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Original Article

Screening of Thyroid Dysfunction and Dyslipidaemia in Patients of Diabetic Nephropathy in a Tertiary Care Centre in Western U.P

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ABSTRACT

Background: *Diabetes mellitus is often associated with multiple organ co-morbidities, including thyroid dysfunction. This has been associated with poorer prognosis, particularly in patients with end-stage renal disease. Hypothyroidism enhances the progression of atherogenesis. CRF is a serious health problem in worldwide. In developing nation, cardiovascular disease (CVD) is the leading cause of mortality in chronic kidney disease (CRF) patients. Therefore, early determination and management of the risk factors for CVD in D.M patients play an important role to develop more effective screening and treatment strategies*

Methods: *.M, Thyroid status, Lipid profile, serum Urea, serum Creatinine, serum Uric acid, serum electrolyte, Catalase, and Superoxide dismutase (SOD) were assayed in 160 subjects in which 80 patients of D.M were having hypertension and 80 healthy controls.*

Results: *There was found significantly increased level ($p<0.001$) of TSH in D.M associated with hypertension patients. We also found deranged lipid profile and renal functions in D.M patients associated with hypertension as compared to controls.*

Conclusions*: In our present study, we arrived at conclusion that dyslipidemia and thyroid dysfunction is very common in D.M patients. Our study revealed that there was significant association between thyroid dysfunction, D.M and dyslipidemia.*

Keywords: *Hypertension (HTN), Chronic Renal failure (CRF), Reactive Oxygen Species (ROS), Glomerular Filtration Rate (GFR)*

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INTRODUCTION

D.M is accompanied by persistent kidney damage, reduction in the glomerular filtration rate and the presence of albuminuria.[1] chronic renal failure is a serious health problem worldwide. In developing nation, DM has severe implication on health and economic output. Cardiovascular disease (CVD) associated with dyslipidemia is the leading cause of mortality in Chronic Renal failure (CRF) patients. Therefore, early determination and management of the risk factors for CVD in CRF patients play an important role to develop more effective screening and treatment strategies to decrease cardiovascular mortality and morbidity in D.M patients.[2] In addition to traditional risk factors for CVD such as older age, male gender, smoking, hypertension, diabetes, and hyperlipidemia, non-traditional risk factors such as anemia, inflammation and oxidative stress, and mineral and bone abnormalities in CKD[3] have an undeniable influence on the

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increased prevalence of CVD observed in CRF. The rapid increase of common risk factors such as hypertension (HTN), obesity and type 2 diabetes (T2D) will result in greater and more burdens to developing country like India It is generally seen that patients suffering from CRF are at high risk of cardiovascular disease.[4] It is a established fact that CRF is associated with number of complications, including dyslipidemia, hypertension, cardiovascular disease (CVD) and thyroid dysfunction[5] It is very often seen that chronic renal failure patients may have various thyroid function complications.[6] We know that our kidney normally plays an important role in the thyroid hormones metabolism, degradation and excretion. There are research evidences showed that dyslipidemia may contribute to progression of renal disease.[7] Dysfunction of thyroid gland can affect the thyroid hormones (T3 and T4) production which is associated with various physiological functions within the body. Thyroid hormone levels have significant affect during the course of progression of CRF. It is commonly seen that disorders of renal function have co-relation with specific thyroid hormone levels. This study is done to establish relations between kidney disease and thyroid function. The Information obtained from this study will help to improve clinical knowledge and facilitate clinicians to give better management and care to their patients who have dysfunctions of kidney or thyroid gland. Many studies have established that T. cholesterol and LDL cholesterol values are important markers of cardiovascular mortality.[8] In patients with CRF, hypertriglyceridemia is a common lipid abnormality.[9,10] There is decrease lipoprotein lipase and hepatic triglyceride lipase activity in CRF patients. As such, there is hindrance in the uptake of triglyceride rich, apolipoprotein B containing lipoproteins by the liver and in peripheral tissue, resulting in atherogenic lipoproteins. Accelerated hypertension is an major risk factor for developing CRF, is reported to occur in 80 to 90% of CRF patients (stages 3-5).[11] Hypertension causes more rapid progression of CRF.[12] Many research guidelines have proved that by lowering blood pressure (BP) ,the progression of kidney disease and cardiovascular morbidity and mortality[13] can be avoided. The oxidative stress generated in CRF patients causes increase in ROS (reactive oxygen species). Resulting various redox sensitive cell signalling molecules activated and cytotoxic materials produced. This is followed by cellular dysfunction and damage. This finally results in micro-vascular complications.[14] It is seen that thyroid dysfunction and dyslipidemia in patients of CRF increases the cardiovascular morbidity and mortality risk.[15,16] Hence, early diagnosis of thyroid dysfunctions and dyslipidemia in CKD patients may be highly helpful to slow the CRF progression.

METHODS

Study Design

This is a Randomized, Prospective and Comparative case control study in Saraswathi Medical College and Hospital, Hapur (Uttar Pradesh).

Study Area:

The study was conducted in Hapur District, Uttar Pradesh, India.

Study Period:

The study was completed from August 2017 to Nov 2018.

Study Setting:

The study was carried out in the metabolic clinic in Department of Medicine , Saraswathi Medical College and Hospital, Hapur (UP).

Study Population:

This study population comprised total 160 subjects in which 80 healthy control (Group I), 80 CRF with hypertension (Group II) . All the people with age group 20 years and above living in the study area were eligible to participate in the study. The proposed study was conducted in SIMS, Hapur .

SELECTION OF CASES

Inclusion Criteria

- History of polyuria, polyphagia and dyspepsia
- History of muscle cramps.
- All the consecutive cases of increased liver enzymes in medical clinical outdoor and indoor departments of the hospital
- History of vague right sided abdominal pain.
- Clinical finding of hepatomegaly.
- Patients not taking alcohol. Obese patients (particularly truncal obesity) with or without diabetes.

Exclusion Criteria includes

- Patients of alcoholic hepatitis/alcoholic steatohepatitis.
- Patients suffering from viral hepatitis (Hepatitis B or C)
- Pregnant women with fatty liver.
- Patients with known thyroid disorders.
- Hypertensive patients suffering from any other medical problems and on medications affecting thyroid function, lipid profile and blood pressure were excluded from the study.
- Patients with history of drug abuse or history of psychiatric disorder
- Other factors causing hypertension
- Cancer or suspicion of malignancy

Study Population:

Sample size was calculated by the probability sampling formula below:

N= Zpq/d

Where, n = sample size, z = statistical certainty chosen, p = proportion of hypothyroid individuals with hypertension, q = 1- p and d = precision desired.

Ethical Approval:

This current study was approved by the Ethical Committee of the Institute and all guidelines of the ethical committee were followed. The aim and objectives of the study were explained to the ethical committee.

Informed Consent:

A written signed informed Consent letter was obtained from each patient before starting the procedure. The involvement of the subject was voluntary.

A structured questionnaire regarding the age, sex, duration of Hypertension, BMI were measured. Personal history was taken from each patient e.g. smoking habit, BP (Blood pressure), family history of renal disease, hypertension and diabetes etc. Ten ml of fasting venous blood sample was taken from all participants to assess the fasting lipid profile,

fasting blood sugar (those with impaired fasting glucose values had repeat blood sugar done 2 hours after food), liver function tests, serum proteins, full blood count, Prothrombin time, HBsAg, anti-HCV were estimated in respective laboratories by designated senior laboratory scientists. All biochemical assays were run on an automated system (spectrophotometer Apoel PD-303) except HBSAg and anti-HCV which were assessed by the ELISA method using test strips (one step hepatitis B surface antigen test strip and one step hepatitis C virus test strip respectively) manufactured by Zhejiang aittone biological pharmaceutical co., Ltd, China. Total cholesterol (TC) was assayed using Lieberman Bur chard reaction, while high-density lipoprotein (HDL) cholesterol was assayed by precipitation method, triglycerides(TG) was estimated using a serum triglyceride determination kit, catalogue number TR0100 employing enzymatic analysis of triglycerides with lipases[15] and low-density lipoprotein (LDL) cholesterol was calculated using the Fried Wald formula[16] [LDL = (TCHOL - HDL-C)-TG/5]. Fasting blood sugar was done using the glucose oxidase method described by Middleton and Griffiths.[17] Diagnosis of fatty liver was established according to Gomercic and colleagues5 as the presence of Hepatic steatosis identified as the characteristic appearance of diffuse increase in parenchymal echo brightness on ultrasound associated with blurring of the vascular wall, hepatorenal contrast and attenuation of the diaphragm. NAFLD was diagnosed in those study participants who satisfied the following Imaging finding of fatty liver by abdominal ultrasound and/or Histology confirmation of NAFLD of one or more of the following-steatosis, mixed inflammatory cell infiltration, hepatocyte ballooning and necrosis, glycogen nuclei, mallory's hyaline and fibrosis. The Adult Treatment Panel III criteria[18] were used to identify patients with the metabolic syndrome.

STATISTICAL ANALYSIS

Biochemical Statistical analyses were done by SPSS 21 software. Results were put in the tables as mean and standard deviation and were significance analyzed by using unpaired Student's t-test. The level of significant was set as P < 0.05: Significant and P > 0.05: Non-significant.

Table 1: Demographic, clinical, and biochemical characteristics of diabetic nephropathy patients (N=100)

CHARACTERISTIC	ALL PATIENTS (100) (MEAN ± SD)
Sex (male: female)	56:44
Age in years	52.9±7.8
Glucose (mg/dL)	127.4 ± 44.6
Urea (mg/dL)	106.3 ± 60.1
Creatinine (mg/dL)	4.0 ± 3.4
eGFR (mL/min/1.73 m²)	28.2 ± 15.3
TSH (mIU/L)	4.4 ± 2.1
Free T3 (pmol/L)	2.33 ± .081
Free T4 (pmol/L)	11.6 ± 3.2
Total cholesterol (mg/dL)	219 ± 5.08
HDL cholesterol (mg/dL)	42.1 ± 5.9
LDL cholesterol (mg/dL)	129.04 ± 23.78
Triglyceride (mg/dL)	206.2 ± 58.02

Table 2: Distribution of diabetic nephropathy patients according to clinical characteristics (N=100)

CHARACTERISTICS	ALL PATIENTS N (%)
1.Thyroid status	
A) Euthyroidism	62 (61.4%)
B) Subclinical hypothyroidism	27(27.2%)
C) Overt hypothyroidism	8(8.1%)
D)Subclinical hyperthyroidism	3(3.3%)
2.Lipid Profile	
A) Total cholesterol < 200 mg/dL ≥ 200 mg/dL	65(65.6%) 35(34.4%)
B) HDL cholesterol ≥40 mg/dL <40 mg/dL)	66(65.9%) 34(34.1%)
C)LDL cholesterol < 100 mg/dL ≥ 100 mg/dL	65(65%) 35(35%)
D)Triglyceride < 150 mg/dL ≥ 150 mg/dL	63(65.4%) 37(36.6%)

Table 3: Pearson's correlation coefficient (r) between mAlb (mg/L) and various variables associated with Lipid profile and Thyroid status among 100 diabetic nephropathy patients.

PARAMETER	CORRELATION COEFFICIANT (R)	P
TSH (mIU/L)	0.50**	<0.001
Free T3 (pmol/L)	0.19	NS
Free T4 (pmol/L)	0.20	NS
Total cholesterol (mg/dl)	0.58**	<0.001
HDL cholesterol (mg/dl)	−0.25	NS
LDL cholesterol (mg/dl)	0.49**	<0.001
Triglycerides (mg/dl)	0.34*	<0.05

P < 0.05: Significant, P < 0.001: Highly significant.

RESULTS

Table 1 showed sex, age, BMI, blood pressure (DBP, SBP) in hypertensive CKD patients and controls. The mean age of the 80 CKD with HTN patients was 51.9 with 56.25% of the patients being male. The mean age of the 80 healthy controls was 49.7 with 52.5% of the controls being male. There was no significant difference in results of sex, age and BMI between the two case and control groups. Blood pressure (SBP & DBP) was significantly increased in the cases compare to control subjects.

Table 2 showed biochemical characteristics of hypertensive CKD patients. Serum creatinine levels, serum urea levels, and serum uric acid levels were significantly increased (P < 0.001) in case group as compared to control group. In case group, we found T. cholesterol, LDL-cholesterol, Triglycerides, and VLDL-cholesterol levels were significantly increase compare than control, whereas HDL-cholesterol level was significantly decreased (P < 0.001) in cases as compare to control group. The data shows the high risk of CVD in patients of CRF.

Table 3 showed Thyroid function of hypertensive CRF patients and controls. Significantly increase TSH level (P < 0.001) and decreasing free T3 and free T4 levels were found (decrease were not significant) across CRF with HTN, which suggest that level of TSH increases with the progression of renal damages (which is indicated by a decrease in GFR).

DISCUSSION

Our present study was of the view that thyroid dysfunction, dyslipidemia are common disorder in Indian D.M patients.[19] In our study we found that thyroid dysfunctions were present in 38.6% CRF patients, in which the most common was subclinical hypothyroidism type around 27.2% patients, followed by 8.1% patients were overt hypothyroidism and subclinical hyperthyroidism patients were only 3.3%. Our result was consistent with the finding of several previous studies.[20] A small study was conducted in CRF patients dependent on hemodialysis in western UP. This study showed the combined prevalence (26.6% patients) of clinical and subclinical hypothyroidism.[21] A previous Study of Lo *et al* concluded that the prevalence of hypothyroidism increased with lower GFR level, they found GFR greater than or equal to 90 in 5.4 % subjects, GFR 60–89 in 10.9% subjects, GFR 45–59 in 20.4% subjects, GFR 30–44 in 23.0% subjects, and GFR < 30 in 23.1 % subjects ($p < 0.001$ for trend). An India study showed prevalence of subclinical hypothyroidism was 24.8% in ESRD (end stage renal failure) patients.[22,23] Our result was of the view that increase in the level of lipid profile (total cholesterol, VLDL-C, TG, and LDL-C) was possible explanation for deranged lipid metabolism to accelerate the progression of CVD in CRF patients through various paths. Firstly, the tubular epithelial cells, reabsorb phospholipids, cholesterol and fatty acids contained in the filtered proteins can stimulate tubulointerstitial inflammation and then formation of foam cell, and causes tissue injury.[24] Secondly, lipoproteins accumulation in glomerular, mesangium can promote production of matrix and glomerulosclerosis.[25] For CRF patients, some of the studies have shown a good association between risk for cardiovascular events and total cholesterol values,[26] whereas other studies did not show any significant correlation.[27] In our CRF patients have reduced plasma HDL-C levels, many other study consistency with us.[28] Possible explanation of decrease level of HDL-C is decrease level of Apo lipoproteins AI and AII, abnormal activity of lecithin: increased activity of Cholesterol, cholesteryl ester transfer protein, which help the transfer of cholesterol esters from HDL-C to TG-rich lipoproteins, and so there is reduction in the serum concentrations of HDL-C.[29] During the course of our study, we observed that there is a strong relationship between some oxidative stress-related parameters and blood pressure. Whenever ROS production is elevated, there is reduction in the endothelium dependent vasodilatation of the vascular smooth muscle cells of hypertensive patients.[30] It is also seen that whenever there is blood pressure increase, there is ROS increase, thus increasing the mechanism of ROS-mediated hypertension. In this present study, there was significant decrease in the superoxide dismutase activity in the case group, indicating that either the scavenging system has been consumed during CRF or is suppressed. The major reason for decreased superoxide dismutase activity is the glycosylation of superoxide dismutase which has been shown to lead to enzyme inactivation.[23] Compromised functions of antioxidant result in the well-known cascade of hypoxic ischemic injury, inflammation, apoptosis and finally cell death.[31] The significant decrease activity of catalase in present study agreement with various previous studies found a lower activity of antioxidant enzyme[19] and a negative correlation between activity of Catalase and both day time DBP and SBP in hypertensive CRF patients.[32] Elevated level of catalase and possible explanation for this is that increase in catalase activity in these groups could be a compensatory mechanism of the body to prevent damages of tissue by the raised free radicals as it was not supported by a corresponding increase of other antioxidant enzymes activities. Possible explanation production of ROS in hypertension elevated lipid peroxidation in cellular membrane as well as enhancing the protein carbonyl derivatives and producing higher level of MDA in the hypertensive CRF patients which is a suggestive feature of oxidative stress in hypertension. Diabetes is said to be the leading cause of CRF in many populations and is associated with excessive cardiovascular morbidity and mortality.[33]

CONCLUSION

Our present study is of the view that thyroid dysfunction and dyslipidemia is very frequent in D.M Patients. It establishes that significant association between thyroid dysfunction and D.M progression and dyslipidemia. Our study comes to the conclusion that D.M patients with dyslipidemia have strong predisposition for developing CVD, so that early treatment for dyslipidemia in CRF patients may reduce the chance of developing CVD later. Thus primary investigation shows that status of antioxidant is controlled through changes in antioxidant enzymatic activity in CRF with hypertensive patients and data provide suggestion of controlling blood pressure by oxidative stress–related parameters. Patients of CRF are affected by multiple associated conditions like dyslipidemia, hypertension and diabetes which are all related with oxidative stress. The presence of chronic kidney disease appears to further increase the oxidative stress independently from the underlying conditions. Hemodialysis also plays important role in contributing to the oxidative stress.

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