



CORRELATION OF THYROID DYSFUNCTION AND DYSLIPIDEMIA IN CHRONIC KIDNEY DISEASE: A TERTIARY CARE BASED STUDY AT JHARKHAND

General Medicine

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ABSTRACT

Background: The interplay between thyroid and kidney functions has been known for several years. There is an increased prevalence of hypothyroidism in chronic kidney disease (CKD). Patients with (CKD) have an unacceptable high risk of premature death due to cardiovascular disease (CVD). This study was undertaken to correlate thyroid function and lipid profile in CKD patients.

Materials and Methods: A cross sectional study was conducted among 50 chronic kidney disease patients at Rajendra Institute Of Medical Sciences Ranchi Jharkhand and compared with 50 age matched healthy controls. Demographic features (age and sex) and medical history of CKD of each were noted. 5ml of blood sample were analyzed for biochemical parameters i.e. .serum urea, creatinine, glucose, plasma proteins, lipid profile and thyroid hormones.

Results: All the 50 CKD patients had thyroid dysfunction and dyslipidemia. Among these 52% had subclinical hypothyroidism and 48% had overt hypothyroidism. Patients in the overt to hypothyroidism group had significantly higher thyroid stimulating hormone (TSH), a lower free triiodothyronine (FT3) and lower free thyroxine (FT4) than those in control group. Hypercholesterolemia, hypertriglyceridemia, undesirable LDL cholesterol and low HDL cholesterol were observed in CKD patients which was statistically significant. Patients with hypothyroidism (clinical and subclinical) had significantly lower serum proteins and significantly higher serum urea, creatinine and plasma glucose. An increased prevalence of hypothyroidism was observed in CKD patients.

Conclusion: On the basis of the data observed in the study, it can be suggested that CKD is associated with thyroid dysfunction, dyslipidemia and increased renal parameters. The study reveals the vulnerability of CKD patients with elevated lipid parameters towards CVD. By the outcomes of our study we can give insight to clinicians that the CKD should be screened for thyroid dysfunction to avoid the risk of CVD morbidity and mortality. As this study has some limitations like sample size, the study with large sample size is needed for establishing the tool to assess the CVD risk.

The interplay between thyroid and kidney functions has been known for several years. There is an increased prevalence of hypothyroidism in chronic kidney disease (CKD). Patients with (CKD) have an unacceptable high risk of premature death due to cardiovascular disease (CVD). This study was undertaken to correlate thyroid function and lipid profile in CKD patients.

KEYWORDS

Chronic kidney disease, cardiovascular disease, hypothyroidism, dyslipidemia

INTRODUCTION

Chronic kidney disease (CKD) is becoming a serious health issue and the number of people with impaired renal functions is rapidly rising in the industrialized era.¹ According to recent reports there has been a rise in CKD in developing countries like India due to increase in concomitant non communicable diseases such as hypertension, cardiovascular diseases and type 2 diabetes mellitus.² Associated with the rise in CKD cases is the extensive rise in the health cost for management of CKD.³ Reports suggest that progression of CKD is associated with a number of complications such as thyroid dysfunction, dyslipidemia and cardiovascular diseases (CVD).⁴ Dyslipidemia is established as a well-known cause of CVD in CKD.⁵ As CKD progresses there is an alteration in lipoprotein metabolism.⁶ Patients with CKD have a reduction in the activity of lipoprotein lipase and hepatic triglyceride lipase. This interferes with the uptake of apoproteins- B by liver and peripheral tissues leading to an increase in atherogenic lipoproteins.⁴ The interplay between thyroid and kidney has been known for several years.⁷ Thyroid hormones influence protein synthesis and cell growth. Studies in neonatal rats have demonstrated the accelerating effect of thyroid hormone on renal development.⁸ Thyroid hormones effect renal functioning by both pre renal and direct renal effects. Thyroid hormone affects renal clearance of water load by effects on GFR. The effects of hypothyroidism on kidney are opposite to that of hyperthyroidism.⁹

The kidney plays an important role in the synthesis, degradation and excretion of thyroid hormones. CKD affects thyroid function in many ways, including low levels of circulating thyroid hormones, insufficient binding to carrier proteins, altered metabolism and altered iodine content in thyroid gland.⁹ CKD is associated with higher levels of primary hypothyroidism, both overt and subclinical type, but not with hyperthyroidism.¹⁰ It has been seen that in CKD as GFR falls, there is a higher possibility of developing subclinical and clinical hypothyroidism.¹¹ With a fall in GFR there is an increase in the abnormalities developing in the thyroid gland at both structural and functional level resulting in an increased thyroid volume as GFR falls.¹⁰ LowT3 syndrome is commonly seen in CKD patients, which is

probably an adaptation of chronic inflammatory and malnourished states prevalent in these patients. Low T3 syndrome is the commonest and the earliest abnormality of the thyroid gland in CKD.

Sub Clinical Hypothyroidism (SCH) is a clinical state defining the function of thyroid gland as mildly low with either minimal symptoms or no symptoms of hypothyroidism.¹² Decline in thyroid function instigates the TSH to increase because of stimulation of the pituitary gland. SCH is characterized by increased TSH, while levels of serum FT4 and FT3 remains normal.¹³ It is more prominent in females than males.¹⁴ Thus the study was to aimed to investigate the relationship between thyroid dysfunction and dyslipidemia in patients with CKD.

MATERIALS AND METHODS

The study was conducted among 50 clinically diagnosed patients in the age group of 35 to 75 years, attending Rajendra Institute Of Medical Sciences Ranchi Jharkhand. 50 healthy individuals in the same age group were enrolled for study as controls. The study span was over a period of one year, from September 2017 to August 2018. Ethical clearance was taken from the Institutional Ethical Committee. Every participant voluntarily participated in the research work. A written informed consent was obtained from each participant. Patients clinically diagnosed with previous medical history of overt hypothyroidism, hepatic disease, gastrointestinal infections and cardiovascular disorders etc. were excluded from the study.

Demographic features (age and sex) and medical history of CKD of the each patient were noted. 5ml of fasting blood in plain tube and 2ml in EDTA tube were collected under aseptic measure by venipuncture for laboratory procedures. Serum was separated and used for the measurement of thyroid profile, lipid profile, serum urea and serum creatinine and serum proteins and Plasma was used for estimation of fasting plasma glucose. Serum FT3, FT4 AND TSH was measured by chemiluminescence method. Thyroid dysfunction was considered if patients thyroid hormones fall outside the reference range: free T3→ 0.8 – 2.0 ng /ml, free T4→ 5.1 – 14.1µg/dl and TSH→ 0.27 – 4.2 µIU/ml. Serum triglycerides were estimated by dynamic extended

stability with lipid clearing agent GPO – Trinder Method, End Point¹⁵. Serum cholesterol by Modified Roeschlaus's method¹⁶. Serum HDL cholesterol by Phosphotungstic Acid method¹⁸. Serum LDL cholesterol: Derived by Fredrickson- Friedwald's formula $[(TC-HDL)-TG/5]$ ¹⁷. Serum urea was estimated by GLDH – Urease Method, Initial rate^{18,19}. Serum creatinine was estimated by Modified Jaffe's reaction^{20,21}. Fasting plasma glucose was estimated by Method Trinder's method^{18,22}.

Data was entered into MS excel sheet and verified for any transcriptional error, statistical analysis was done using SPSS 11.0.

RESULTS

The study subject consists of 50 clinically diagnosed CKD patients and 50 healthy controls. Among 50 CKD patients, 40% (n=20) were females and 60% (n=30) were males, while the percentage of female patients in the control group was high (78% (n=39) were females and 22% (n=11) were males. The mean age group was 51.18 ± 11.03 years and 62.52 ± 11.95 years in controls and CKD patients respectively. Serum urea, serum creatinine, plasma glucose was significantly increased in CKD patients compared to controls. 66.34 ± 50.65 (P<0.0001); 4.75 ± 3.23 (P<0.0001); 142.00 ± 23.77 (P<0.0001) in CKD patients versus 22.39 ± 0.07; 0.88 ± 0.29 and 89.76 ± 0.53 in controls respectively. Plasma proteins were significantly decreased in CKD patients 5.40 ± 7.03 (P<0.0001) versus 7.44 ± 0.53 in control. The demographic characteristics and biochemical parameters of study population is shown in Table No. 1.

Table 1: Demographic profile and biochemical parameters of study population

Parameter	Controls (Mean ±SD)	Cases (Mean ±SD)	p value
Age in years	51.18±11.03	62.52±11.95	< 0.0001**
Serum urea mg/dl	22.39 ± 6.07	66.34 ± 50.65	<0.0001**
Serum creatinine mg/dl	0.88 ± 0.19	4.75 ± 3.23	<0.0001**
Serum protein g/dl	7.44 ± 0.53	5.40 ± 1.03	<0.0001**
Fasting plasma glucose mg/dl	89.76 ± 11.51	142.00 ± 23.77	<0.0001**

** Statistically significant

The levels of TSH were markedly increased in CKD patients when compared to controls and it was statistically highly significant (P<0.0001). Free T3 levels were marginally increased in CKD patients when compared to controls (P<0.0003). Free T4 levels were decreased in CKD patients when compared to controls and it was statistically significant (P<0.0001). Thyroid hormone status in healthy controls and CKD patients is shown in Table 2.

Table 2 : Serum thyroid hormone status in healthy controls and CKD patients.

Thyroid profile	Controls (Mean ±SD)	Cases (Mean ±SD)	P value
Serum TSH μIU/ml.	2.17 ± 1.57	5.11 ± 2.73	< 0.0001**
Serum FT3 μg/dl.	1.07 ± 0.35	1.73 ± 1.21	<0.0003**
Serum FT4 μg/dl.	8.66 ± 2.00	6.53 ± 2.93	<0.0001**

** Statistically significant

Total cholesterol, LDL-C and Triglycerides were significantly higher in CKD patients when compared to controls (P<0.0001). HDL-C was decreased in CKD patients when compared to controls (P<0.07). Table 3 illustrates dyslipidemia status in CKD patients and controls.

Table 3: Comparison of lipid profile parameters in healthy controls and CKD patients

Lipid profile (mg/dl)	Controls Mean ±SD	Cases Mean ±SD	P value
T C	167.49 ± 18.24	218.63 ± 76.03	<0.0001**
TG	124.28 ± 14.29	229.94 ± 89.77	<0.0001**
HDL-C	50.81 ± 9.49	46.68 ± 13.06	0.0735**
LDL-C	90.20 ± 19.15	130.35 ± 72.53	0.0003**

** Statistically significant

Pearson's correlation with TSH, FT3, FT4 and lipid profile was carried. TSH showed positive correlation with TC (r = 0.11), TG (r = 0.0421) and LDL-C (r = 0.1129), and showed negative correlation with HDL-C (r = -0.015). FT3 showed negative correlation with TC (r = -0.27), TG (r = -

0.12), LDL-C (r = -0.23) and HDL-C (r = -0.14). FT4 showed positive correlation with TC (r = 0.18), TG (r = 0.20), LDL-C (r = 0.1305) and HDL-C (r = 0.10). However the correlation was not statistically significant.

The prevalence of thyroid dysfunction was seen in 48% of CKD patients where as 52 % of them are in the normal range. Hypercholesterolemia 48%, hypertriglyceridemia in 90 % and 38% showed high LDL-C. HDL-C was low in 26% of the study cases. Prevalence of disease in CKD patients with respect to Thyroid dysfunction and Dyslipidemia is shown in Table 4.

Table 4: Prevalence of disease in CKD patients with respect to Thyroid dysfunction and dyslipidemia.

parameter	Cut off value	Frequency N	Cases with disease range (%)	Cases with normal range (%)
TSH μIU/ml	4.2	24	48	52
T3 μg/dl.	0.8	11	22	78
T4 μg/dl.	5.1	16	32	68
T C mg/dl	200	24	48	52
TG mg/dl mg/	150	45	90	10
HDL-C mg/dl	40	13	26	16
LDL -C mg/dl	129	19	38	62

DISCUSSION

Patients with chronic kidney disease shows unacceptably high risk for premature death, mainly due to cardiovascular disease (CVD) compared with general population²³. Recent studies indicate that low thyroid hormone levels in CKD patients act as an intermediate link between the inflammatory stress and impaired CVD²⁴

The present study identifies thyroid dysfunction and dyslipidemia as a common disorder in Indian patients with CKD undergoing hemodialysis. Thyroid dysfunction was found in all patients with CKD, the most common being 52% subclinical hypothyroidism followed by 48% hypothyroidism. Higher prevalence of thyroid dysfunction was observed in patients with CKD is shown by other studies. 10 A small study in hemodialysis patients in western UP showed the combined prevalence of subclinical and clinical hypothyroidism in 26.6% of patients²⁵. Study by Lo et al reported that the prevalence of hypothyroidism increased with lower levels of GFR, 56% of hypothyroidism cases were subclinical. 10 In a study conducted in India among end stage renal disease (ESRD) patients, prevalence of subclinical hypothyroidism was found to be 24.8%⁶. A study by Ng et al in peritoneal dialysis patients of Taiwan showed that 80.3% were having euthyroidism, 15.6% subclinical hypothyroidism and 4% subclinical hyperthyroidism²⁷. High rate of thyroid dysfunction in CKD patients undergoing hemodialysis is observed in the present study. The present study showed increased free T3 & decreased free T4 levels compared to controls; 1.73 ± 1.21 & 6.53 ± 2.93 in CKD patient's v/s 1.07 ± 0.35 & 8.66 ± 2.00 in controls. [Though the decrease was not significant]. TSH level is increased significantly (P<0.0001); 5.11 ± 2.73 in CKD patients v/s 2.17 ± 1.57 in controls suggesting that TSH level increases with the progression of renal impairment [low GFR].

Both genetic and environmental factors are responsible for triggering a complex series of pathological and physiological events. Chronic kidney disease (CKD) influences hypothalamo - pituitary - thyroid axis. Secretion of hypophyseal thyroid stimulating hormone (TSH) is disturbed and the TSH response to the hypothalamic thyrotropin releasing hormone (TRH) is reduced²⁸.

Chronic kidney disease (CKD) causes alterations in thyroid hormones in the absence of an underlying intrinsic thyroid disorder, known as the syndrome of nonthyroidal illness, characterized by a decrease in total (T3) and free triiodothyronine (FT3) plasma concentration, whilst thyroid-stimulating hormone (TSH) levels are usually increased.²⁸

Thyroid dysfunction in present study may also be due to thyroid autoimmunity in study population²⁷. Our findings are par with the study of Song et al who found that there was decreasing FT3 levels with increase in stages of CKD.²⁹ In the present study, we found that patients with ESRD had significantly high risk for thyroid dysfunction.

In our present study, also showed significant increases in total

cholesterol and triglycerides ($P \leq 0.001$) and LDL-C ($P \leq 0.003$) in hemodialysis CKD patients when compared to healthy controls, whereas no significant change ($P \leq 0.07$) was observed in HDL-C levels. Generally the prevalence of hyperlipidemia increases as renal function decline with the increase in the degree of hypertriglyceridemia and elevated LDL-C levels being proportional to severity of renal impairment. Our findings are similar to the study of Sinha³⁰ & Poudel²⁵ who reported the prevalence of dyslipidemia in CKD patients. A study by Singh³¹ showed that the dyslipidemia in CKD patients have significant impact for CVD. Our results suggest that there is a significant association between hypercholesterolemia & increased LDL-C with CVD risk in hemodialysis CKD patients. This indicates that CKD progression is strongly associated with CVD prevalence. A large number of epidemiological studies has suggested the independent role of dyslipidemia on cardiovascular morbidity and mortality in general population.³¹ The study on the role of dyslipidemia in CVD in CKD patients has not been established. But, it has been proposed that the presence of phenomena such as inflammation or protein energy wasting may significantly confound the relationship between the traditional risk factors for CVD and mortality in CKD patient population.³²

Our results are similar to the study of Chen et al who demonstrated that dyslipidemia is the leading risk factor for CVD in CKD patients, and CVD remains the leading cause for death in CKD patients.³¹ Thus all the adults and adolescents with CKD should be evaluated for dyslipidemia which may help to identify high risk factors for CVD.

Diabetic condition had also significant association with progression of CKD. Diabetes is the leading cause of CKD in many populations and is associated with cardiovascular morbidity and mortality. Plasma proteins was decreased in CKD patients (5.40 ± 1.03) when compared to controls (7.44 ± 0.53) significantly ($P < 0.0001$). It is clearly evidenced since CKD patients are malnourished.

The present study suggest for the importance of regular screening and treatment of thyroid dysfunction and dyslipidemia 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. So, regular checkup of thyroid function and lipid profile was recommended in patients with CKD.

This study has several limitations. First, the numbers of patients studied were small. Second, the study was conducted in a region of poor socio-economic status where conditions [Nutrition status, disease status, thyroid autoimmunity status, genetic components] of patients may be slightly different than other parts of the world. Third, the patients with non thyroidal illness were not identified, since thyroid testing was done only once.

A prospective study is desirable to explore potential causal mechanisms through CKD may be associated with increased TSH and reduced thyroid function, which can throw light on the effect of thyroxine treatment on GFR and give a better picture of the true prevalence of hypothyroidism in CKD patients.

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