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LIPID PROFILE PATTERN IN THE PATIENTS WITH CKD (CHRONIC KIDNEY DISEASE): AN INSIGHT TO THE RISK OF CARDIOVASCULAR DISEASES

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Abstract

Background: CKD at all stages is accompanied with impaired lipid metabolism that not only favours the pathogenesis of atherovascular diseases but also facilitates the progression of the disease. As the renal function declines, oxLDL (oxidized LDL) and HDL impairment becomes more prominent and serves as important biomarkers for prediction of CVD risks in CKD. Therefore, this study was framed with an aim to evaluate lipid profile in the patients with CKD and compare that with the healthy control.

Methods: This study included 60 healthy controls and 60 CKD patients. In both the groups, total cholesterol (TC), LDL, HDL, triglyceride (TG) and VLDL were estimated using standard kit based methods. Statistical analysis was done using student's t test and ANOVA.

Results: TC, LDL, TG and VLDL concentration increased significantly in the CKD patients compared to the control group. The level of HDL was low but the difference in mean value was insignificant. As the renal impairment progressed, the values of lipid parameters (TC, LDL, TG and VLDL) progressively increased while HDL decreased.

Conclusion: Our study showed that the patients with CKD have atherogenic lipid profile that put them at an increased CVD risks. Hence, timely diagnosis by screening with lipid profile assessment along with therapeutic intervention and life style modification is suggested to prevent the associated long term cardiovascular complications.

Key words: Chronic kidney disease (CKD), atherosclerosis, hypertriglyceridemia.

Introduction

One of the major causes of mortality in the patients of chronic kidney disease (CKD) is associated cardiovascular complication which is attributed to abnormal metabolism of serum lipids [1]. Most often encountered lipid abnormalities are hypertriglyceridemia and decreased concentration of serum HDL. There is minor alteration in other lipid fractions [2]. In CKD, the prevalence of coronary artery disease is about 40% that is associated with 10-30 times higher mortality rates compared to age and sex matched normal individuals [3].

According to large scale and observational studies, total cholesterol (TC), low density lipoprotein (LDL) and high density lipoprotein (HDL) are important and independent predictors of abnormal cardiovascular events in CKD [4]. Several prospective studies also have reported the principal lipid abnormalities in CKD to be hypertriglyceridemia in association with increased level of very low density lipoprotein (VLDL) and decreased level of HDL [5]. Hypercholesterolemia can be observed in 48% of stage 1-2 CKD patients and 80% of stage 3-4 CKD patients [6]. Cholesterol level can further be abnormally high in CKD associated with proteinuria. The increase in the level of TG is a consequence of impaired lipoprotein lipase (LPL) activity and inhibition of enzymes required for lipid metabolism by various uremic toxins. Retention of pre β HDL, an inhibitor of LPL, also contributes to hypertriglyceridemia [7].

The level of LDL may be normal or marginally increased. When CKD is associated with proteinuria, it leads to abnormalities in the transport of lipoproteins. Atherogenic lipoproteins such as LDL and probably chylomicron remnants when increased, contribute to the development of atherosclerosis. This is because sub-endothelial accumulation of lipoproteins accelerates when their level is increased in plasma and it is further favoured by the reduction in their diameter. When these lipoproteins are modified via oxidation, they are no longer subjected to clearance by normal mechanisms. Rather, they trigger an inflammatory response causing their uptake by macrophages leading to the formation of foam cells which is a hallmark for atherosclerosis progression [8].

Several experimental studies have shown that hyperlipidemia leads to tubular interstitial disease and progressive glomerulosclerosis, thereby accelerating the renal damage. Lipid abnormalities also favour the progression of renal disorder [9]. Use of hypolipidemic drugs may aid in correcting lipid abnormalities in CKD, but proper clinical trials are needed to evaluate their efficacy. Therefore, early diagnosis and management of patients at a risk of CKD and associated cardiovascular disorders is required so as to develop effective screening methods and treatment strategies in order to decrease the mortality rates in CKD patients. Additionally, other risk factors of CVD like old age, smoking, male gender, diabetes, hypertension, inflammation and oxidative stress should also be monitored regularly in these patients. All these preventive measures will ultimately reduce the frequency and duration of hospitalization and also prevent long term serious complications. With this background, the present study was conducted on CKD patients to evaluate the patterns of lipid parameters in various stages of CKD and compare that with the healthy controls.

Materials and methods

The study was conducted in the Department of Biochemistry, Prasad Institute of Medical Sciences. The duration of the study was September 2021 to July 2022. 60 cases of CKD and 60 age and sex matched healthy controls were selected for the study. The diagnosis of CKD was done by clinical examination, sonological

analysis and biochemical investigations. Kidney disease outcomes quality initiative (KDOQI) 2012 criteria was followed.

Inclusion criteria

- All the patients above 20 years of age and who were ready to give consent for the study.

Exclusion criteria

- Patients not consenting to participate
- Patients who are dyslipidemic prior to CKD
- Patients with acute renal failure, diabetes mellitus, cardiovascular diseases or any other conditions that can alter serum lipids
- Patients on hypolipidemic drugs

After obtaining clearance from the ethical committee of the institute, fasting blood samples were collected from the control group and the patients. The samples were immediately sent to laboratory for biochemical investigations. The investigations carried out were as follows:

- Serum urea by urease-GLDH method
- Serum creatinine by modified Jaffe's method
- Serum total cholesterol (TC) by CHOD-POD method
- Serum HDL by direct enzymatic method
- Serum triglyceride (TG) by Trinder's method
- The levels of serum VLDL and LDL were calculated using Friedwald's equations as:

LDL= TC-(HDL + VLDL) where VLDL= TG/5

The percentage of patients having desirable, borderline and high risk levels of lipid parameters were also determined. The following table shows the desirable, borderline and high risk levels of lipid parameters:

Lipid	**Desirable**	**Borderline**	**High risk**
TC (mg/dL)	<200	200-239	>240
HDL (mg/dL)	51-60	41-50	<40
TG (mg/dL)	<150	150-199	>200
LDL (mg/dL)	<100	130-159	>160

After collecting the data, statistical analysis was done using SPSS 20. The comparative analysis between the two groups (Control and Cases/Patients) was done by student's t test while the comparative analysis involving more than two groups (different stages of CKD) was done using ANOVA. The p value <0.05 was considered statistically significant.

Results

In this study, most of the patients suffering from CKD were in the age group of 41-50 years (figure 1). We found preponderance of male patients with the male: female ratio of 1.61:1 (figure 2). Most of the patients included in this study had stage II CKD (35%), followed by stage V (25%) and Stage III (16.7%) (figure 3). The concentration of urea and creatinine increased significantly in the patients with CKD (table 1). On comparative evaluation of lipid parameters (TC, HDL, TG, LDL and VLDL), it was found that the levels of TC, TG, LDL and VLDL significantly increased ($p<0.05$) in the patient group compared to the control group. HDL level though low in patient group, was not significant ($p>0.05$) (table 2). The concentrations of lipid parameters were also compared among the patients at different stages of CKD. It was observed that the concentrations of TC, TG, LDL and VLDL increased and that of HDL decreased with the progression of CKD to

the successive stages (table 3). On categorizing the patients with respect to the level of lipid parameters as those having desirable, borderline and high risk values, it was found that 43.4%, 30%, 25% and 23.3% of the patients respectively had the TG, LDL, TC and HDL levels that corresponded to the significant risk of cardiovascular diseases while 28.3%, 36.7%, 40% and 43.3% of patients respectively had desirable TG, LDL, TC and HDL levels (figure 5).

Figure 1: Age based distribution of patients

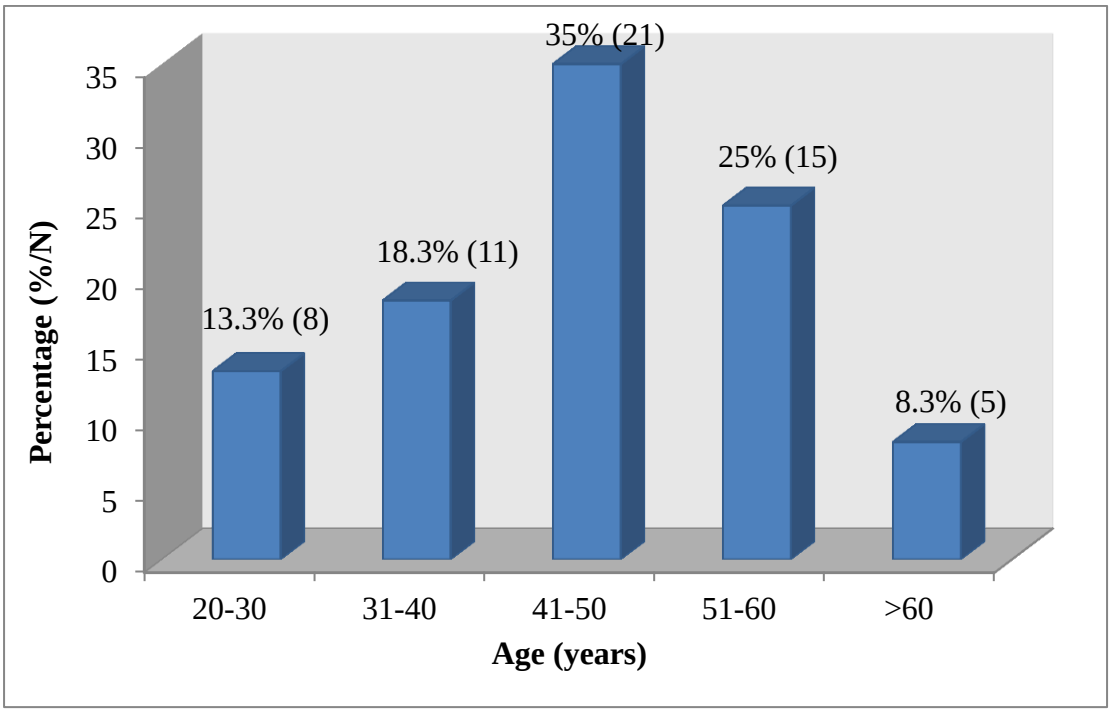


Figure 2: Gender based distribution of patients

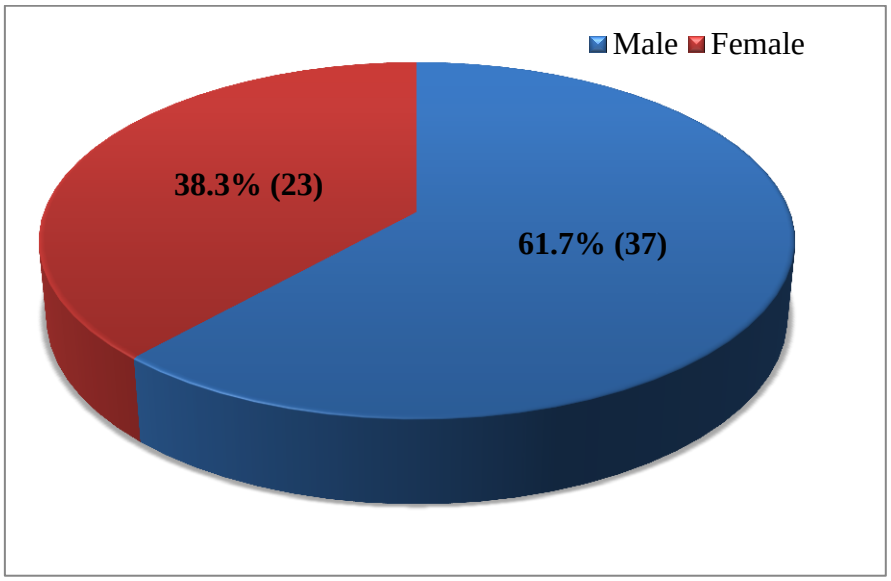


Figure 3: Distribution of patients based on the stages of CKD

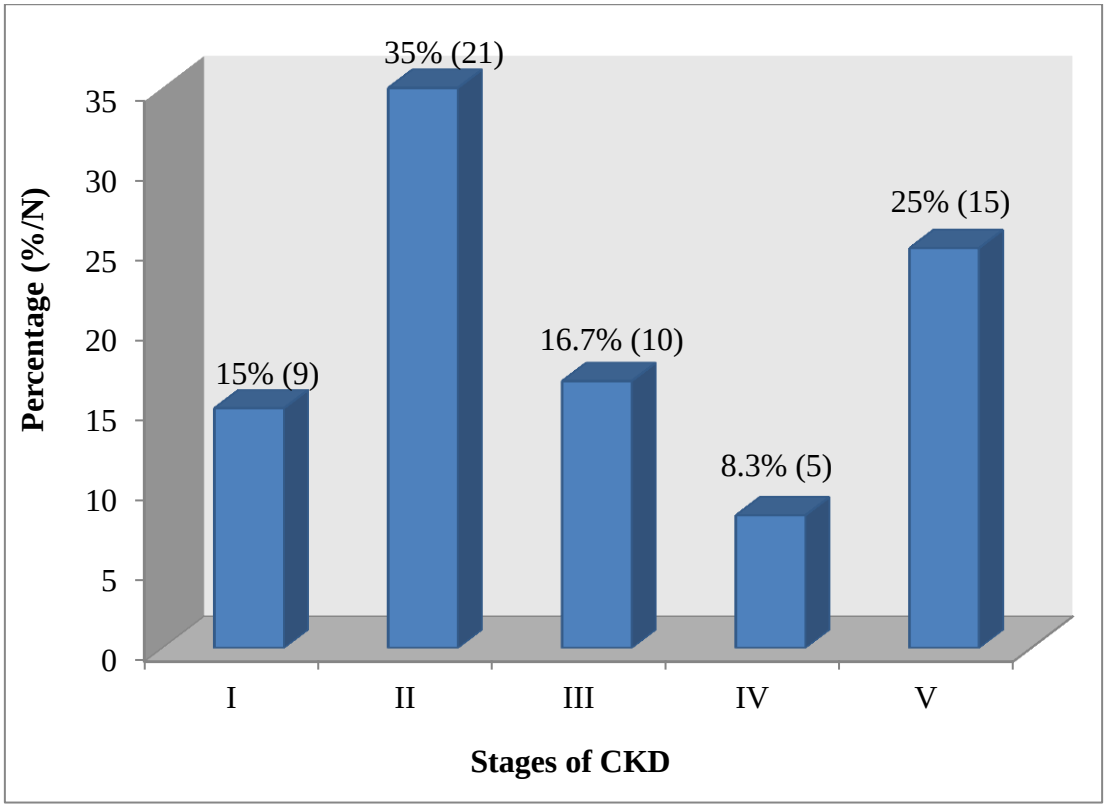


Figure 4: Distribution of patients based on the duration of CKD

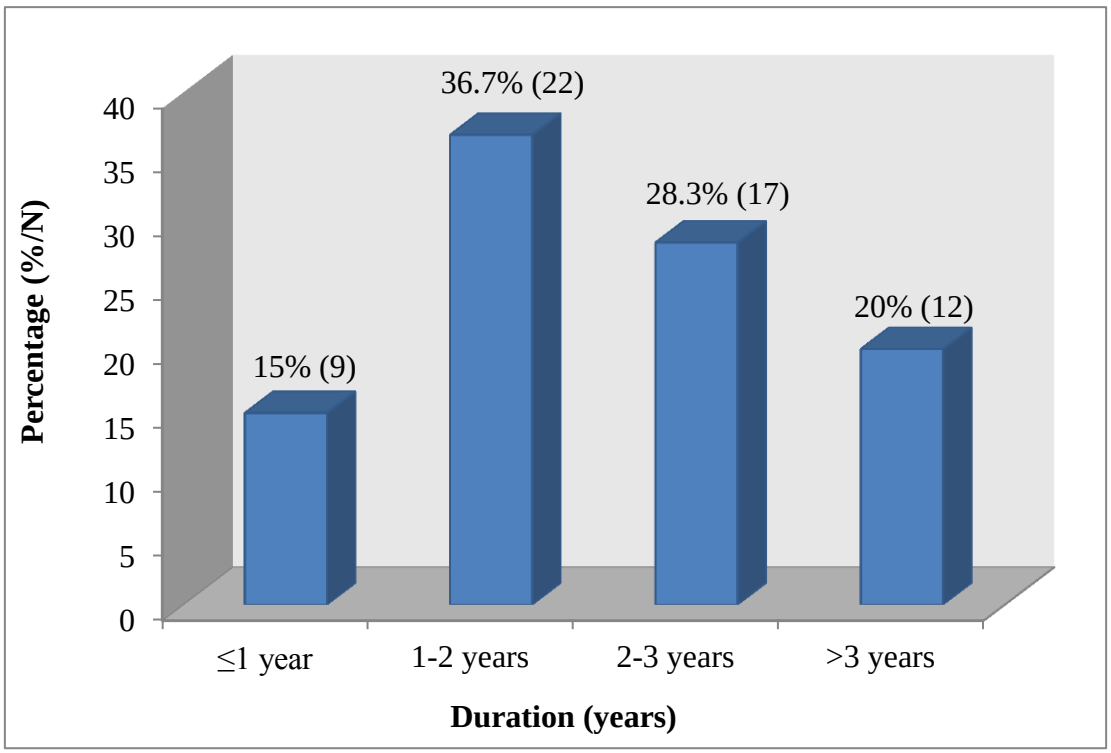


Table 1: Comparative analysis or urea and creatinine in control and cases

Parameters	Control	Cases	p
Urea (mg/dL)	25.3±4.1	208±20.6	<0.05*
Creatinine (mg/dL)	0.88±0.15	10.35±2.4	<0.05*

*→Statistical significance

Table 2: Comparative analysis of lipid profile parameters among cases and controls

Parameters	Control	Cases	p
TC (mg/dL)	146.5±31.41	196.7±41.51	<0.05*
HDL (mg/dL)	46.8±5.3	39.5±4.7	>0.05
TG (mg/dL)	117.2±42.6	186.2±21.7	<0.05*
LDL (mg/dL)	98.5±31.1	137.3±42.5	<0.05*
VLDL (mg/dL)	21.5±8.4	39.2±6.2	<0.05*

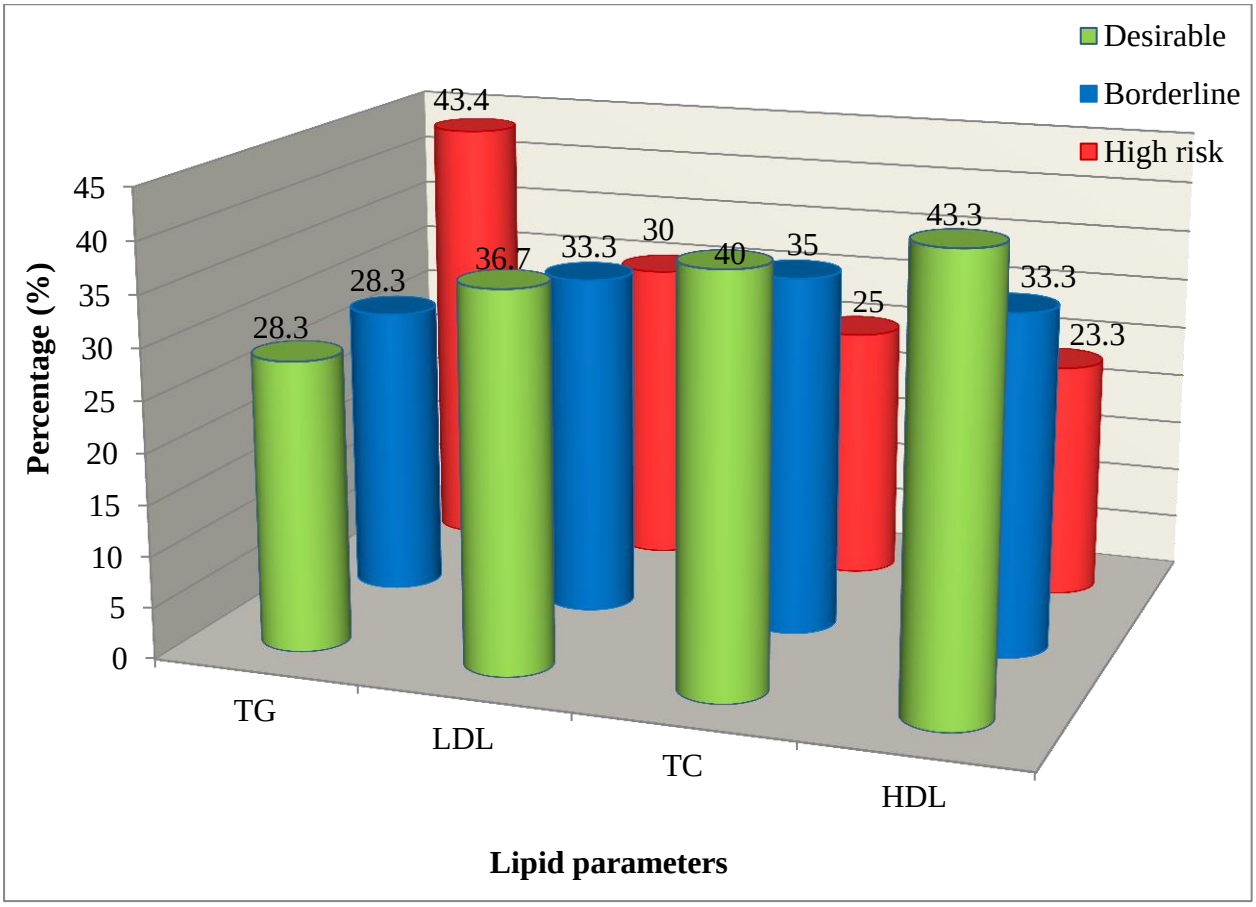
*→Statistical significance

Table 3: Level of lipid profile parameters in different stages of CKD

Lipid	Stage I	Stage II	Stage III	Stage IV	Stage V	p
TC (mg/dL)	120.7±33	138.2±20	163.7±20.1	188.7±14.6	209±16.3	<0.05*
HDL (mg/dL)	38.6±4.1	31.3±5.8	37±3.5	30.5±3.1	28.2±4.1	>0.05
TG (mg/dL)	115.3±28	141.6±27.6	187.2±41.7	161.7±36.3	230.1±40.7	<0.05*
LDL (mg/dL)	77.1±18.3	90.1±15.5	115.3±10.2	133.7±14.2	148.1±23.8	<0.05*
VLDL (mg/dL)	24.8±2.8	30.5±4.4	38.1±3.6	34.6±3.5	47±5.9	<0.05*

*→Statistical significance

Figure 5: Distribution of patients with the level of lipid ranges in CKD



Discussion

CKD is one of the major health hazards leading to fatality due to the associated cardiovascular complications. Of the many factors inducing atherogenesis and CVD, dyslipidemia appears to be a major culprit. It is a triad comprising hypercholesterolmia, hypertriglyceridemia and low HDL levels [10]. In the present study significantly high TC and TG levels were observed in CKD patients compared to the control group. HDL level though decreased in case group, it was not significant statistically. Similarly, the concentration of VLDL and LDL were also significantly increased in the patients with CKD. These results were in line with that of Attman PO *et al* who showed increased level of TG and decreased level of HDL in the CKD patients. However, they couldn't report any significant difference in the concentration of serum TC level [11]. In the study of Vaziri ND *et al* hypertriglyceridemia along with high VLDL and pre β HDL levels were reported while the concentrations of apolipoprotein A and HDL were decreased [12].

Likewise Gerald A *et al* [13] showed increased level of VLDL in CKD patients in their study. Chan CM *et al* [14] evaluated abnormal lipid profile in CKD patients due to nephrotic syndrome and observed that elevation in the levels of TG and LDL is directly associated with the severity of the renal damage. Nayak KC *et al* [15] on analysis of serum lipid between CKD patients with and without diabetes observed elevated TG, LDL and VLDL levels however the elevation was insignificant statistically. Similar reports were document in the study of Gupta DK *et al* [16].

Increased levels of TG, TC, VLDL and decreased level of HDL in blood facilitate the development of atherosclerosis and cardiovascular complications in CKD patients. Normally, endogenous TG synthesized in liver is secreted from hepatocytes as VLDL particles that transport hepatic TG to peripheral tissues. In the circulation, after hydrolysis of TG by LPL, the VLDL particles are reduced to IDL (intermediate density lipoprotein). IDL is taken up by liver and hydrolyzed further to form LDL particles. During this process of hydrolysis, the TG content of the lipoprotein particles is significantly reduced while the cholesterol will be present in considerable amounts [17]. LDL transports cholesterol to both hepatocytes and peripheral tissues. LDL-receptors present in the cells recognize Apo B100 present in LDL particles resulting in their cellular uptake. In normal individuals, about 60-80% of LDL is cleared by LDL receptors while the rest are cleared by the receptors such as scavenger receptors or LRP (LDL receptor related protein). Scavenger receptors presents on macrophages and vascular endothelium take up the oxidized LDL, also called as ox-LDL particle. But overloading of these macrophages with cholesterol ester causes transformation of those cells to foam cells, one of the major step in atherosclerosis development [18].

HDL is involved in the transport of cholesterol from peripheral tissue to liver, a process also known as reverse cholesterol transport that clears excess cholesterol from the peripheral cells thus preventing its accumulation [19]. HDL particles take up cellular free cholesterol in presence of ATP binding cassette transporter 1, apoprotein A-I (apo A-I) and apoprotein A-IV (apo A-IV). Apo AI causes activation of LCAT (lecithin cholesterol acyl transferase) enzyme that esterifies free cholesterol in HDL thereby favoring more efficient packaging and transport [20].

In CKD, impairment in the normal mechanism of lipoprotein metabolism occurs resulting in their altered levels in blood. Hypertriglycerdemia observed in CKD could be due to decreased clearance from plasma caused by inhibition of enzymes hydrolyzing TG, especially LPL and hepatic lipase [21]. The level of VLDL increases in CKD due to its delayed catabolism. In uremia there is decrease in the cholesterol and apo C-II of HDL particles. Apo C-II in normal case is transformed to VLDL from HDL. However, due to decreased level of apo C-II, the catabolism of TG is decreased with simultaneous reduction in VLDL metabolism. Hence, the level of VLDL increases in blood [22]. In CKD, there is also reduction in the level of Apo AI, an activator of LCAT, due to down regulation of Apo AI genes in hepatocytes. It leads to decrease in the activity of this enzyme leading to reduced esterification of cholesterol and impairment in HDL maturation thus level of HDL decreases in CKD [23].

Increase in the secretion of hepatic VLDL induced by hypertriglyceridemia causes activation of CETP (cholesteryl ester transfer protein) that transfers TG to HDL and LDL resulting in the formation of HDL and LDL rich in TG. The TG content of these particles is hydrolyzed by hepatic lipase ultimately leading to the formation of HDL and small dense LDL (sdLDL). The features of sdLDL particles are: low affinity to LDL receptors, ability to easily penetrate the endothelium and increased susceptibility to oxidation. oxLDL particles are highly atherogenic and increases the risk of CVD [24].

The mean values of TC, TG, HDL, LDL and VLDL were compared between the stages of CKD in this study. We found that the levels of lipid parameters like TG, TC, LDL and VLDL increased significantly with the progression of CKD. Incase of HDL, the level decreased with progression of CKD to the successive stages. Our

results were supported by the previous studies like that of Rao AM *et al* [23], Noor S *et al* [20], Aharwar S *et al* [19] and Garg G *et al* [17]. All these authors reported similar trends of increase in TC, TG, LDL, VLDL and decrease in HDL levels with the progression of renal impairment or CKD stages. Study of Khatiwada S *et al* [25] demonstrated significant association between CVD and abnormal TC, TG and LDL levels. Also progression of CKD is exclusively associated with prevalence of CVD. Their study indicated that the patients at higher stages of CKD (i.e stages III, IV, V) are at increased risk of CVD and associated fatalities compared to the patients at lower CKD stages (i.e. stages I, II).

Conclusion

Our study demonstrated the prevalence of deranged (atherogenic) lipid profile that can lead to atherovascular diseases in CKD patients. It increases the rate of morbidity and mortality in these patients. The patients with CKD must be screened regularly for CVD risk through the evaluation of lipid parameters as they are the simplest and cost effective measures. It is also important to maintain normal lipid profile either by dietary control or pharmacotherapy in order decrease the risk of associated long term cardiovascular complications.

Conflict of interest: Nill

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