PREVALENCE OF THYROID DYSFUNCTION IN CKD PATIENTS IN A TERTIARY CARE HOSPITAL

J. Siva Somana1, T. Uma2, R. Mahalakshmi3

1Assistant Professor, Department of Biochemistry, Government Thoothukudi Medical College, Thoothukudi.
2Junior Consultant, Department of Biochemistry, I0G Hospital, Chennai.
3Professor & HOD, Department of Biochemistry, Government Stanley Medical College, Chennai.

ABSTRACT

BACKGROUND
Subclinical hypothyroidism, an independent predictor of cardiovascular morbidity and mortality, is 4-10% prevalent in the general population. A higher prevalence of clinical and subclinical primary hypothyroidism exists in CKD patients leading to ESRD earlier.

The objective is to study the prevalence of subclinical hypothyroidism and its correlation with various stages of chronic kidney disease.

MATERIALS AND METHODS
50 CKD patients in the predialysis phase and 50 healthy controls, who attend the regular OPD in a tertiary care hospital were selected for our study. Staging of CKD done with the eGFR calculated using MDRD formula and the prevalence of subclinical hypothyroidism with TSH levels <10 mIU/mL were studied in these patients and compared with the control population.

RESULTS
Subclinical hypothyroidism is more prevalent in CKD patients (40%) when compared with the general population (6%). Subclinical hypothyroidism was found to be 8%, 10%, 20% and 12% in the stages II, III, IV and V of CKD patients and it gradually increases as the stage of the CKD advances. As the eGFR falls, TSH starts increasing and it may be due to alteration in the hypothalamo-pituitary axis, TSH glycosylation and diurnal rhythm. It may also be due to altered metabolism of thyroid hormones and decreased peripheral conversion of T4 to T3. The exact mechanisms linking CKD and hypothyroidism are still unclear.

CONCLUSION
From the results of our study, we conclude that the prevalence of subclinical hypothyroidism is high among all the stages of CKD patients. Need for treatment depends on the patient’s clinical scenario and decision of the clinician based on the presentation. Many more clinical trials are needed to prove the need for thyroxine replacement.

KEYWORDS
Chronic Kidney Disease, Predialysis Phase ESRD, Subclinical Hypothyroidism, MDRD Formula, TSH, Free T4 Levels.

Aims & Objectives
- To estimate TSH and Free T4 levels in chronic kidney disease patients.
- To calculate the eGFR using MDRD Formula and classify the patients with CKD into 5 stages.
- To study the prevalence of subclinical hypothyroidism in patients with various stages of chronic kidney disease.

MATERIALS AND METHODS
50 apparently normal healthy persons aged more than 20 years and 50 patients aged more than 20 years with CKD illness of >6 months duration and not undergone dialysis from Nephrology OPD in Govt. Stanley Hospital were included in the study.

After getting clearance from the institutional ethical committee, study population was selected and examined after informed consent. Fasting morning blood sample was collected under strict aseptic precautions in red topped clot-activator venepuncture tubes.

Blood was allowed to clot. After centrifugation at 2000-2500 rpm for 15 minutes, serum samples were separated immediately from the cells and stored at -20°C in deep freezer. Renal and thyroid function tests were done in the serum.

eGFR calculated using MDRD formula with serum creatinine done using enzymatic kit from Agappe and patients were classified into 5 stages according to American Kidney Foundation as follows: Stage 0 > 90 mL/min. With risk factors for CKD; Stage I ≥ 90 mL/min. With demonstrated kidney damage Stage II -60-89 mL/min., Stage III - 30-59 mL/min., Stage IV - 15-29 mL/min., Stage V - < 15 mL/min.

Statistical Analysis
Clinical and hormonal assessment of thyroid function in patients with chronic kidney disease were compared with control patients and studied using Excel software. Statistical significance is considered when p-value is <0.001.

RESULTS

Prevalence of thyroid disorders are 71.4%, 62.5%, 56% and 80% in the stages II, III, IV and V of CKD respectively. Patients with subclinical hypothyroidism increase as the stage of CKD advances.

Based on Chi-square test, Calculated \( \chi^2 \) value = 39.06; Tabulated \( \chi^2 \) value at \( p < 0.05 = 3.841 \)

Calculated \( \chi^2 \) value > tabulated \( \chi^2 \) value and hence there is statistically significant difference in the prevalence of thyroid abnormalities among CKD patients when compared with the control population.

| Positive predictive value: | \( \frac{TP}{TP+FP} \) = 33/36 = 91.7% |
| Negative predictive value: | \( \frac{TN}{TN+FN} \) = 47/64 = 73.4% |

The positive predictive and negative predictive values were 91.75 and 73.46 respectively. The positive predictive value suggests an increased chance of subclinical hypothyroidism association with chronic kidney disease than the control population. Prevalence of subclinical hypothyroidism is about 6% in normal population when compared with patients.

Pearson’s correlation coefficient of different analytes among CKD patients shows: TSH varies directly with urea (positive correlation) and inversely with eGFR (negative correlation). Free T4 varies directly with eGFR (positive correlation) and inversely with urea & creatinine (negative correlation).

TSH values have a negative correlation with eGFR as indicated by the downward slope of linear regression analysis and the \( r \) value is equal to 0.056. TSH values have a negative correlation with creatinine indicated by the downward slope of the linear regression value and the \( r \) value is equal to 0.1. TSH values have negative correlation with urea values as indicated by the downward slope of the linear regression analysis and the \( r \) value is equal to 0.2.

DISCUSSION
The case-control study with 50 healthy control subjects and 50 patients of CKD demonstrated the increased prevalence of subclinical hypothyroidism among CKD patients in the predialysis phase.

GFR was estimated using MDRD formula and the CKD patients were divided into 6 stages using the National Kidney Foundation. K/DOQI Clinical Practice Guidelines for chronic kidney disease. Cases were 50%, 20%, 16% & 15% in stages IV, V, III and II respectively.

No cases in stage 0 and I, suggesting a delay in seeking medical attention and thereby very late presentation of the patients to the OPD. The duration of illness was less than two years in most patients (24 out of 50).

There was an increase in the TSH values with fall in eGFR and free T4 levels sustain in the normal range despite low eGFR in the CKD patients. Kapstein et al demonstrated a low total T4 levels in their patients. Also, they explained that low total T4 levels are due to altered protein binding in CKD patients and hence not much variation observed in free T4 levels.14

We found the prevalence rates of subclinical hypothyroidism, hypothyroidism, subclinical hyperthyroidism and hyperthyroidism in CKD patients as...
40%, 20%, 4% and 2% respectively. 34% of patients have normal thyroid profile. Ghanshyam et al showed increased prevalence of SCH in CKD patients in contrast to healthy controls in their studies.

The prevalence of subclinical hypothyroidism was found to be 8%, 10%, 20% and 12% in the stages II, III, IV and V of CKD patients.

It gradually increases as the stage of CKD advances. Lo et al showed in their studies, 10 to 20% of patients with stage II to V chronic kidney disease (CKD) are hypothyroid and the subclinical cases among them are >50%. Giovanni et al showed subclinical hypothyroidism was about 20% prevalent in earlier stages of CKD independent of other biochemical parameters.

In our study, the prevalence of thyroid abnormalities were found to be more in stages IV and V suggesting an increased prevalence as the stage of CKD advances. Most of them are with hypothyroidism either subclinical or overt on testing. Kapstein et al showed prolonged Wolff-Chaikoff effect, blunted response to thyroid stimulation tests and abnormal rhythm of TSH secretion as the reasons for reduced serum T4 levels among CKD patients.

Based on chi-square test, there is a statistically significant difference in the prevalence of subclinical hypothyroidism among CKD patients when compared with the general population. Positive predictive value of SCH in CKD is found to be 91.7%. Prevalence of subclinical hypothyroidism was about 6% in the control population. SCH has been found to be 8% prevalent in the general population.

On comparison of cases and controls using Student’s unpaired “t” test, a statistically significant difference in their TSH, eGFR, urea and creatinine values except free T4 values suggests that TSH, eGFR, Urea and Creatinine levels are higher than the controls except the free T4 values which are mostly comparable between cases and controls.

Student’s unpaired ‘t’ test between quantitative variables among cases suggests that TSH, eGFR, Urea and Creatinine levels are dependent on each other but the free T4 values are independent of these variables among CKD patients.

TSH values increase with decrease in the eGFR values suggesting that there was a negative correlation between eGFR and TSH levels. Giovanni et al showed that high TSH levels were more closely related to the low eGFR values in their studies.

There is a positive correlation between TSH and Urea suggesting that TSH increases as the urea level increases with advanced stage of CKD. Ramirez et al showed that uraemia causes alteration in hypothalamo-pituitary axis and thereby high urea levels cause an elevation in the TSH levels.

With decrease in the GFR, free T4 starts decreasing. In contrast, Giovanni et al showed that there is no much variation in free T4 levels among different stages of CKD. A negative correlation exists between free T4 and Urea among CKD patients. Zoccali et al found no reduction of FT4 levels when compared with low T3 levels among ESRD patients as the defect is mainly due to inhibition of peripheral conversion of T4 to T3 by inflammatory mediators.

Shin et al showed that there is attenuation of fall in GFR on thyroid replacement therapy and also TRT reduces the progression rate to ESRD. High total and LDL cholesterol levels have been demonstrated in SCH. According to some studies, treatment of SCH with Eltroxin improves the cardiac contractility and lowers the total cholesterol and LDL levels than the pretreatment levels. No beneficial effects have been demonstrated in some other studies. Also the treatment in CKD to bring euthyroidism to preserve renal function has not yet been extensively studied.

In overt hypothyroidism, there is decreased renal blood flow and GFR, high creatinine levels and hypoaetraemia leading to worsening of kidney function. Makino et al showed that thyroid replacement therapy improves the renal function in these patients and more so in patients with ischaemic renal failure. No such definite pathology has been found in subclinical hypothyroidism by Villabona et al. Fatourechi et al showed that patients with SCH and TSH levels more than 10 mIU/mL and also patients with TPO antibodies and TSH levels less than 10 mIU/mL were benefitted on treatment.

In this study, we found an increased prevalence of subclinical primary hypothyroidism in persons with reduced estimated GFR independent of other parameters compared with the general population. The incidence of subclinical hypothyroidism was found to increase with progressively lower eGFR values. But the exact mechanism linking CKD and hypothyroidism still remains unclear.

CONCLUSION
From the results of our study, we conclude that

- Prevalence of subclinical hypothyroidism is high among all the stages of CKD patients.
- Incidence of thyroid abnormalities increases as the stage of CKD advances with fall in GFR.
- But the need for treatment depends on the patient’s clinical scenario and decision of the clinician based on the presentation. Many more clinical trials are needed to prove the need for thyroxine replacement.

REFERENCES


