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A Study of Thyroid and Renal Tests in Patients with Hyper, Hypo and Euthyroid Diseases

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ABSTRACT
Thyroid hormones influence renal development, renal glomerular filtration rate (GFR), electrolytes and water homeostasis. The location of the present study is situated at regions with high prevalence of thyroid dysfunctions. The objective of this Longitudinal case-control 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 thyroid patients under treatment for more than 2 months and age-and sex-matched control group. The study includes 48 patients with thyroid dysfunction in a drug naïve status, 40 thyroid dysfunction patients under treatment and 44 healthy control in the age group of 25-55 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. 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 signifi- cantly correlated with thyroid-stimulating hormone (TSH) values. 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.

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Key Words
Albumin-to-creatinine ratio, estimated glomerular filtration rate, hypothyroidism, renal function, euthyroidism

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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 hyper functioning 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[6]. In such 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 this institution-based longitudinal 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.

MATERIALS AND METHODS

This institution-based longitudinal case control study with mixed design[10] has been conducted over a period of 1 year Study population has been chosen from the patients referred to the laboratory of Department of Biochemistry Govt General Hospital, Siddipet, 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 25-55 years have been selected for the study. In this process, patients having the following conditions have been excluded from the study. Instrument name Abbott , kitts Architect Total T3,T4 and TSH, Reagent Kitt, Quality control, RANDOX, Approval ethical commity, consent taken from the patient"s.

Exclusion Criteria:

- Hypertension.
- Previously diagnosed cardiovascular disorder.
- Frank diabetes and impaired glucose toleran.
- 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 hypothyroid- ism and hyperthyroidism.
- Under treatment with those drugs that affect renal functions like angiotensin converting enzyme inhibi- tors/angiotensin receptor blockers, diuretics, allopu- rinol, steroids, etc.
- History of drugs affecting thyroid hormonal status, e.g., Li, amiodarone, phenytoin, carbamazepine, salicylates, beta blockers, rifampicin, cytotoxic drugs, etc.
- Malignancy.

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 categorizid 2 groups:

- Newly diagnosed drug naïve thyroid dysfunction patients (n=48).
- Thyroid dysfuntion 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 2.5ng/dL, TSH 0.4-4.2µIU/mL. Individuals are considered as in hypothyroid state if TSH >4.2µIU/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 trace-able 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 and urinary creatinine, to determine ACR.

Four-variable MDRD Study Equation[12]
GFR=175 × (sCr-1.154) × (age-0.203) × (0.742 if female)
where sCr is serum creatinine in mg/dL.
CKD-EPI eGFR Calculator[13]
GFR=141 × min (sCr /k, 1)a × max(sCr /k, 1)-1.209 × 0.993 × age × 1.018 (if female) × 1.159 (if black)
where sCr is serum creatinine in mg/dL, k is 0.7 for females and 0.9 for males, a is -0.329 for females and-0.411 for males, min indicates the minimum of sCr/k or 1 and max indicates the maximum of sCr/k or 1.

RESULTS AND DISCUSSIONS

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, 25-34 years age group consists of 44.67% population, 30.67% fall into 35-44 years age group and the rest into 45-55 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±1.16µIU/mL with the drug naïve primary hypothyroid patients having mean TSH 18.54±9.29µIU/mL and primary hypothyroid patients on treatment having 3.76±1.61µIU/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 hypothyroid dysfuntion as a whole and by Pearson's correlation analysis (Table 3).

Thyroid hormones have effect on nearly every organ system of the human body, for kidney it is no exception. Since the period of embryo genesis, they are involved in general tissue growth as well as glomerular filtration, tubular functions and electrolyte handling of kidney[15-17]. 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 , 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 prevalance diagnosed drug naïve primary thyroid patients, patients under treatment for more than 2 months for primary thyroidism 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 It has been seen that the control group (n=44) is having mean serum TSH (1.54±1.16µIU/mL) and serum free T4 (1.29±0.17ng/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±1.61µIU/mL) and serum free T4 (0.78±0.23 vs 1.25±0.19ng/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 (0.6-1.2mg/dL). A 60-year-old white woman with a serum creatinine level of 1mg/dL, which is well within the typical reference range, has an eGFR of only 57mL/min per 1.73m2, whereas the same creatinine concentration in a 20-year-old African-American male is consistent with normal renal function. 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 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[2,21,23].

The decrease in GFR has several causes:

- Thyroid disease is associated with decreased cardiac output and circulating volume, impaired activity of the renin-angiotensin-aldosterone system and a decreased atrial natriuretic factor level[19,22,24,25] 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 chlol ride load, sensed in the distal tubules, the tubulo-glomerular feedback mechanism decreases GFR.

it has been seen so far in the present study that both hypothyroidism and hyperthyroidism associate with significant alteration in kidney function. These effects

Table 1: Descriptive Statistics of Study Parameters

	Control group (mean±SD)	Drug naïve thyroid dysfunction patients (mean±SD)	thyroid dysfunction 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 m2 body surface area)	103.53±5.29	66.06±9.3	92.38±11.62
MDRD eGFR (mL/min per 1.73 m2 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: Correlation Analysis of Serum TSH with Renal Function Parameters

		Control group (n = 44)		Patients with thyroid dysfunction (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 3: Correlation Analysis of Serum Free T4 with Renal Function Parameters

		Control group (n=44)		Patients with thyroid dysfunction (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

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 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 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 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 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.

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