Assessment of Thyroid Dysfunction, Dyslipidaemia and Oxidative Stress in Hypertensive End Stage Chronic Renal Disease Patients in a Teaching Hospital in Western U. P.

Poonam Kaechawa[1], Vivek Sinha[2]

[1]Associate Professor, Department of Biochemistry, Saraswathi Institute of Medical Sciences (SIMS), Hapur, Uttar Pradesh, India. [2]Associate Professor, Department of Biochemistry, Saraswathi Institute of Medical Sciences (SIMS), Hapur, Uttar Pradesh, India.

ABSTRACT

BACKGROUND

CKD is a serious health problem worldwide. In developing nation, CKD has severe implication on health and economic output. The rapid increase of common risk factors such as hypertension (HTN), obesity and type 2 diabetes will result in greater burden on developing countries. There are many complications associated with CKD including thyroid dysfunction, dyslipidaemia, hypertension and cardiovascular disease (CVD). It is generally seen that patients suffering from CKD are at high risk of cardiovascular disease.

METHODS

This is a cross sectional comparative study conducted in Saraswathi Medical College and Hospital, Hapur (Uttar Pradesh). Thyroid status, lipid profile, serum urea, serum creatinine, serum uric acid, serum electrolyte, catalase, malondialdehyde (MDA) and superoxide dismutase (SOD) were assayed in 160 subjects of which 80 patients of CKD were having hypertension and 80 healthy controls.

RESULTS

In our study, we found statistically significant increase in the level of ($p<0.001$) malondialdehyde (MDA) and significantly decreased level ($p<0.001$) of catalase and superoxide dismutase (SOD). Significantly increased level ($p<0.001$) of TSH was found in CKD patients with associated hypertension. We also found deranged lipid profile and renal functions in CKD patients with associated hypertension as compared to controls.

CONCLUSIONS

Dyslipidaemia and thyroid dysfunction are very common in CKD patients. Our study revealed that there was significant association between thyroid dysfunction and CKD progression and dyslipidaemia. The antioxidant status is assessed through changes in antioxidant enzymatic activity in patients of CKD with associated hypertension and data provides evidence of blood pressure modulation by measurable oxidative stress–related parameters.

KEY WORDS

Hypertension (HTN), Chronic Kidney Disease (CKD), Reactive Oxygen Species (ROS), Oxidative Stress, Glomerular Filtration Rate (GFR)

Corresponding Author:
Dr. Vivek Sinha,
Associate Professor,
Department of Biochemistry,
Saraswathi Institute of Medical Sciences, (SIMS), Hapur Road, Hapur,
Uttar Pradesh, India.
E-mail: drviveksinha13@gmail.com

DOI: 10.14260/jemds/2019/641

Financial or Other Competing Interests: None.

How to Cite This Article:
Kaechawa P, Sinha V. Assessment of thyroid dysfunction, dyslipidaemia and oxidative stress in hypertensive end stage chronic renal disease patients in a teaching hospital in Western U. P.. J. Evolution Med. Dent. Sci. 2019;8(39): 2948-2952, DOI: 10.14260/jemds/2019/641

Submission 08-03-2019,
Peer Review 10-09-2019,
Acceptance 17-09-2019,
Published 30-09-2019.

BACKGROUND

Chronic kidney disease is accompanied by persistent kidney damage, reduction in the glomerular filtration rate and the presence of albuminuria.[1] Chronic kidney disease is a serious health problem in worldwide. In developing nation, CKD has severe implication on health and economic output. 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 are not easy to handle. It is a established fact that CKD is associated with number of complications, including dyslipidaemia, hypertension, cardiovascular disease (CVD) and thyroid dysfunction.[2] It is very often seen that chronic renal failure patients may have various thyroid function complications.[3] We know that our kidney normally plays an important role in the thyroid hormones metabolism, degradation and excretion. There are research evidences showed that dyslipidaemia may contribute to progression of renal disease.[4] 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 CKD. 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.[5] In patients with CKD, hypertriglyceridemia is a common lipid abnormalities.[6,7]

There is decrease lipoprotein lipase and hepatic triglyceride lipase activity in CKD 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.[2] Accelerated hypertension is an major risk factor for developing CKD, is reported to occur in 80 to 90% CKD patients (stages 3-5).[8] Hypertension causes more rapid progression of CKD.[9] Many research guidelines have proved that by lowering blood pressure (BP),the progression of kidney disease and cardiovascular morbidity and mortality [10] can be avoided. The oxidative stress generated in CKD 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.[11] It is seen that thyroid dysfunction and dyslipidaemia in patients of CKD increases the cardiovascular morbidity and mortality risk.[12,13] Hence, early diagnosis of thyroid dysfunctions and dyslipidaemia in CKD patients may be highly helpful to slow the CKD progression. This could be done by regular screening of the patients. This study was therefore aimed to evaluate the effect of thyroid dysfunction, dyslipidaemia and degree of oxidative stress in Hypertensive CKD patients.

METHODS

Study Design
This is a cross sectional comparative 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 Biochemistry Department, Saraswathi Medical College and Hospital, Hapur (U. P.).

Inclusion Criteria
1. Adult patients (More than or 18 years aged) reporting first time/regularly associated with SIMS hospital for management of Hypertension issue are selected.
2. Only mild to moderate grade hypertensive patients were taken.
3. Patients consenting for the study.

Exclusion Criteria
1. Patients with known thyroid disorders.
2. Hypertensive patients suffering from any other medical problems and on medications affecting thyroid function, lipid profile and blood pressure were excluded from the study.
3. Patients with history of drug abuse or history of psychiatric disorder.
4. Other factors causing hypertension.
5. Cancer or suspicion of malignancy.
6. Pregnancy.
7. Angina.
8. Hypertensive emergency.

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.

The study population comprised total 160 subjects in which 80 healthy control (Group I), 80 CKD 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.

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. Total 5 ml of blood sample was taken from the antecubital vein after overnight fasting. The collected blood samples were centrifuge for 15 min. at 3000 rpm at room temperature. The separated serums were stored in refrigerator at 4°C for biochemical investigations. Samples were analysed for serum urea, creatinine, uric acid, lipid profile, TSH (Thyroid stimulating hormone), T3 (Triiodothyronine) and T4 (Thyroxine). Serum Urea, creatinine, uric acid, and lipid profile were measured by enzymatic method on auto analyser. Serum T. Cholesterol, HDL- Cholesterol, and TG were estimated using commercially available kit of auto analyser. All biochemical investigation was done by fully automated analyser (CPC chem100).Serum TSH, free T3, and free T4 were estimated by fluorescent immunoassay on minividas. Thyroid dysfunction was considered if patient's thyroid hormones profiles deranged; TSH (Normal range = 0.25–5 mIU/L), free T3 (Normal range= 2.30 – 5.0 ng/mL) and free T4 (normal range = 10.6 –19.4 pmol/L). Subclinical hyperthyroidism was considered as free T3 and free T4 within reference range and TSH < 0.25 mIU/L. Subclinical hypothyroidism was defined if free T3 and free T4 within reference range and TSH > 5 mIU/L. Overt hypothyroidism was considered as free T3 < 2.30 ng/mL and free T4 < 10.6 pmol/L and TSH > 5 mIU/L. SOD (Serum super oxide dismutase) activity was measured by the Marklund and Marklund (1988) method.[14] Serum catalase activity was estimated by the Aebi (1984) method.[15] Plasma MDA (Malondialdehyde) was estimated by Jeanet et al.[16]

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.

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 CKD.

Table 3

Showed Thyroid function of hypertensive CKD 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 CKD with HTN, which suggest that level of TSH increases with the progression of renal damages (Which is indicated by a decrease in GFR).

Table 4

Showed oxidative stress markers and eGFR of hypertensive CKD patients. eGFR were significantly lower (P<0.001) in hypertensive CKD patients as compared to control group. In case group antioxidant level (SOD and Catalase activity) showed significantly decreased (P<0.001) and MDA was found significantly high (P<0.001) in comparison to control subjects.

Parameters	Control (N = 80)	CKD with HTN (N = 80)	p Value
Age	49.7±5.8	51.9±7.8	NS
Male: Female	42:38	45:35	NS
BMI (kg/m^2)	22±1.7	23.5±2.7	<0.001
SBP (mmHg)	119.2 ± 5.2	137.2 ± 6.9	<0.001
DBP (mmHg)	79.6 ± 4.4	91.7± 4.8	<0.001

Table 1. Demographic Data of Hypertensive CKD Patients and Controls (Mean± SD)

HTN: Hypertension, CKD: Chronic kidney disease, SBP: Systolic blood pressure, DBP: Diastolic blood pressure and BMI: body mass index.

Parameters	Control (N = 80)	CKD with HTN (N = 80)	p Value
Serum Urea (mg/dL)	25.3 ± 5.7	91.6 ± 27.3	<0.001
Serum Creatinine (mg/dL)	0.8 ± 0.3	5.3 ± 1.7	<0.001
Serum Uric Acid (mg/dL)	4.5 ± 1.2	6.6 ± 1.8	<0.001
Total cholesterol (mg/dl)	165.6 ± 16.13	229.9 ± 45.2	<0.001
HDL-cholesterol (mg/dl)	46.7 ± 5.93	40.8 ± 5.37	<0.001
LDL-cholesterol (mg/dl)	118.7 ± 27.6	158.9 ± 35.5	<0.001
Triglycerides (mg/dl)	125.8 ± 38.3	276.3 ± 54.3	<0.001
VLDL-cholesterol (mg/dl)	22.9 ± 8.5	50.5 ± 24.6	<0.001

Table 2. Biochemical Features of Hypertensive CKD Patients and Controls (Mean± SD)

LDL: Low density lipoprotein, VLDL: Very low-density lipoprotein and HDL: High density lipoprotein

Parameters	Control (N = 80)	CKD with HTN (N = 80)	p Value
Free T3 (ng/mL)	2.94 ± 0.81	3.21 ± 0.21	NS
Free T4 (pmol/L)	15.6 ± 3.2	16.48 ± 4.61	NS
TSH (mIU/L)	3.2 ± 0.34	7.39 ± 2.61	<0.001

Table 3. Thyroid Function of Hypertensive CKD Patients and Controls (Mean± SD)

TSH: Thyroid stimulating hormone and T3: Triiodothyronine, T4: Thyroxine.

Parameters	Control (N = 80)	CKD with HTN (N = 80)	p Value
SOD activity (Units/gmHb)	6.1±1.1	3.1±0.6	<0.001
Catalase activity (Units/gmHb)	7.2±0.9	4.1±0.5	<0.001
MDA (nmol/mL)	1.5±0.2	5.1±0.8	<0.001
eGFR measured by MDRD equation (mL/min/1.73 m2)	95.8±26.3	44.4±8.9	<0.001

Table 4. Oxidative Stress Markers and eGFR of Hypertensive CKD Patients and Controls (Mean± SD)

eGFR: Estimated glomerular filtration rate.

DISCUSSION

Our present study was of the view that thyroid dysfunction, dyslipidaemia and oxidative stress are common disorder in Indian CKD patients. In our study we found that thyroid dysfunctions were present in 38.6% CKD 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.[17] A small study was conducted in CKD patients dependent on haemodialysis in western UP. This study showed the combined prevalence (26.6% patients) of clinical and subclinical hypothyroidism.[18] 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).[12] An India study showed prevalence of subclinical hypothyroidism was 24.8% in ESRD (End stage renal failure) patients.[19,20] 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 CKD 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.[21] Secondly, lipoproteins accumulation in glomerular, mesangium can promote production of matrix and glomerulosclerosis.[22] For CKD patients, some of the studies have shown a good association between risk for cardiovascular events and total cholesterol values,[23] whereas other studies did not show any significant correlation.[24] In our CKD patients have reduced plasma HDL-C levels, many other study consistency with us[1,25] possible explanation of decrease level of HDL-C is decrease level of apolipoproteins 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.[26] 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 reduce in the endothelium dependent vasodilatation of the vascular smooth muscle cells of hypertensive patients.[27] It is also seen that whenever there is blood pressure increases, there is ROS increase, thus increasing the mechanism of ROS-mediated hypertension. In this present study, there was significantly decrease the superoxide dismutase activity in the case group, indicating that either the scavenging system has been consumed during CKD 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.[16] Compromised functions of antioxidant result in the well-known cascade of hypoxic ischemic injury, inflammation, apoptosis and finally cell death.[28] The significant decrease activity of catalase in present study agreement with various previous studies found a lower activity of antioxidant enzyme[16] and a negative correlation between activity of Catalase and both day time DBP and SBP in hypertensive CKD patients.[29] 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.[30] 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 CKD patients which is a suggestive feature of oxidative stress in hypertension. These results are also consistent with the previous study.[16]

CONCLUSIONS

Thyroid dysfunction and dyslipidaemia are very frequent in CKD patients. It establishes that there is significant association between thyroid dysfunction and CKD progression and dyslipidaemia. Our study comes to the conclusion that CKD patients with dyslipidaemia have strong predisposition for developing CVD, so that early treatment for dyslipidaemia in CKD 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 patients of CKD with associated hypertension and data suggests controlling blood pressure by oxidative stress–related parameters. Patients of CKD are affected by multiple associated conditions like dyslipidaemia, 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. Haemodialysis also plays an important role in contributing to the oxidative stress. Enhancing evidence indicates that oxidative stress is a probable independent CVD risk factor in CKD. CVD is a significant cause of morbidity and mortality in patients of impaired kidney functions. Additionally, identification of functional and/or biochemical biomarkers could be used in clinical practice to monitor oxidative imbalance in CKD.

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