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Study of Thyroid and Lipid Profile in Chronic Kidney Disease

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Abstract
CKD encompasses a spectrum of different pathophysiology processes associated with abnormal kidney function, and a progressive decline in GFR. CKD affects thyroid function in many ways and is often associated with altered lipid metabolism. Hence, the present study was done to the present study was done in undialyzed CKD patients to determine serum Total T_3, T_4, TSH and serum lipid profile and compare them with healthy controls. The study group consisted of 130 subjects. Of these - 40 belong to stage 3 CKD (Group 2), 30 belong to stage 4 & 5 CKD (Group 3) and 50 were age and sex matched controls (Group 1). Results show that serum total T_3, T_4 and HDL were decreased while TSH and other lipid profile parameters were increased in CKD patients, when compared to control group. Hence CKD is associated with thyroid dysfunction and dyslipidemia.

Keywords: CKD, GFR, Thyroid, Dyslipidemia

1. Introduction

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiology processes associated with abnormal kidney function, and a progressive decline in glomerular filtration rate (GFR). [1, 2] CKD is a clinical syndrome due to irreversible kidney dysfunction leading to excretory, metabolic and synthetic failure culminating into accumulation of non-protein nitrogenous substances and presenting with various clinical manifestation.[3] According the 2010 Global Burden of Disease study, chronic kidney disease was ranked 18th in the list of causes of total number of deaths worldwide. It is estimated that number of cases of kidney failure will increase disproportionately in developing countries, such as China and India, where the number of elderly people are increasing. [4]

Kidney is involved in the metabolism and elimination of thyroid hormones. [5] CKD affects thyroid function in many ways, including low circulating thyroid hormone levels, altered peripheral hormone metabolism, insufficient binding to carrier proteins, reduced tissue thyroid hormone content and altered iodine storage in the thyroid gland. Thus, in CKD, thyroid hormone metabolism is impaired. [6]

CKD is often associated with dyslipidemia. Several factors contribute to these changes. Patients with CKD have a reduction in the activity of lipoprotein lipase and hepatic triglyceride lipase. This interferes with uptake of triglyceride rich, apolipoprotein B containing lipoproteins by the liver and in peripheral tissue, yielding increased circulation of these atherogenic lipoproteins.[7] There is also growing evidence that abnormalities in lipid metabolism may contribute to renal disease progression. [8]

Thyroid dysfunction and dyslipidemia in CKD may further increase CVD risk leading to increased morbidity and mortality. Hence, early diagnosis of thyroid and lipid disorders by regular screening, and treatment of such disorders in CKD patients may be highly beneficial to slow the progression of CKD, in addition to prevention of CVD risk. [9] Keeping in view the above literature, the present study was done in undialyzed CKD patients with an objective to determine-

(a) Serum Total T_3, T_4, TSH and compare them with healthy controls.

(b) Serum Lipid profile and compare them with healthy controls.

2. Materials & Methods

2.1. Study centre and Period: This research was conducted at clinical laboratory, Department of Biochemistry, Rangaraya Medical College between August 2015 and January 2016.

2.2. Subjects Selection: Patient selection was done by simple random sampling of individuals presenting to Government General Hospital, Kakinada, of age group 30-70 years and both sex. The patients were diagnosed as CKD based on clinical profile and renal function tests. An informed consent was taken from the patients and controls before the collection of blood sample. The subjects were selected based on following inclusion and exclusion criteria.

2.3. Inclusion criteria: All patients diagnosed with moderate to severe CKD. eGFR was calculated using MDRD formula. eGFR between 30-60 ml/min was considered as moderate CKD (Stage 3) and eGFR < 30 ml/min was considered as severe CKD (Stage 4 & 5) in the present study.

2.4. Exclusion criteria

1. Patients with history of hyper or hypothyroidism.
2. CKD patients who were or underwent previous dialysis.
3. Obesity
4. Nephrotic Syndrome.
5. Patients on estrogens, corticosteroids, anti-thyroid drugs, dietary supplements.
6. Pregnant Woman etc;

2.5. Study Pattern: Group 1: CONTROLS - 50 age and sex matched normal individuals.
Group 2: CASES – 40 patients with moderate CKD and
Group 3: CASES - 30 patients with severe CKD.

2.6. Specimen Collection: Fasting venous blood sample (3ml) was obtained from each of the subjects. The blood samples were then transferred into clean sterile centrifuge tubes and allowed to clot. Each clotted sample was centrifuged at 3000 rpm for 3min at room temperature to obtain the serum. The serum was removed from the mixture using a micropipette and transferred to appendroff tubes. The biochemical assay was carried out within 24hrs of collection.

2.7. Assay of parameters: Total T3, T4 and TSH were analyzed by Beckman Coulter Chemi luminescence Immuno Assay (CLIA). The reference ranges were T_3: 0.7-2.0 ng/ml; T_4: 4.5-12.5 ng/ml; TSH: 0.4-4.0 µU/ml. Lipid profile (Total cholesterol, Triglycerides and HDL cholesterol) were analyzed on ERBA Semiautoanalyzer. Serum triglycerides and LDL cholesterol were calculated by Friedewald's formula.

2.8. Statistical Analysis: The data obtained were analyzed using Student's t-test and level of significance was set at $p < 0.05$. $p < 0.001$ was considered as highly statistically significant and $p < 0.0001$ extremely statistically significant. All results were expressed as Mean ± SD.

3. Results and Observations
The results obtained for various parameters are tabulated as follows –

Table 3.1: Renal and Thyroid profile in CKD patients Vs Controls.

Value (mg/dl)	Group 1 (N=50)	Group 2 (N=40)	Group 3 (N=30)	Group 2 + Group 3
Urea	29.56 ± 5.43	56.21 ± 3.89	88.70 ± 13.12	70.01 ± 18.55
Creatinine	0.81 ± 0.24	1.72 ± 0.13	5.87 ± 1.42	3.49 ± 2.25
Total T_3	1.45 ± 0.36	1.25 ± 0.52	1.02 ± 0.42	1.15 ± 0.49
Total T_4	8.17 ± 1.67	7.58 ± 0.82	7.29 ± 0.58	7.45 ± 0.74
Total TSH	2.28 ± 0.99	2.36 ± 0.76	2.45 ± 0.83	2.40 ± 0.79

From the above data (Table 2) it was observed that the thyroid profile parameters were elevated in both Group 2 & 3, compared to control subjects (Group 1).

Table 3.2: Lipid profile parameters in CKD patients Vs Controls.

Value (mg/dl)	Group 1 (N=50)	Group 2 (N=40)	Group 3 (N=30)	Group 2 + Group 3
Total-C	179.62 ± 15.61	214.17 ± 21.54	221.03 ± 22.24	217.11 ± 22.10
Triglycerides	141.07 ± 10.86	188.87 ± 19.81	200.60 ± 29.82	193.90 ± 25.27
HDL-C	38.40 ± 3.66	34.52 ± 3.19	33.23 ± 4.68	34.40 ± 3.90
VLDL-C	28.22 ± 2.19	37.82 ± 4.07	40.16 ± 5.97	38.82 ± 5.11
LDL-C	102.62 ± 18.28	142.90 ± 21.10	151.30 ± 25.47	146.50 ± 23.45

From the above data (Table 2) it was observed that the lipid profile parameters were elevated in both Group 2 & 3, compared to control subjects (Group 1).

Table 3.3:

	p value (Gr.2/ Gr.1)	p value (Gr.3/ Gr.1)	p value (Gr.3/ Gr.2)	p value (Gr.2+3/ Gr.1)
Total T_3	0.0342^{*}	$< 0.0001^{***}$	$0.0513^{n.s}$	0.0004^{***}
Total T_4	0.0439^{*}	0.0068^{**}	$0.1034^{n.s}$	0.0018^{**}
Total TSH	$0.6746^{n.s}$	$0.4329^{n.s}$	$0.6389^{n.s}$	$0.4622^{n.s}$
Total-C	$<0.001^{**}$	$<0.001^{**}$	$0.197^{n.s}$	$<0.001^{**}$
Triglycerides	$<0.001^{**}$	$<0.001^{**}$	$0.052^{n.s}$	$<0.001^{**}$
HDL-C	$<0.001^{**}$	$<0.001^{**}$	$0.174^{n.s}$	$<0.001^{**}$
VLDL-C	$<0.001^{**}$	$<0.001^{**}$	$0.055^{n.s}$	$<0.001^{**}$
LDL-C	$<0.001^{**}$	$<0.001^{**}$	$0.136^{n.s}$	$<0.001^{**}$

*** Statistically extremely significant, **very significant, *significant, $^{n.s}$ not significant

4. Discussion
In our present study, thyroid dysfunction and dyslipidemia was observed in CKD patients. Total T_3 and T_4 values were significantly reduced when compared to the control group. Decrease in total T_3 values can be attributed to impairment of peripheral deiodination of T_4 which is the main source of T_3 [10]. No significant reduction in serum T_3 was observed in severe CKD, when compared to moderate CKD patients in our present study. Most of the circulating T_4 is bound to Thyroid hormone Binding Globulin (TBG). Toxic uremic solutes such as urea, creatinine inhibits protein binding of T_4. [11] Since CKD is associated with increased concentrations of serum urea and creatinine, low T_4 levels are observed. No significant reduction in serum T_4 was observed in severe CKD, when compared to moderate CKD patients in our present study.
In contrast, serum TSH levels did not show significant elevation in CKD patients when compared to control group, in our present study. This may be attributed to its inhibited response to thyroid releasing hormone (TRH) [12] and intact thyroid-pituitary axis[13]. Apart from the above mechanisms, systemic inflammation [14, 15] and metabolic acidosis[16] have

also been implicated as causative factors for thyroid dysfunction in CKD patients.

CKD affects lipoprotein metabolism, leading to hypercholesterolemia, hypertriglyceridemia and excess LDL cholesterol [17]. In our present study, all lipid profile parameters except HDL cholesterol were significantly elevated in CKD patients when compared to control group. The predominant mechanism responsible for increased concentration of triglyceride is reduced catabolism [18]. The reduced catabolic rate is due to diminished lipoprotein lipase activity as a consequence of the down regulation of the apo C-II gene [19] and the presence of lipase inhibitors [20]. Apolipoprotein C-III is a potent inhibitor of lipoprotein lipase whereas apolipoprotein CII is an activator of the same enzyme. A decrease in apolipoprotein C-II/C-III ratio due to a disproportionate increase in plasma apolipoprotein C-III is a possible cause of lipoprotein lipase inactivation in CKD [21, 22]. Diminished activity of lipoprotein lipase and hepatic lipase also causes decreased catabolism of chylomicrons and intermediates such as chylomicron remnants and VLDL remnants and hence their concentrations are elevated [23].

Also, patients with CKD exhibit decreased levels of apolipoproteins AI and AII (the main protein constituents of HDL) [24], diminished activity of LCAT (the enzyme responsible for the esterification of free cholesterol in HDL particles) [25, 26], as well as increased activity of cholesteryl ester transfer protein (CETP) [27] that facilitates the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins thus reducing the serum concentrations of HDL-cholesterol.

5. Conclusion

The results of present study provide valuable information and association between thyroid, lipid abnormalities and chronic kidney disease patients. Thyroid dysfunction and dyslipidemia both contribute to renal disease progression and risk of cardiovascular disease. Hence, we recommend a regular screening of thyroid and lipid profile in CKD patients.

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