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SUBCLINICAL THYROID DYSFUNCTION IN CHRONIC KIDNEY DISEASE PATIENTS ON MAINTAINANCE HEMODIALYSIS

General Medicine

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ABSTRACT

BACKGROUND : Chronic kidney disease(CKD) disrupts the homeostasis of the body by ill effects on various physiologic systems, endocrine system being one of them . There have been many studies about thyroid dysfunction in persons with acute systemic illness and in CKD patients not on maintainance hemodialysis. The data regarding prevalence of thyroid dysfunction in persons with chronic kidney disease (CKD) requiring chronic dialysis is sparse.

OBJECTIVE: The present study was done to assess the prevalence and type of subclinical thyroid dysfunction in patients of chronic kidney disease(CKD) on maintainance hemodialysis

STUDY METHODOLOGY: Cross-sectional data from 100 adult patients who were registered in the hemodialysis unit of Guru Gobindsingh Civil Hospital, Jamnagar, Gujarat, India, was analyzed with Multivariable logistic regression analysis.The data consisted of estimated Glomerular filtration rate (eGFR), calculated by the abbreviated Modification of Diet in Renal Disease(MDRD) equation and serum TSH, serum free T3 and serum free T4.

RESULTS: Statistically nonsignificant negative correlation was found between estimated GFR and serum TSH, serum free T3, serum free T4 (Pearson's correlation r= - 0.178, - 0.052 and -0.110 respectively).

CONCLUSION: In our study we found that although subclinical thyroid dysfunction, more of subclinical hypothyroidism is detected in patients of chronic kidney disease on maintainance hemodialysis, it is not statistically significant.

KEYWORDS

CKD, Hemodialysis, Subclinical Thyroid Dysfunction, TSH, Serum Free T4

INTRODUCTION:

Subclinical thyroid dysfunction is purely a biochemical definition.It may be in the form of subclinical hypothyroidism or subclinical hyperthyroidism.Subclinical hypothyroidism is biochemically defined as elevated serum TSH levels with serum free thyroxine (fT4) levels and serum free triiodothyronine (fT3) levels within normal laboratory reference range and subclinical hyperthyroidism is defined as decreased serum TSH concentrations and normal fT4 and serum free triiodothyronine (fT3) levels(1).

Thyroid hormone is metabolized in human body by deiodination, glucuronation, sulphation, deamination and decarboxylation of the alanine side chain of thyroid hormones, ether link cleavage. Liver, peripheral tissues and kidneys play an important role in metabolism of thyroid hormones, mainly by action of various deiodinases.(2)

Chronic kidney disease affects thyroid function in multiple ways(2-3)

- including low circulating thyroid hormone concentration,
- altered peripheral hormone metabolism
- decreased plasma protein levels
- disturbed binding to carrier proteins
- possible reduction in tissue thyroid hormone content
- increased iodine store in thyroid glands

Although various possible mechanisms affecting thyroid function in kidney disease are hypothesized, the exact mechanism is not known.

The implications of the subclinical thyroid dysfunction are myriad.In various studies, subclinical primary hypothyroidism has been recognized to be associated with markers of 'increased cardiovascular risk and cardiac impairment and increased atherosclerosis(4–6). Chronic kidney disease is itself a risk factor for cardiovascular mortality. Subclinical primary hypothyroidism has been identified as a strong predictor of all-cause mortality in chronic dialysis(peritoneal) patients and as a risk factor for nephropathy and cardiovascular events in type 2 diabetic patients (7,8).So it becomes necessary to study the prevalence of subclinical thyroid dysfunction in CKD patients(with/without renal replacement therapy, hemodialysis here)

MATERIALS AND METHODS-

We have performed a cross-sectional analysis of patients registered for maintainance hemodialysis at Guru Gobindsingh Civil Hospital, Jamnagar, Gujarat, India, with the purpose of estimating the prevalence of subclinical thyroid dysfunction in patients of CKD on maintainance hemodialysis.

We collected data of serum creatinine, serum urea and thyroid function tests, which have been performed on 100 outpatient adults (≥18 yr of age) on maintenance hemodialysis (once weekly to thrice weekly) registered at Guru Gobindsingh Civil Hospital, Jamnagar, Gujarat, India. Patients who are currently on maintenance dialysis in the year 2018-2019 were chosen. For these analyses, we excluded participants who were diagnosed cases of thyroid disorder. Among multiple test results of thyroid function and kidney function available, the most recent results of same blood sample subjected to both tests were chosen. All participants gave their informed consent.

Morning venous blood samples of fasting subjects were collected and serum creatinine, serum urea were assayed by enzymatic procedures according to manufacturer's specifications and employing proprietary reagents. Thyroid function tests (serum TSH, free t3 and free t4) were quantified by two-site, chemiluminescent, immunometric assays on the IMMULITE-2000 analyzer (Diagnostics Products, Los Angeles, CA).

Estimated GFR was calculated by using the formula developed and validated in the Modification of Diet in Renal Disease study. The Modification of Diet in Renal Disease formula was as follows: estimated GFR = 175.0 × (serum creatinine−1.154) × (age−0.203) × 1.212 (if black) × 0.742 (if female) (11).

STATISTICAL ANALYSIS:

Data are expressed as mean ± SD(Standard Deviation) or proportions. Statistical analyses included the unpaired t test (for continuous measures) and the $\chi 2$ test with Yates' correction for continuity (for categorical variables). Skewed variables (triglycerides) were logarithmically transformed to improve normality before analysis. The independent relationship between subclinical thyroid dysfunction (as

mIU/L for subclinical hypothyroidism and TSH <0.5 mIU/L with FT4 levels within the reference range) and chronic kidney disease (CKD) (categorized as eGFR <60 ml/min per 1.73 m2) was tested by multivariable logistic regression analysis. All known potential confounders (age, gender, plasma glucose, total cholesterol, and triglycerides) were entered in the multivariable model to ensure giving an unbiased estimate for the relation between subclinical hypothyroidism and CKD. P values <0.05 were considered to be statistically significant.

OBSERVATION:

Table: 1

	Mean ± SD				P Value
Variable	Normal (n=70)	Hyperthyroidism (n=6)	Hypothyroidism (n=24)	Total (n=100)	
Age (years)	52.30 ± 12.454	59.33 ± 4.18	54.96 ± 11.62	53.26 ± 11.848	0.297
FT3 (pg/ml)	365.391 ± 101.865	459.99 ± 333.72	345.48 ± 249.27	367.554 ± 166.2751	0.329
FT4 (ng/dl)	1.361 ± 0.265	1.278 ± 0.467	1.167 ± 0.375	1.31 ± 0.3156	0.033
TSH (mIU/L)	2.56 ± 1.48	0.28 ± 0.098	8.0 ± 1.77	2.875 ± 3.71	3.873×10^{-28}
Blood urea (mg/dl)	74.99 ± 33.86	79.67 ± 26.87	80.92 ± 31.85	76.63 ± 33.054	0.733
Serum creatinine (mg/dl)	6.03 ± 2.91	6.467± 3.34	6.99 ± 3.12	6.24 ± 3.014	0.398
eGFR(ml/min/1.73 sq m BSA)	13.78 ± 0.50	10.16 ± 4.00	11.48 ± 9.02	13.29 ± 10.244	0.480

defined as TSH >4.5

Total 100 patients were included in the study. Out of the total, 70(70%) had normal thyroid function. 6(6%) has subclinical hyperthyroidism and 24(24%) had subclinical hypothyroidism.

Mean age of the study group was 53.26years with SD of 11.848 years. Mean age of normo-thyroid group was 52.3(± 12.454)years. Mean age of subclinical hyperthyroid group was 59.33 (± 4.18) years and that of subclinical hypothyroid group was 54.96 (± 11.62) years These differences in the mean age are not statistically significant. (p=0.297)

Mean value of fT3 level was 367.554(± 166.2751) pg/ml.Patients with normal thyroid function had mean of fT3 level of 365.391(± 101.865) pg/ml.Mean fT3 levels of subclinical hyperthyroid and subclinical hypothyroid groups were 459.99 (± 333.72)pg/ml and 345.48(± 249.27) pg/ml respectively These differences in the mean fT3 levels are not statistically significant. (p=0.329)

Mean value of fT4 level was 1.309ng/ml with SD of 0.316ng/ml. Among the patients of normal thyroid function, mean of fT4 level was 1.361ng/ml (± 0.265). Hyperthyroid patients had a mean fT4 level of 0.1278 ng/ml with SD of 0.467.ng/ml Hypothyroid patients had mean fT4 level at 1.167 ng/ml with SD of 0.375 ng/ml. This difference in the mean fT4 levels is statistically significant. (p=0.033)

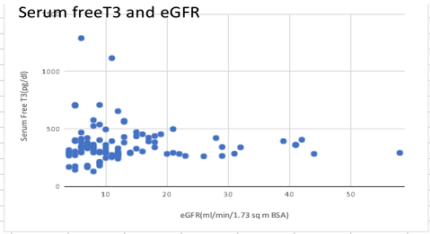
Mean value of serum TSH level was 2.875mIU/L with SD of 3.71.mIU/L Among the patients of normal thyroid function, mean of serum TSH level was 2.56mIU/L with SD of 1.48.mIU/L Hyperthyroid patient has mean serum TSH level of 0.28mIU/L with SD of 0.098.mIU/L Hypothyroid patients had mean serum TSH level at 8.0 mIU/L with SD of 1.77.mIU/L This difference in the mean serum TSH levels is statistically significant. ($p=3.837 \times 10^{-28}$)

The difference in blood urea in the normo thyroid, subclinical hyperthyroid and subclinical hypothyroid groups (74.99 ±33.86, 79.67± 26.87, 80.92± 31.85 mg/dl respectively) was not statistically significant from the mean blood urea of the study group 76.63± 33.054 mg/dl(p=0.733).

Among the 100 patients recruited for the study, 6 (6%) were below 30 years of age, 13(13%) were between 31 and 40 years of age and 81(81%) were above 41 years of age. 60(60%) were males and 40(40%) were females. Mean age of males was 56.59 years with SD of 10.031 years. Mean age of females was 48.63% with SD of 13.15 %. Mean age of males was significantly higher than that of females (p=0.001)

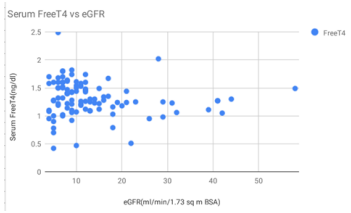
There was no statistically significant association between thyroid function of the patient and age group (p=0.586) or gender (p=0.855)

Chart 1



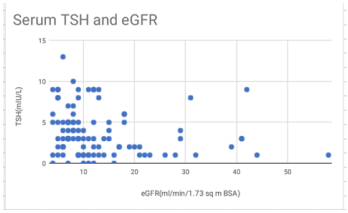
Scatter plot of fT3 against eGFR and its corelation analysis shows that fT3 value decreases with increasing eGFR ®= -0.052 and $r^2 = 0.0027$) but this correlation between fT3 and eGFR is not statistically significant (p=0.644).

Chart 2:



Similarly, corelation analysis of fT4 and eGFR shows that fT4 value decreases with increasing eGFR ®= -0.110 and $r^2 = 0.0121$) but this correlation between fT3 and eGFR is not statistically significant (p=0.290).

Chart 3:



Corelation analysis that serum TSH and eGFR shows that TSH values decrease with increasing eGFR ®= -0.178 and $r^2 = 0.0316$) but this correlation between serum T3 and eGFR is not statistically significant (p=0.322).

DISCUSSION

Subclinical thyroid dysfunction in the form of subclinical hypothyroidism is well known in CKD.CKD and subclinical hypothyroidism are independent risk factors for cardiovascular disease (4-6).Similarly, subclinical hyperthyroidism is also a risk factor for atrial fibrillation(9).

In many studies, subclinical hypothyroidism was found to be commonly prevalent in patients of chronic kidney disease not on hemodialysis(10-15).Studies in North India and South India also showed similar results(16,17)

In our study, out of the total 100 CKD patients studied, 30 patients had subclinical thyroid dysfunction.Subclinical hypothyroidism was found in 24 patients(80%) and subclinical hyperthyroidism was found in 6 patients(20%). It was also observed that most of the patients(27 out of the 30 of thyroid dysfunction patients) were in the age group above 40 yrs.Compared to previous studies, the results of our study differ in that, subclinical hyperthyroidism was also found in addition to subclinical hypothyroidism.The subclinical thyroid dysfunction seen in CKD patients on maintainance hemodialysis was not statistically significant.Simarly, the difference of age seen in the thyroid

dysfunction groups was not statistically significant.
Though, Serum fT4 levels were within normal range in the normo-thyroid, subclinical hypothyroid and subclinical hyperthyroid patients, the difference in the mean values of subclinical hyperthyroid patients and normo-thyroid patients was statistically significant with p=0.033.
Mild negative corelation was found between eGFR and each of serum TSH, fT3 and fT4, but without statistical significance.

This study has several limitations that should be noted. First, because this study is cross-sectional, the present analysis is limited in its ability to establish causal or temporal relationships between subclinical thyroid dysfunction and kidney disease.Second, the definition of kidney function was based on eGFR rather than on more precise measurement of kidney function, such as iothalamate clearance.Strengths of the study included all diagnosed thyroid abnormality patients were excluded from our study.Our clinical laboratory used uniform methods to collect data on serum urea, serum creatinine, thyroid function(serum TSH, fT3 and fT4)

CONCLUSION

In our study we found that, though subclinical thyroid dysfunction, more of subclinical hypothyroidism is found in patients with CKD requiring chronic dialysis, the prevalence of that is not statistically significant. Some cases of subclinical hyperthyroidism were also found. Future large scale studies are needed to find out if there is a significant prevalence of subclinical thyroid disorders in CKD patients on maintainance hemodialysis and whether patients with CKD should be routinely screened for subclinical thyroid disorders and whether treatment of the same has a beneficial effects on the patients in terms of general well-being and beneficial cardiovascular benefits.

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