

Evaluation of Thyroid Dysfunction in Patients of Chronic Kidney Disease.

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Abstract

Introduction:

Chronic kidney disease (CKD) is an emerging health problem that affects 5-10% of world population with increasing prevalence and adverse outcomes. Progression of renal disease is associated with number of complications such as anemia, secondary hyperparathyroidism, CVD, thyroid dysfunction, dyslipidemia and CKD-BMD (Bone mineral disease). This study was conducted to investigate thyroid function in CKD patients.

Methods:

The present study was a prospective observational study conducted on 150 adult patients of CKD, 50 each from stage 3, 4, and 5 on regular follow up of kidney and dialysis clinic. Demographic features (age and sex) and medical history of diabetes mellitus, hypertension and cardiovascular diseases of each patient were noted, and blood samples (5 ml) were analyzed for serum urea, creatinine, glucose, complete lipid profile, free triiodothyronine (T3), free thyroxine (T4), thyroid stimulating hormone (TSH).

Results:

Thyroid dysfunction was found in 32% CKD patients, the most common thyroid dysfunction being subclinical hypothyroidism (19.33%). Overt hypothyroidism was present in 4.67% of patients. Subclinical hypothyroidism became significantly common with CKD progression. Prevalence of subclinical hypothyroidism in stage 3, stage 4 and stage 5 was 10, 16 and 32% respectively.

Conclusions:

Thyroid dysfunction significantly affects the CVD outcome in CKD. Our study showed significantly increased TSH level across CKD stages. This study emphasizes on the importance of regular screening and treatment of thyroid dysfunction in patients with CKD, which may further help to prevent CVD risk. This would help in better clinical management of patients with CKD and thus better quality of life and improved morbidity and mortality. So, the regular checkup of thyroid functions is recommended in patients with CKD.

Keywords:

Chronic kidney disease, Dyslipidemia, Subclinical hypothyroidism, Thyroid dysfunction.

Introduction

Chronic kidney disease (CKD) is an emerging health problem that affects 5-10% of world population with increasing prevalence and adverse outcomes. The rapid rise in CKD in developing countries can be attributed to increase in chronic diseases like diabetes mellitus, hypertension and cardiovascular disease (CVD) [1]. In India, the overall prevalence of CKD is 17.2% and prevalence of CKD stage 1,2,3,4 and 5 are 7%, 4.3%, 4.3%, 0.8% and 0.8% respectively [2]. Compared to general population, CKD patients have 7 to 10-fold higher

mortality risk, out of which 40% deaths occur due to cardiovascular causes [3]. Anemia, secondary hyperparathyroidism, CVD, dyslipidemia and CKD-BMD (Bone mineral disease) are major complications of CKD.

Progression of renal disease is also associated with abnormalities in thyroid functions [4]. Thyroid is the one of the important gland in human body, as it regulates various vital physiological processes in our body. Kidney is involved in the metabolism, degradation and excretion of thyroid hormones. Any abnormalities in the thyroid functions can be linked to various pathologies throughout the body. CKD not only interferes with hypothalamus-pituitary-thyroid axis, but also affects the peripheral metabolism of thyroid hormones. CKD has been known to affect the thyroid function in many ways like, low circulating thyroid hormone levels, altered peripheral metabolism, insufficient binding to carrier proteins, reduced tissues thyroid hormone content and, altered

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iodine storage in thyroid gland [5]. Progression of CKD is associated with higher prevalence of primary hypothyroidism, especially the subclinical form [6]. Low T3 (Triiodothyronine) is most common laboratory finding and subclinical hypothyroidism is most common thyroid disorder seen in CKD [4]. Hyperthyroidism has been known to accelerate the kidney dysfunction, but it is not usually associated with CKD.

Thyroid disease increases the CVD risk which may further increase the morbidity and mortality in CKD. So the earlier screening and diagnosis of thyroid abnormalities in CKD may retard further progression. Many studies have been done on thyroid function in CKD. Still the results of these studies seemed to be inconsistent. There is paucity of data from developing countries like India and most of the available data is from developed countries. Hence the present study was done at our tertiary care centre to more elaboration of the thyroid function in CKD patients.

Material and Methods

The present study was a prospective observational study conducted on 150 adult patients of CKD, 50 each from stage 3, 4, and 5 on regular follow up of kidney and dialysis clinic. After taking written informed consent and a thorough history, each participant had undergone detailed clinical, biochemical and radiological examination to establish the stage of CKD. All the patients were assessed for thyroid functions. Pregnant patients, patients on hormone replacement therapy, on lipid lowering agents and having thyroid malignancy were excluded. The study was approved by ethical committee of Pt. B.D. Sharma University of Health Sciences. The patients were divided into three groups: Group A, B and C based on CKD staging.

- Group A** consisted of 50 patients with eGFR between 30-59 ml/min/1.73m² (CKD Stage III).
- Group B** consisted of 50 patients with eGFR between 15-29 ml/min/1.73m² (CKD Stage IV)
- Group C** consisted of 50 patients with of eGFR < 15 ml/min/1.73m², not on Hemodialysis (CKD stage V)

Morning blood samples were taken after an overnight fasting for generation of plasma and serum for biochemical parameters analysis. Blood hemoglobin, blood urea, random blood sugar, serum creatinine, uric acid, sodium, potassium, calcium, phosphate, total protein, fasting lipid profile (Triglycerides, Total Cholesterol, HDL, LDL, VLDL) and creatinine were analyzed using certified methods at the department of biochemistry at PGIMS, Rohtak. Creatinine clearance was calculated using MDRD formulae. Free triiodothyronine

(FT3), free thyroxine (FT4), Thyroid stimulating hormone (TSH) and Anti-Thyroid Peroxidase (TPO) antibodies were measured by chemiluminescent immunoassay and high sensitivity C-reactive protein (hsCRP) was measured by immuno-turbidimetry.

Thyroid dysfunction was considered if patients thyroid hormone levels fall outside the reference range; free T3 (1.71–3.71 pg/ml), free T4 (0.80–1.70 ng/ml) and TSH (0.35–4.94 mIU/ml). Euthyroid was considered if thyroid hormone levels fall within reference range. Overt hypothyroidism was defined as TSH > 4.94 mIU/ml and free T3 < 1.71 pg/ml and free T4 < 0.80 ng/ml. Subclinical hypothyroidism was considered if TSH > 4.94 mIU/ml and free T3 and free T4 within reference range. Anti-Thyroid Peroxidase (TPO) antibodies > 34 IU/ml was taken as abnormal.

Statistical Analysis

At the end of the study, the data was expressed as mean ± 1SD or range. Probability values of <0.05 were considered to be significant in all the analyses. ANOVA test was used to analyze differences in quantitative variables between the groups. The correlations were tested using Pearson correlation coefficient analysis. All statistical calculations were carried out using SPSS 21.0 software.

Results

Study group comprised of 150 cases of CKD. Out of total 150 patients, 94 were male and 56 were female. Majority of patients (84.67%) were above 40 years of age and were equally distributed in all groups. The mean age of study population was 52 years, ranging from 18 to 75 years. The most common cause of CKD in all groups was diabetes mellitus (38%) followed by hypertension (23.33%) and chronic glomerulonephritis (14%). General characteristics of the studied population are summarized in Table-1. Various biochemical parameter, lipid and thyroid profile as shown in Table-2. Blood urea, creatinine and TSH level increased significantly across CKD stages 3–5. Thyroid function status according to CKD stages is shown in Table-3. Thyroid dysfunction was found in 32% CKD patients, the most common thyroid dysfunction being subclinical hypothyroidism (19.33%). Subclinical hypothyroidism became significantly common with CKD progression. Prevalence of subclinical hypothyroidism in stage 3, stage 4 and stage 5 was 10, 16 and 32% respectively. Serum creatinine, serum apolipoprotein-B and hs-CRP were significantly positively correlated with TSH with p value <0.05 and significant negative correlation exist between serum albumin and TSH (p value <0.05) as shown in Table-4.

On performing univariate logistic regression only hs-CRP and serum apolipoprotein-B were the significant risk factors of low T3 syndrome. With the increase in hs-CRP by 1 unit, risk of low T3 syndrome increases by 53.1% and with the increase in serum apolipoprotein-B by 0.01 unit, risk of low T3 syndrome increases by 13.39% and with multivariate logistic regression only serum apolipoprotein-B was the significant risk factor of low T3 syndrome resulting in an increased risk of 10.25% for the low T3 syndrome with a rise of apolipoprotein-B by 0.01 unit.

On performing univariate logistic regression BMI, eGFR, hs-CRP, serum apolipoprotein-B and serum creatinine were the significant risk factors of subclinical hypothyroidism. With the increase in BMI by 1 unit, risk of subclinical hypothyroidism decreases by 15.8%, with the increase in eGFR by 1 unit, risk of subclinical hypothyroidism decreases by 4.1%, with the increase in hs-CRP by 1 unit, risk of subclinical hypothyroidism increases by 87.3%, with the increase in serum apolipoprotein-B by 0.01 unit, risk of subclinical hypothyroidism increases by 26.72% and with the increase in serum lipoprotein by 1 unit, risk of subclinical hypothyroidism increases by 16.7% and with multivariate logistic regression only serum apolipoprotein-B was the significant risk factor of subclinical hypothyroidism. With the increase in serum apolipoprotein-B by 0.01 units, risk of subclinical hypothyroidism increases by 42.30%. On performing multivariate linear regression, after adjusting for confounding factors, only cholesterol was significantly affecting TSH. With the increase in serum cholesterol by 1 unit, TSH significantly decreases by .070 units.

On performing univariate logistic regression only hs-CRP and serum apolipoprotein-B were the significant risk factors of overt hypothyroidism. With the increase in hs-CRP by 0.1 unit, risk of overt hypothyroidism increases by 10.43% and with the increase in serum apolipoprotein-B by 0.01 unit, risk of overt hypothyroidism increases by 17.09% and with multivariate logistic regression, after adjusting for confounding factors, both hs-CRP and serum apolipoprotein-B were the significant risk factors of overt hypothyroidism. With the increase in hs-CRP by 0.1 unit, risk of overt hypothyroidism increases by 12.04% and with the increase in serum apolipoprotein-B by 0.01 unit, risk of overt hypothyroidism increases by 17.12%.

TSH is positively correlated with LDL cholesterol, total cholesterol, triglycerides and VLDL cholesterol, while it has a negative correlation with HDL cholesterol. FT3 has a reciprocal correlation with all these lipid parameters with respect to TSH.

Discussion

CKD is one of the serious health problems worldwide, especially in industrialized countries with significant mortality. With progressive decline in renal functions, number of complications become common such as thyroid abnormalities, dyslipidemia, bone mineral disorder, anemia etc. CKD also affects the function of endocrine organ including, impaired secretion of kidney derived hormone, peripheral hormone metabolism, accumulation of hormone inhibitors as well abnormal target organ responsiveness. These complications increase the mortality as well as health care cost of management in CKD patients.

CKD and thyroid dysfunction are interlinked conditions which mutually affect each other. One can find a thyroid dysfunction in CKD and renal dysfunction in thyroid disorders. The prevalence of thyroid abnormalities becomes common with the progression of CKD. In CKD the pituitary receptor response to thyrotropin releasing hormone (TRH) is blunted causing decrease in thyroid stimulating hormone (TSH) release. In addition the response of TSH to thyrotropin releasing hormone (TRH) is decreased because of decreased clearance and increased half life of TSH resulting in feedback inhibition of TRH [7]. The abnormal serum constituents seen in CKD patients also displace the T3 and T4 (Thyroxine) from normal protein binding sites. There is a transient increase in the T4 levels are usually seen after hemodialysis (HD). This effect is due to use of heparin as anticoagulant which affects T4 binding to proteins and leads to increase in T4 levels [7]. The decreased T3 levels in CKD is also due to the iodothyronine deiodinase which helps in synthesis of T3 from T4 whose activity is affected by fasting, chronic metabolic acidosis and chronic protein malnutrition seen in CKD. These factors interfere with protein binding to T3 [7]. The decreased T3 level is because of decreased peripheral conversion from T4 to T3 due to decreased clearance of inflammatory cytokines such as TNF- α (Tumour necrosis factor alpha) and IL-1 (Interleukin-1). These cytokines interfere with expression of 5'-deiodinase that help in conversion of T4 to T3. Thyroid function regulates a wide range of metabolic parameters. Thyroid function has significant impact on lipid metabolism as well as on some CVD risk factors [8, 9]. Overt hypothyroid patients display a variety of lipid abnormalities such as elevated Triglycerides (TG) levels associated with increased levels of VLDL and occasionally fasting chylomicronemia [10,11]. These lipid abnormalities in the patients of hypothyroidism predispose to the development of cardiovascular disease [12,13]. Subclinical hypothyroidism is also associated with dyslipidemia and has been recognized as marker of

Table 1: Baseline Demographics and Clinical Parameters

Baseline Parameters (Mean±SD)	Group A (n=50)	Group B (n=50)	Group C (n=50)	p value
Age (yrs)	52.82 ± 11.44	53.2 ± 11.04	51.32 ± 14.58	> 0.05*
Weight (kg)	65.26 ± 11.63	59.92 ± 8.92	58.42 ± 9.43	< 0.05*
Height (m)	166.18 ± 7.99	164.54 ± 8.92	163.51 ± 8.76	> 0.05*
Body Mass Index (kg/m ²)	23.71 ± 3.61	22.12 ± 2.58	21.8 ± 2.58	< 0.05*
Duration of disease (yrs)	5.61 ± 4.63	5.84 ± 2.66	6.55 ± 5.42	> 0.05*
Pulse rate (bpm)	79.82 ± 8.59	77.6 ± 9.28	79.56 ± 7.52	> 0.05*
Systolic Blood Pressure (mmHg)	128.68 ± 15.58	128.68 ± 17.33	135.22 ± 21.91	> 0.05 [#]
Diastolic Blood Pressure (mmHg)	81.28 ± 8.61	81.04 ± 9.21	82.14 ± 10.4	> 0.05 [#]
Mean Arterial Pressure (mmHg)	97.08 ± 10.46	96.92 ± 11.42	99.83 ± 13.28	> 0.05 [#]

* Analyzed by Kruskal Wallis test

Analyzed by ANOVA

Table 2: Baseline Bio-chemical Parameters, Lipid Profile and Thyroid Profile

Baseline Parameters (Mean±SD)	Group A (n=50)	Group B (n=50)	Group C (n=50)	p value
Haemoglobin (g/dL)	11.06 ± 1.51	9.86 ± 1.78	8.47 ± 1.38	< 0.05*
Total Leukocyte Count	7246.8±	7769 ± 2086.18	8113.4 ± 2864.54	> 0.05 [#]
Blood sugar (mg/dL)	2088.02	111.52 ± 35.59	129.3 ± 38.95	< 0.05*
Blood urea (mg/dL)	100.5 ± 21.7	108.8 ± 38.79	196.34 ± 75.39	< 0.05*
S. uric acid(mg/dL)	83.93 ± 35.72	7.68 ± 2.32	8.08 ± 2.76	< 0.05*
Serum Sodium (mEq/L)	5.83 ± 1.48	139.92 ± 3.02	140.96 ± 4.81	> 0.05*
Serum potassium (mEq/L)	139.52 ± 3.27	4.17 ± 0.45	4.25 ± 0.6	> 0.05*
Serum creatinine (mg/dL)	4.27 ± 0.54	3 ± 0.59	7.43 ± 2.71	< 0.05*
Serum calcium (mg/dL)	1.98 ± 0.57	8.68 ± 0.66	7.77 ± 0.51	< 0.05*
Serum phosphate (mg/dL)	9.2 ± 0.75	4.75 ± 1.57	6.38 ± 1.81	< 0.05*
Serum protein(g/dL)	3.84 ± 1.11	6.6 ± 0.61	6.38 ± 0.6	> 0.05*
Serum albumin(g/dL)	6.4 ± 0.67	3.44 ± 0.36	3.24 ± 0.4	> 0.05*
eGFR (ml/min/1.73m ²)	3.36 ± 0.41	21.58 ± 4.12	8.68 ± 3.18	< 0.05*
hs-CRP (mg/dL)	40.36 ± 7.34	1.24 ± 1.06	2.51 ± 1.39	< 0.05*
Serum Apo B(g/L)	0.85 ± 0.84	1.24 ± 0.36	1.27 ± 0.31	> 0.05*
S. Triglycerides (mg/dL)	1.21 ± 0.43	159.98 ± 46.43	165 ± 44.68	> 0.05*
S. Cholesterol(mg/dL)	154.16 ± 42.63	190.48 ± 36.25	192.66 ± 44.02	> 0.05*
S. HDL-Cholesterol(mg/dL)	199.78 ± 40.89	37.16 ± 12.44	30.88 ± 12.14	< 0.05*
S. LDL Cholesterol(mg/dL)	39 ± 10.9	151.48 ± 19.63	160.24 ± 23.13	< 0.05*
S. VLDL Cholesterol(mg/dL)	145.28 ± 23.29	31.34 ± 10.18	38.82 ± 14.74	< 0.05*
Free Triiodothyronine(FT3)	26.88 ± 7.83	1.96 ± 0.54	1.74 ± 0.31	< 0.05*
Free Thyroxin(FT4)	2.54 ± 0.58	1.29 ± 0.27	1.28 ± 0.26	> 0.05*
Thyroid Stimulating	1.25 ± 0.29	5.23 ± 4.56	8.09 ± 6.37	< 0.05*
Anti-TPO(IU/ml)	2.74 ± 1.85	45.68 ± 105.14	48.2 ± 111.81	> 0.05*
	28.52 ± 59.85			

*eGFR–Estimated Glomerular Filtration Rate,

Apo B–Apolipoprotein-B,

HDL–High Density Lipoprotein,

LDL–Low Density Lipoprotein,

VLDL–Very Low Density Lipoprotein

*-Analyzed by KruskalWalis test

#-Analyzed by ANOVA

Table 3: Thyroid Dysfunction in different CKD Stages

Thyroid Dysfunction	Group A (n=50)	Group B (n=50)	Group C (n=50)	Total	p value*
Euthyroidism	41 (82.00%)	35 (70.00%)	26 (52.00%)	102 (68.00%)	< 0.05
Low T3 syndrome	3 (6.00%)	4 (8.00%)	5 (10.00%)	12 (8.00%)	> 0.05
Overt	1 (2.00%)	3 (6.00%)	3 (6.00%)	7 (4.67%)	> 0.05
Hypothyroidism Subclinical Hypothyroidism	5 (10.00%)	8 (16.00%)	16 (32.00%)	29 (19.33%)	< 0.05

*Analyzed by Chi square test

Table 4: Correlation of Demographic, Clinical and Bio-chemical Parameters with Thyroid Profile

Baseline Parameters		Anti TPO (IU/ml)	FT3 (pg/ml)	FT4 (ng/dl)	TSH (mIU/ml)
Age (yrs)	Correlation Coefficient	-0.008	0.002	0.055	-0.051
	P value	>.05	>.05	>.05	>.05
Weight (kg)	Correlation Coefficient	-0.107	0.084	0.053	-0.161
	P value	>.05	>.05	>.05	<.05
Height (m)	Correlation Coefficient	-0.11	-0.022	0.055	-0.002
	P value	>.05	>.05	>.05	>.05
Body Mass Index (kg/m ²)	Correlation Coefficient	-0.041	0.09	0.024	-0.218
	P value	>.05	>.05	>.05	<.01
Haemoglobin (g/dL)	Correlation Coefficient	-0.083	-0.198	0.008	-0.125
	P value	>.05	<.05	>.05	>.05
Serum creatinine (mg/dL)	Correlation Coefficient	0.059	0.159	0.096	0.176
	P value	>.05	>.05	>.05	<.05
eGFR (ml/min/1.73m ²)	Correlation Coefficient	-0.085	-0.152	-0.067	-0.205
	P value	>.05	>.05	>.05	<.05
Serum albumin (g/dL)	Correlation Coefficient	-0.079	0.28	0.037	-0.284
	P value	>.05	<.01	>.05	<.01
Serum protein (g/dL)	Correlation Coefficient	-0.127	0.267	-0.028	-0.253
	P value	>.05	<.01	>.05	<.01
hs-CRP (mg/dL)	Correlation Coefficient	0.096	-0.079	-0.02	0.287
	P value	>.05	>.05	>.05	<.01
Serum Apo B (g/L)	Correlation Coefficient	0.23	-0.366	-0.024	0.469
	P value	<.01	<.01	>.05	<.01

Spearman rank correlation coefficient

CVD risk and cardiac dysfunction in various studies [14,15]. So these complications are increasing the overall mortality in CKD patients. In present study, the prevalence of thyroid dysfunction was found in 32% of CKD patients, the most common being the subclinical hypothyroidism (19.33%), followed by low T3 syndrome (8%) and overt hypothyroidism (4.67%), while 68% of the patients were euthyroid. Prevalence of subclinical hypothyroidism varies from 4 to 10% in general population and it has been found that hypothyroidism (overt or clinical) increases the risk of coronary artery disease. We observed significant decreasing trend for free T3 and increasing trend for TSH level across CKD stages 3-5, which suggests that prevalence of hypothyroidism increases with progression of renal impairment. Our study showed similar results with study done by Khatiwada et al in which they found thyroid dysfunction in 38.6% of CKD patients, the most common being subclinical hypothyroidism (27.2%), followed by overt hypothyroidism (8.1%) and subclinical hyperthyroidism (3.3%).¹⁶ Negative correlation of serum TSH with serum albumin was seen in this study which is consistent with the study done by Shantha et al [17]. Some studies showed that subclinical hypothyroidism is associated with low grade inflammation that subsequently leads to raised hsCRP levels. Positive association of TSH with serum hsCRP was observed in our study which was also reported by YT Yu et al [18]. There was also positive association between subclinical hypothyroidism and serum apolipoprotein-B consistent with the findings of Efstathiadou Z et al [19].

CKD is progressive disease and these patients are at increased risk of developing thyroid dysfunction. Subclinical hypothyroidism is common finding in CKD, the prevalence increases with degree of renal impairment. Subclinical hypothyroidism has been recognized as a strong predictor of all-cause mortality in chronic dialysis patients and as a risk factor for nephropathy and cardiovascular events in type 2 diabetic patients [20]. Various studies demonstrated improvement in cardiac dysfunction caused by subclinical hypothyroidism with the thyroid hormone supplementations. At present it is still debatable about the hormone replacement therapy in CKD patients with subclinical hypothyroidism and no guidelines exist for the recommending the hormone replacement therapy in CKD patients [7]. Further studies are needed to establish advantage of thyroid hormone supplementation in CKD.

The present study was associated with certain limitations. One of the limitations of this study was that it was a cross-sectional study and no follow up was done. No intervention was done in this study as well as sample size

was small and no control group was included in this study. A longitudinal study can assess the association between thyroid dysfunction and long term outcomes in CKD patients.

Conclusions

Thyroid dysfunction significantly affects the CVD outcome in CKD. Our study showed significantly increased TSH level across CKD stages. The findings of present study have great clinical significance. It emphasizes on the importance of regular screening and treatment of thyroid dysfunction in patients with CKD, which may further help to prevent CVD risk. This would help in better clinical management of patients with CKD and thus better quality of life and improved morbidity and mortality. So, the regular checkup of thyroid functions is recommended in patients with CKD.

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