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ORIGINAL RESEARCH

A STUDY ON RELATIONSHIP BETWEEN HYPOTHYROIDISM AND RENAL FUNCTION

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ABSTRACT:

Background:Thyroid hormones influence renal development, renal hemodynamic, glomerular filtration rate (GFR), electrolytes, and water homeostasis. The location of the present study is situated at dDepartment of Biochemistry, Maheswara Medical College, Hyderabad with moderate 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 primary hypothyroid patients with age- and sex-matched control group. 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. In the present study the mean values of serum creatinine, urea, and ACR are significantly increased among untreated patients with hypothyroidism, with the decrease in the eGFR, in comparison to healthy control group ($p < 0.001$). 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.

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

INTRODUCTION:

Kidney functions are guided by endocrine secretions from thyroid gland of, both during embryonic development and in the mature condition and can alters the clinically important renal functions like glomerular function,[1] tubular secretory and absorptive capacities, electrolyte, and water homeostasis, cardiovascular changes in the mall functioning of the gland in both hypo- and hyper functioning thyroid gland.[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]

Various epidemiological studies in various countries including India shows increasing prevalence rate of hypothyroidism varying between 10%-15% and also its relation to the kidney function is not well established.[5] With respect to the great concern about the above facts, we took the present cross-sectional study objective 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 hypothyroidpatientsandage- and sex-matched control group and to correlate the effects of thyroid hormones on renal functions more precisely in a population with greater risk of developing hypothyroidism.

Aim of the Study

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 primary hypothyroid patients and age- and sex-matched control group.

MATERIALS & METHODS:

The study includes 120 patients with primary hypothyroidism and 120 healthy controls in the age group of 29 to 68 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.[6]

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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. Random urine samples are processed to measure urine micro albumin and urinary creatinine, to determine ACR.

Four-variable MDRD Study EquationGFR = 175 × (sCr − 1.154) × (age − 0.203) × (0.742 if female)where sCr is serum creatinine in mg/dL.
CKD-EPI eGFR CalculatorGFR = 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.

Statistical Analysis:
The data obtained was analysed and the difference in the mean of various parameters were compared using students t test and Karl Pearson's correlation coefficient.

RESULTS:
Table 1:Age & sex wise distribution of cases

Age	Cases	Percentage %	Controls	Percentage %
29-38	60	50 %	55	45.83 %
39-48	28	23.33 %	33	27.5 %
49-58	20	16.66 %	20	16.66 %
59-68	12	10 %	12	10 %
Total	120	100 %	120	100 %

In the total study population, 29 to 38 yr age group consists of (60) 50 % population, (28) 23.33% fall into 39 to 48 yr age group, (20) 16.66% are in 49-58 yr category and the rest (12) 10% into 59 to 68 yr age group. About 75.83% (91) of the studied individuals are females and 24.16% of them are males as observed in table 1 & 2. Using chi-square test, it was evident that the population with thyroid disorders is having a significant female preponderance in the study ($p < 0.001$).

Table 2: Sex wise distribution of cases

Sex	Cases	Percentage %	Controls	Percentage %
Males	29	24.16 %	29	24.16 %
Females	91	75.83 %	91	75.83 %
Total	120	100 %	120	100 %

Table 3: Comparison of Thyroid Hormones with Various Renal Parameters

	Control group	Hypothyroid patients	P value
No. of cases	120	120	
TSH (μIU/mL)	1.24 ± 3.16	20.56 ± 9.99	<0.001
Free T4 (ng/dL)	1.39 ± 1.17	0.84 ± 0.95	<0.001
Serum creatinine (mg/dL)	0.89 ± 0.11	1.89 ± 1.11	<0.001
Serum urea(mg/dL)	17.42 ± 3.22	32.66 ± 5.1	<0.001
CKD-EPI eGFR(mL/min per1.73 m2 bodysurface area)	102.49 ± 5.29	89.26 ± 12.89	<0.001
MDRD eGFR(mL/min per1.73 m2 body surface area)	82.54 ± 5.25	69.33 ± 11.21	<0.001
ACR (mg/gm)	24.21 ± 3.43	156.69 ± 28.14	<0.001

The control group is having TSH mean value in normal range, i.e., 1.54 ± 1.16 μ IU/mL and primary hypothyroid patients having 20.56 ± 9.99 μ IU/mL. The descriptive statistical data of other study parameters are arranged in [Table 3].
We found a highly significant difference in the mean values of FT4, TSH, serum creatinine, eGFR by MDRD, and eGFR by CKD-EPI equation among all the groups indicates a strong positive correlation between hypothyroidism and renal functional impairment as shown in [Table 3& 4].

Table 4: Correlation analysis of serum TSH with renal function parameters

		Control		**Cases**	
Thyroid-stimulating hormone	**Parameterscorrelated**	**r-value**	**P value**	**r-value**	**P value**
	Serumcreatinine	0.254	0.23	0.715	<0.001
	Serum urea	0.158	0.12	0.587	<0.001
	CKD-EPI eGFR	0.215	0.51	0.858	<0.001
	MDRD eGFR	0.002	0.99	0.828	<0.001
	ACR	0.319	0.16	0.699	<0.001

Table 5: Correlation analysis of serum T4 with renal function parameters

		Control group		**Primary hypothyroidism**	
Free T4	**Parameterscorrelated**	**r- value**	**P value**	**r- value**	**P value**
	Serum creatinine	0.068	0.865	0.260	<0.001
	Serum urea	0.098	0.895	0.589	<0.001
	CKD-EPI eGFR	0.825	0.187	0.969	<0.001
	MDRD eGFR	0.169	0.051	0.752	<0.001
	ACR	0.6	0.6	0.729	<0.001

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. In the present study, the alteration in renal function has been observed among the patients with thyroid disorders. To segregate the population with thyroid disorders, serum TSH > 4.2 μIU/mL is considered as hypothyroidism. 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 just as predicted as experiments on animal model.[6]

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, which could lead to decreased renal perfusion.[7-12]
- 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 tubulo- glomerular feedback mechanism decreases GFR.[13]
- 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. In the present study, eGFR is considered as an important yardstick for assessment of renal function.[14,15]

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. The data support the earlier findings by Adrees et al and Woodward et al. In primary hypothyroidism also, reversible increase in GFR was observed following thyroxine treatment.

The HUNT study used only four-variable MDRD study equation to estimate GFR.In the present study, the findings are in harmony with the observations of Åsvold et al and Den Hollander et al. Lippi et al studied on relationship between thyroid status and renal function in a general population of unselected outpatients. Significant alteration in blood urea level in primary hypothyroid patients ($p < 0.05$) was also observed by Montenegro et al while comparing the patients' pretreatment and post treatment status. Attaullah et al observed that among hypothyroid subjects serum creatinine is positively correlating with TSH and negatively with serum T4.

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.

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