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CORRELATION OF THYROID HORMONES IN PATIENTS WITH CHRONIC KIDNEY DISEASE: AN OBSERVATIONAL STUDY

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Abstract

Introduction: Chronic kidney disease (CKD) is an international public health problem affecting about 5–10% of the population. It is the ninth leading cause of death. A trend towards increased incidence and prevalence is being reported worldwide with epidemic proportions in many countries. CKD is associated with variety of endocrine disturbances among which thyroid dysfunction is most common. This is probably due to reduce circulating hormone levels, altered binding of hormone to carrier protein or due to reduced peripheral metabolism of hormone.

Materials and Methods: The study included 100 patients diagnosed with CKD. Both male and female patients aged between 30-70 years were selected for the study. Estimated Glomerular Filtration Rate (eGFR) was calculated using Modification of Diet in Renal Disease (MDRD) formula. Total T3, Total T4, TSH levels were measured by CLIA methodology.

Results: Statistically significant alteration in TSH ($p<0.01$) values were seen with eGFR suggesting that alteration in the eGFR may lead to thyroid hormone resistance.

Keywords: Chronic Kidney Disease(CKD), Estimated Glomerular Filtration Rate (eGFR), Modification of Diet in Renal Disease (MDRD)

Introduction:

Chronic kidney disease (CKD) is a progressive disease causing an irreversible damage in kidney function. It is a problem in both industrialised and developing countries of the world, having ranked 13th leading cause of death worldwide in 2013. (1)

It is a major public health problem associated with premature mortality and decreased quality of life as well as high cost of health care. A trend towards increased incidence and prevalence is being reported worldwide with epidemic proportions in many countries (2).

The kidney plays an important role in thyroid hormone metabolism, degradation, and excretion, so any disturbance in the hypothalamic–pituitary–thyroid axis is associated with reduced kidney functions (3).

CKD affects the hypothalamus-pituitary-thyroid axis and the peripheral circulation and metabolism of thyroid hormone release and excretion. The response of thyroid-stimulating hormone (TSH) to thyrotropin-releasing hormone is delayed because of the decreased clearance and the increase of half-life of TSH (4)

The earliest and the most common thyroid function abnormality in patients with CKD is low T3 level Circulating levels of T3 are low in progressive CKD owing to reduced deiodinase activity, which reduces the peripheral conversion of thyroxine T4 to T3(5-6).

Many studies have concluded that, thyroid hormone replacement therapy has noticeable positive effects on kidney functions, especially GFR, and prevents worsening of renal disease, this in turn decreases the morbidity and mortality of CKD and improves outcomes (7-8).

Thus, the study was undertaken to know the changes in thyroid profile in patients with chronic kidney disease.

Materials & Methods:

The study was conducted at Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka. The study was approved by the institutional ethics committee. A Written informed consent was taken from all participants. 100 patients diagnosed with CKD were included in the study. Patients with auto immune disorders and paediatric patients were Excluded from the study.

The base line demographic data, personal history, family history was collected from each patient.

Fasting venous samples were collected into vacutainer tubes. Samples were immediately transported to the laboratory. Samples were centrifuged at 4000 rpm for 10 minutes. Serum was separated and analyzed.

Patients were categorized into various stages of CKD depending on their GFR. It was calculated using MDRD formula.

Modification of Diet in Renal Disease (MDRD) equation is: 186× plasma creatinine$^{-1.154}$ × age$^{-0.203}$ (× 0.742 if female).

Normal GFR in young adults is approximately 120 to 130 mL/min per 1.73 m^2 and declines with age . A GFR level less than 60 mL/min per 1.73 m^2 represents loss of half or more of the adult level of normal kidney function. Below this level, the prevalence of complications of chronic kidney disease increases.

Methodology:

The samples collected were analysed using the following methodology.

Measurement of Creatinine: CR-S reagent was used to measure the creatinine concentration by a modified rate Jaffé method in Beckman Coulter UniCel DxC 600 System using controls AQUA CAL 1 and 2(10)

Measurement of Urea: Serum Urea was measured by enzymatic urease method using Beckman Coulter Unicell DxC 600 System, controls AQUA CAL 1, 2 and 3 were used. (11)

Measurement of Thyroid Hormones: Serum TSH, Total T3, Total T4 were measured using Beckman Coulter Access 2 Immuno assay system by CLIA. (12-14)

All patients with CKD were divided to different stages depending on eGFR calculated using *MDRD formula*

Stage 1: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m^2),

Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m^2).

Stage 3: Moderate reduction in GFR (30-59 mL/min/1.73 m^2).

Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m^2).

Stage 5: Kidney failure (GFR < 15 mL/min/1.73 m^2 or dialysis). (15)

Statistical analysis: Analysis of data was performed using the SPSS software. Data of CKD patients were compared using student's t test, $\chi 2$ test or Fisher exact test. Pearson correlation was performed with eGFR versus study parameters and Correlation Co-efficient (r) is considered as <0.1: Trivial Correlation, 0.1-0.3: Small Correlation, 0.3-0.5: Moderate Correlation, 0.5-0.7: Large Correlation, 0.7-0.9: Very Large Correlation, 0.9- 1.0: Nearly Perfect correlation, 1: Perfect correlation.(16)

Results:

All patients included in the study were from the southern states of India and belonged to the same socioeconomic group.

Table 1: Age distribution

Age in years	Number of Patients	%
19-20	4	4.0
21-30	10	10.0
31-40	18	18.0
41-50	30	30.0
51-60	20	20.0
61-70	14	14.0
>70	4	4.0
Total	100	100.0

Mean ± SD :46.64±14.70

Table 2: Gender distribution of patients studied

Gender	Number of Patients	%
Male	66	66.0
Female	34	34.0
Total	100	100.0

Maximum number of patients was in the age group of 40-50 years, and the mean age was 46.64±14.70 years. There were 66% male patients and 34% female patients.

Table 3: Mean distribution of age and other biochemical parameters in CKD

Parameters	Mean value
Age	46.64±14.70
T3	1.05 ng/mL
T4	8.29 mg/dL
TSH	14.26 IU/mL
Serum Urea	34.36 mg/dL
Serum Creatinine	1.47 mg/dL

94% of patients studied were in stage 2 of CKD . Among the patients studied the mean creatinine levels were 1.47 mg/dL, mean levels of urea were 34.36 mg/dL, mean level of Total T3 were 1.05 ng/mL, mean level of Total T4 value was 8.29 mg/dL and mean TSH levels 14.26 IU/mL.

Pearson correlation co-efficient was calculated and it was observed that the GFR levels were negatively correlated with age: -0.351 (p=0.012), Urea: -0.711(p<0.001), Creatinine: -0.787 (p<0.001), and TSH: -0.534(p<0.001). GFR levels were positively correlated with total T3: 0.246(p=0.085) and total T4: 0.280 (p=0.049).

Table 4: Correlation of GFR with study parameters in CKD patients:

Correlation of GFR with various biochemical parameters	Pearson correlation Co-efficient (r)	p value
GFR vs Urea (mg/dL)	-0.711	<0.001**
GFR vs Creatinine(mg/dL)	-0.787	<0.001**
GFR vs T3 ng/mL	0.246	0.085+
GFR vs T4 µg/dL	0.280	0.049*
GFR vs TSH µIU/mL	-0.534	<0.001**

No significant differences in eGFR were found in relation to the gender distribution of patients.
+ Suggestive significance (p value: 0.05<p<0.10)* Moderately significant (p value: 0.01<p ≤ 0.05)** Strongly significant (p value: p≤0.01)

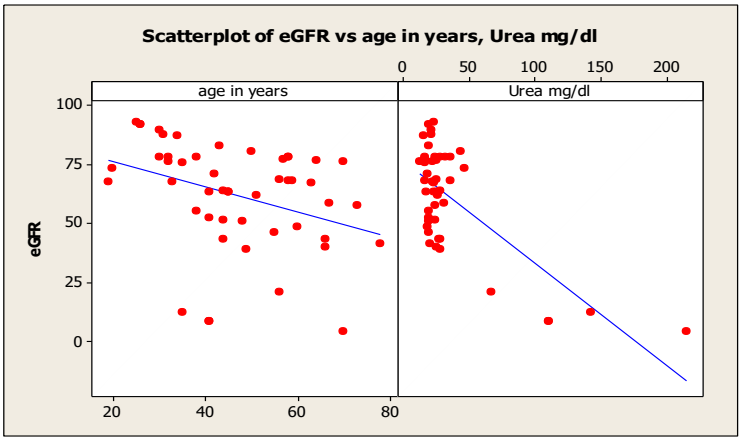

Figure 1: scatterplot of GFR vs age in years and eGFR vs Urea

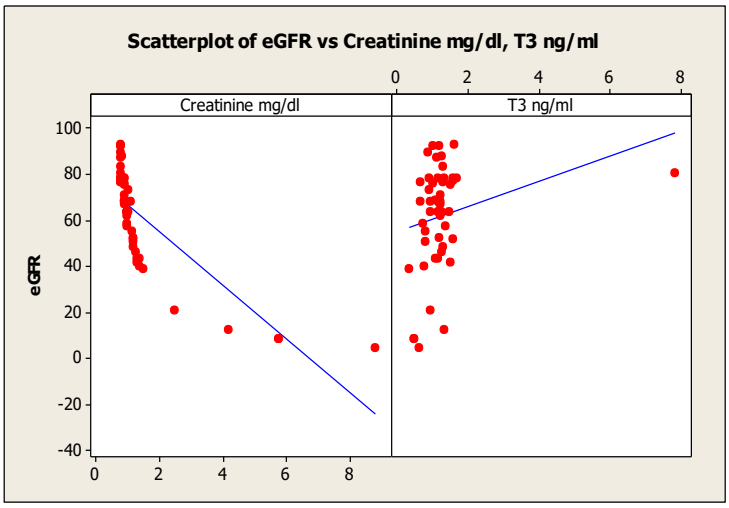

Figure 2: Scatterplot of GFR Vs Creatinine and eGFR with Total T3

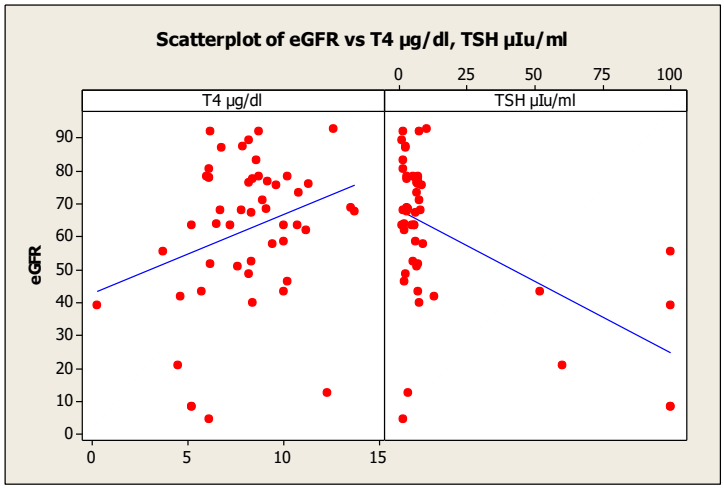

Figure 3: Scatterplot of eGFR Vs Total T4and eGFR with TSH

Discussion:

Our study has shown an increased prevalence of hypothyroidism in more than 50% of patients. The results are concordant with studies conducted in other populations. Similar findings were documented by Lim et.al, who found that the prevalence of hypothyroidism in End stage renal disease was 0–58% and of Sub clinical hypothyroidism is 0–9.5% (17).

Study conducted by **Kaptein et al.** showed that the prevalence of hypothyroidism was as 43% compared to only 6.7% in the control group (18).

In another study conducted by **Ramirez et.al,** the prevalence of hypothyroidism and in End stage renal disease was 58% (19).

Lo et al. studies showed an increased prevalence of hypothyroidism in persons with reduced estimated GFR, independent of age, gender, and race/ethnicity.

In agreement with our study, in their study prevalence of hypothyroidism amounted to 23.1% in CKD patients with an estimated GFR 30 ml/min/1.73 m^2. In addition, with progressively lower GFR, there was a graded, increased likelihood of hypothyroidism (20).

Layla K. Ali et al studies have shown that highly significant reduction in T3 and T4 concentration in patient's serum with CRF compared to control group ($p \leq 0.05$). In our study moderately significant correlation was seen between eGFR and T4 levels, p value being (<0.049) and with T3 levels (<0.084).

Multiple studies have revealed that thyroid hormones affect the renal function by both pre-renal and direct renal effects. Pre renal effects are mediated by influence of thyroid hormones on cardiovascular system and renal blood flow. Direct renal effects are mediated by the effect of thyroid hormones on, Glomerular filtration rate (GFR), tubular secretion and re absorptive process and also the hormonal influence on renal tubular functions. (21)

Studies done have concluded that thyroid hormones mainly influence Na^+ reabsorption at the PCT by increasing the activity of Na^+/K^+ ATPase and tubular potassium permeability. Thus, thyroid dysfunction affects RBF, GFR, tubular function, electrolyte homeostasis and kidney structure. (21)

According to study done by **Vargas F et.al,** 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 metabolism (hyperlipidaemia), and indirect effects through paracrine or endocrine mediators, such as insulin-like growth factor type 1 (IGF-1) and vascular endothelial growth factor.(22,23,24)

Conclusion:

Many studies have suggested that fall in GFR may lead to thyroid hormone resistance in the body. The present study finds Subclinical hypothyroidism to be very common in CKD patients and reveals significant association between CKD progression and thyroid dysfunction. Hence, routine monitoring of thyroid hormones in CKD patients is helpful in early detection of hormone resistance as well as its associated cardiovascular complications. Due to high prevalence of hypothyroidism in patients with renal dysfunction, hypothyroidism may be considered as a viable prognostic marker and target for potential intervention. Additional studies are needed to confirm findings, elaborate underlying mechanisms, and efficacy and effectiveness of thyroid hormone supplementation.

Limitations of the study: sample size is small, FT3, FT4 and rT3 were not measured in patients the values would be much more specific.

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