that these patients have lower than normal eGFR, elevated serum creatinine, serum urea, and microalbuminuria, compared with euthyroid controls. Fortunately, the alteration in renal function has been found to be reversible while observing primary hypothyroid patients under treatment for more than 2 months. It has also been seen that TSH values are negatively correlated with eGFR and positively correlated with microalbuminuria among primary hypothyroid patients regardless of the treatment status. For free T4, these relationships are just the opposite of serum TSH among them.

Thus with these observations, it can be suggested that patients with unexplained abnormal renal function should be screened for thyroid disorders, especially for primary hypothyroidism. But it is still not certain about the possible outcome of the deranged renal function among the untreated patients with hypothyroidism in the long run. As microalbuminuria is recognized as a predictor of adverse renal outcome even in nondiabetic subjects, the possibility of nephropathy in near future should not be turned down for untreated overt hypothyroid patients. Thus, it should be recommended to check for alteration in renal functions among untreated hypothyroid patients and take necessary actions in the form of hormone replacement therapy to abort any possibility of future nephropathy.

REFERENCES

1. Feinstein EI, Kaptein EM, Nicoloff JT, Massry SG. Thyroid function in patients with nephrotic syndrome and normal renal function. Am J Nephrol 1982;2(2)70-76.

2. Den Hollander JG, Wulkan RW, Mantel MJ, Berghout A. Correlation between severity of thyroid dysfunction and renal function. Clin Endocrinol 2005 Apr;62(4):423-427.
3. Mariani LH, Berns JS. The renal manifestations of thyroid disease. J Am Soc Nephrol 2012 Jan;23(1):22-26.
4. Iglesias P, Diez J. Thyroid dysfunction and kidney disease. Eur J Endocrinol 2009 Apr;160(4):503-515.
5. Vanderpump MP, Tunbridge WMG. Epidemiology and prevention of clinical and subclinical hypothyroidism. Thyroid 2002 Oct;12(10):839-847.
6. Sethi V, Kapil U. Iodine deficiency and development of brain. Indian J Pediatr 2004 Apr;71(4):325-329.
7. Rafiq M. Prevalence survey of iodine deficiency disorders in 8-10 years old school children and use of iodized salt, Swat District NWFP Pakistan. UNICEF report. 1998.
8. Bashir H, Farooq R, Bhat MH, Majid S. Increased prevalence of subclinical hypothyroidism in females in mountainous valley of Kashmir. Indian J Endocrinol Metab 2013 Mar-Apr; 17(2):276-280.
9. Risal P, Maharjan B, Koju R, Makaju R, Gautem M. Variation of total serum cholesterol among the patient with thyroid dysfunction. Kathmandu Univ Med J 2010 Apr-Jun;8(30):265-268.
10. Zheng M. Conceptualization of cross-sectional mixed methods studies in health science: a methodological review. Int J Quant Qual Res Methods 2015 Sep;3(2):66-87.
11. Salvatore D, Davies TF, Schlumberger MJ, Hay ID, Larsen PR. Thyroid physiology and diagnostic evaluation of patients with thyroid disorders. In: Melmed S, editor. Williams textbook of endocrinology. 13th edition. Elsevier Health Sciences; 2015 Nov:333-368.
12. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999 Mar;130(6):461-470.
13. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009 May;150(9):604-612.
14. Stevens LA, Schmid CH, Zhang YL, Coresh J, Manzi J, Landis R, Bakoush O, Contreras G, Genuth S, Klintmalm GB, et al. Development and validation of GFR-estimating equations using diabetes, transplant and weight. Nephrol Dial Transplant 2010 Feb;25(2):449-457.
15. van Hoek I, Daminet S. Interactions between thyroid and kidney function in pathological conditions of these organ systems: a review. Gen Comp Endocrinol 2009 Feb;160(3):205-215.
16. Basu G, Mohapatra A. Interactions between thyroid disorders and kidney disease. Indian J Endocrinol Metab 2012 Mar-Apr;16(2):204-213.
17. Killeen Anthony A. The clinical laboratory in modern health Care. In: Fauci AS, Kasper DL, editors. Harrison's principles of internal medicine, 19th edition. New York: McGraw-Hill, Medical Publishing Division; 2015. p. 480e1-480e5.
18. Karanikas G, Schütz M, Szabo M, Becherer A, Wiesner K, Dudczak R, Kletter K. Isotopic renal function studies in severe hypothyroidism and after thyroid hormone replacement therapy. Am J Nephrol 2004 Jan-Feb;24(1):41-45.
19. Suher M, Koc E, Ata N, Ensari C. Relation of thyroid dysfunction, thyroid autoantibodies, and renal function. Renal Failure 2005;27(6)739-742.
20. Katz AI, Lindheimer MD. Renal sodium-and potassium-activated adenosine triphosphatase and sodium reabsorption in the hypothyroid rat. J Clin Invest 1973 Apr;52(4): 796-804.
21. Montenegro J, González O, Saracho R, Aguirre R, González Ó, Martínez I. Changes in renal function in primary hypothyroidism. Am J Kidney Dis 1996 Feb;27(2):195-198.
22. Zimmerman R, Gharib H, Zimmerman D, Heublein D, Burnett Jr J. Atrial natriuretic peptide in hypothyroidism. J Clin Endocrinol Metab 1987 Feb;64(2):353-355.
23. Schmid C, Brändle M, Zwimpfer C, Zapf J, Wiesli P. Effect of thyroxine replacement on creatinine, insulin-like growth factor 1, acid-labile subunit, and vascular endothelial growth factor. Clin Chem 2004 Jan;50(1):228-231.
24. Fricker M, Wiesli P, Brändle M, Schwegler B, Schmid C. Impact of thyroid dysfunction on serum cystatin C. Kidney Int 2003 May;63(5):1944-1947.
25. Jayagopal V, Keevil BG, Atkin SL, Jennings PE, Kilpatrick ES. Paradoxical changes in cystatin C and serum creatinine in patients with hypo- and hyperthyroidism. Clin Chem 2003 Apr;49(4):680-681.
26. Åsvold BO, Bjøro T, Vatten LJ. Association of thyroid function with estimated glomerular filtration rate in a population-based study: the HUNT study. Eur J Endocrinol 2011 Jan;164(1): 101-105.
27. Adrees M, Gibney J, El-Saeity N, Boran G. Effects of 18 months of l-T4 replacement in women with subclinical hypothyroidism. Clin Endocrinol 2009 Aug;71(2):298-303.
28. Woodward A, McCann S, Al-Jubouri M. The relationship between estimated glomerular filtration rate and thyroid function: an observational study. Ann Clin Biochem 2008 Sep;45(5):515-517.
29. Arora S, Chawla R, Tayal D, Gupta VK, Sohi JS, Mallika V. Biochemical markers of liver and kidney function are influenced by thyroid function-a case-controlled follow up study in Indian hypothyroid subjects. Indian J Clin Biochem 2009 Oct;24(4):370-374.
30. Tsuda A, Inaba M, Ichii M, Ochi A, Ohno Y, Nakatani S, Yamada S, Mori K, Tahara H, Ishimura E. Relationship between serum TSH levels and intrarenal hemodynamic parameters in euthyroid subjects. Eur J Endocrinol 2013 Jun;169(1):45-50.
31. Lippi G, Montagnana M, Targher G, Salvagno GL, Guidi GC. Relationship between thyroid status and renal function in a general population of unselected outpatients. Clin Biochem 2008 May;41(7-8):625-627.
32. Zhou Y, Ye L, Wang T, Hong J, Bi Y, Zhang J, Xu B, Sun J, Huang X, Xu M. Free triiodothyronine concentrations are inversely associated with microalbuminuria. Int J Endocrinol 2014;2014:959781.
33. Xiang GD, He YS, Zhao LS, Hou J, Yue L, Xiang HJ. Impairment of endothelium-dependent arterial dilation in Hashimoto's thyroiditis patients with euthyroidism. Clin Endocrinol 2006 Jun;64(6):698-702.
34. Saini V, Yadav A, Arora MK, Arora S, Singh R, Bhattacharjee J. Correlation of creatinine with TSH levels in overt hypothyroidism—a requirement for monitoring of renal function in hypothyroid patients? Clin Biochem 2012 Feb;45(3):212-214.
35. Attaullah S, Haq BS, Ahmed Z. Correlation of thyroid dysfunction with serum creatinine. Int J Multidiscip Res Dev 2015 Aug;2(8):88-90.
36. Elgadi A, Verbovszki P, Marcus C, Berg UB. Long-term effects of primary hypothyroidism on renal function in children. J Pediatr 2008 Jun;152(6):860-864.