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Original Article

Biochemistry Section

Unusual Dyslipidemia in Patients with Chronic Kidney Diseases

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ABSTRACT

Introduction: Chronic Kidney Disease (CKD) is a major and globally increasing health problem in the general population arising from a spectrum of diseases. Majority of the patients die even before reaching End Stage Renal Disease (ESRD) due to cardiovascular complications which arise due to altered lipoprotein compositions.

Aim: Present study was aimed at evaluating the serum lipid profile in CKD patients and to find the pattern of its alteration in both haemodialyzed and conservatively treated CKD patients.

Materials and Methods: Seventy one randomly selected CKD patients attending a tertiary care hospital of Assam during one year of time frame (40 haemodialyzed and 31 conservatively treated) along with 50 apparently healthy controls were included in the study. Test for serum lipid profile, urea creatinine, FBS, PPBS, total protein and albumin were carried out in all the cases and controls. The results were analyzed and compared with the controls using Microsoft Excel software.

Results: Triglyceride Level (TGL) of CKD group 157.88±61.82, controls 96.98±37.52, Very Low Density Lipoprotein (VLDL) of CKD group 31.58±12.36, controls 19.39±7.50 was marginally elevated and High Density Lipoprotein (HDL) of CKD group 33.40±9.06, controls 45.95±10.35 was significantly reduced in the patient group as compared to the controls and the results were statistically highly significant with p-value<0.001. Total cholesterol (CKD group 128.2±53.57, controls 142.53±31.44) and LDL (CKD group 63.23±46.47, controls 77.35±26.81) were lower in the patient group as compared to the controls, however the difference was statistically not significant (p value 0.09 and 0.059 respectively). There was no statistically significant difference of lipid profile between hemodialyzed and conservatively treated CKD groups and there was no gender related variation of lipid profile too.

Conclusion: Increased TGL and reduced HDL, rather than increased total cholesterol and increased LDL are responsible for the high incidence of cardiovascular complications in CKD patients. Hypolipidemic drugs and low fat diet may be helpful in impeding the progression of cardiovascular complications and decrease mortality and morbidity in such patients.

Keywords: Cardiovascular complications, Dyslipidemia, Haemodialysis, Hypertriglyceridemia

INTRODUCTION

CKD is a condition characterized by progressive loss of renal function over a period of time. CKD leads to deterioration of renal function, which results from diminished effective functioning of renal tissues.

Cardiovascular disease is a major cause of morbidity and mortality among patients with CKDs [1-3]. Most of the patients with CKD die from cardiovascular system complications before ever reaching Stage 5 CKD [3].

Dyslipidemia is a major risk factor for coronary heart disease [4,5] and it has prompted interest in the identification and management of abnormalities in plasma lipids and lipoproteins.

The association between renal disease and hyperlipidemia has been known for decades and is now well accepted. But the pattern of lipid abnormalities as observed by different workers is not consistent.

Lipid abnormalities are characterized by accumulation of partly metabolized triglyceride rich particles (predominantly VLDL) and Intermediate Density Lipoprotein (IDL) [6]. This is mainly due to abnormal lipase function. It leads to hypertriglyceridemia and low HDL cholesterol [6]. Although, total cholesterol concentration may be normal, there is often a high abnormal lipid subfraction profile with a predominance of atherogenic small dense LDL particles [6].

Experimental studies suggest that hyperlipidemia accelerates renal damage due to progressive glomerulosclerosis and tubulointerstitial disease [7]. Lipid-lowering treatment can reduce renal damage and preserve renal function [8]. The triglyceride rich apoB containing lipoproteins are found to be associated with accelerated deterioration of renal function [5], however the pathophysiological mechanism are not fully understood. Use of lipid lowering agents may be helpful in correcting the lipid abnormalities but a proper clinical trial is needed to establish the efficacy of hypolipidemic drugs on attenuation of lipid abnormalities and to prevent the progression of renal disease [9].

The aim of the present study was to evaluate the pattern of different lipoprotein changes, if any, in CKD patients treated conservatively as well as by haemodialysis and to study the difference of lipid profile between these two groups.

MATERIALS AND METHODS

In the present randomized case control study, we included 71 CKD patients attending a tertiary care hospital of Dibrugarh, Assam, India, from September 2010 to August 2011. These patients were further subdivided into two groups (31 conservatively treated and 40 treated by haemodialysis). Fifty apparently healthy age and sex matched controls were also included in the study for comparison.

Written consent from all the 71 cases and 50 controls was taken for being included in the study.

The study was conducted after getting approval from institutional human ethics committee of Assam Medical College and Hospital, Dibrugarh, Assam, India.

Inclusion Criteria

Diagnostic criteria for CKD:

1. Clinical signs and symptoms of uremia;
2. The presence of CKD was established based on presence of kidney damage and level of kidney function Glomerular filtration rate (GFR). Markers of kidney damage included abnormalities in the composition of blood (elevated blood urea and serum

creatinine, abnormalities in serum electrolytes, serum total protein and fraction) or imaging tests (ultrasonogram);

3. Bilateral shrunken kidney/ loss of corticomedullary differentiation on ultrasonography.

Exclusion Criteria

1. Patients with diabetes mellitus;
2. Patients with ischemic heart disease;
3. Patients who have undergone coronary artery bypass graft surgery;
4. Patients on lipid lowering drugs;
5. Patients with history of alcohol consumption and smoking;

All the selected patients were subjected to detailed history and complete physical examination and data collected was noted.

Blood Urea, serum creatinine, fasting blood sugar, post prandial blood sugar, serum total protein, serum albumin, serum globulin, lipid profile: total cholesterol, triglycerides, HDLc, LDLc, VLDLc were estimated by using semiautoanalyzer, Microlab 300, Merck in all 71 cases and 50 controls.

STATISTICAL ANALYSIS

The results were analyzed by using unpaired student's t-test with the help of Microsoft Excel software.

RESULTS

In [Table/Fig-1], mean values for urea and creatinine in controls and CKD patients are shown. There is considerable difference between cases and controls, which was found to be highly significant (p<0.001).

[Table/Fig-2] shows statistically significant difference of TGL, VLDL, and HDL between CKD cases and controls. Total cholesterol and LDL values were low in CKD cases as compared to controls although the result was statistically not significant.

In [Table/Fig-3], the mean total cholesterol, triglyceride, HDL, VLDL, and LDL values between patients treated conservatively and by haemodialysis were shown. The differences of lipid profile between the two groups were statistically not significant.

In [Table/Fig-4], lipid profile in male and female CKD patients were shown. There is no statistically significant difference of lipid profile in male and female CKD patients.

Groups	Blood urea (Mean±SD)	Serum creatinine (Mean±SD)
Controls	22.84±5.82	0.88±0.19
CKD patients	137.75±64.98	6.73±2.68
Significance	<0.001	<0.001

[Table/Fig-1]: Blood urea and serum creatinine in controls and ckd patients (Mean±SD) mg/dl.

Groups	Controls mg/dl	CKD patients mg/dl	p-value
Total cholesterol	142.53±31.44	128.2±53.57	0.09
TGL	96.98±37.52	157.88±61.82	< 0.001
HDLc	45.95±10.35	33.40±9.06	< 0.001
LDLc	77.35±26.81	63.23±46.47	0.059
VLDLc	19.39±7.50	31.58±12.36	< 0.001

[Table/Fig-2]: Data of lipid profile in controls and CKD patients (Mean±SD).

Groups	CKD patients treated conservatively mg/dl	CKD patients treated by haemodialysis mg/dl	p-value
Total cholesterol	138.85±51.86	119.95±54.05	0.141
TGL	163.87±66.42	153.25±58.45	0.476
HDLc	31.75±8.86	41.43±37.77	0.167
LDLc	74.52±42.28	54.64±48.04	0.072
VLDLc	32.57±13.55	30.65±11.69	0.522

[Table/Fig-3]: Data of lipid profile in CKD patients on conservative treatment and haemodialysis (Mean±SD).

Lipid profile mg/dl	Male (Mean±SD)	Female (Mean±SD)	p-value
Total cholesterol	114.91±39.19	127.62±55.02	0.229
TGL	148.85±51.86	157.70±62.79	0.477
HDLc	31.89±8.03	33.94±9.15	0.269
LDLc	53.24±32.86	62.14±47.66	0.327
VLDLc	29.77±10.37	31.54±12.56	0.477

[Table/Fig-4]: Biochemical (lipid profile) data among male and female ckd patients.

DISCUSSION

Several other studies on lipid profile in CKD patients observed hypertriglyceridemia, hypercholesterolemia, increased LDL and decreased HDL [10-15]. Whereas in present study, we have observed hypertriglyceridemia, increased VLDL, decreased HDL and decreased serum cholesterol and LDL which is contradictory.

Triglycerides:

In the present study, triglycerides were marginally elevated and the difference with the control group was statistically highly significant (p-values <0.001). Decreased triglyceride clearance from the plasma due to inhibition of both hepatic and Lipoprotein Lipase (LPL) may lead to hypertriglyceridemia [16]. The reduced catabolism is likely due to the decreased activity of LPL and hepatic triglyceride lipase, which cleaves triglycerides into Free Fatty Acid (FFA) for energy production or storage.

The decreased activity of the hepatic and LPL is probably due to [9,16-18]:

1) Frequent heparinization of the haemodialyzed patients;
2) Increased apo C-III/apo C-II ratio;
3) Presence of other lipase inhibitors in the plasma;
4) Decreased LPL synthesis secondary to hyperparathyroidism and suppressed insulin level.

The plasma apo C-III level is increased disproportionately as compared to apo C-II. The apo C-III is an inhibitor while apo C-II is an activator of LPL [9,16-18].

Hypertriglyceridemia leads to alteration of size and composition of HDL and LDL. Hypertriglyceridemia leads to increased VLDL secretion from liver which activates Cholesteryl Ester Transfer Protein (CETP). CETP transfers triglycerides to LDL and HDL leading to formation of triglyceride rich LDL and HDL. Hepatic triglyceride lipase hydrolyses the triglyceride content of the HDL and LDL particles leading to formation of a subfraction called small dense LDL and HDL. Small dense LDL (sdLDL) has low affinity for LDL receptor, can penetrate arterial wall easily and are more susceptible to oxidation [19]. Oxidized sdLDL is highly atherogenic which increases the risk of cardiovascular diseases [19].

Maheshwari N et al., reported hypertriglyceridemia and low HDLc and elevated lipoprotein-a, which could contribute to atherosclerosis and cardiovascular disease that may increase the morbidity and mortality in patients on maintenance haemodialysis [20].

HDL Cholesterol:

In the present study, there was decrease in HDL cholesterol seen in patients compared to controls, which was statistically significant (p<0.001). Patients with impaired renal function exhibit decreased levels of apolipoproteins A-I and A-II (which are the main protein constituents of HDL) [9,21].

In CKD patients there is decreased activity of LCAT (Lecithin Cholesterol Acyl Transferase, the enzyme responsible for the esterification of free cholesterol in HDL particles) [9,22], and increased activity of Cholesteryl Ester Transfer Protein (CETP) which facilitates the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins which are responsible for reduced serum concentrations of HDL cholesterol [9,23].

A major function of HDL is to act as a repository for the apo C and apo E required in the metabolism of chylomicrons and VLDL [24]. DSSK Raju et al., in their study observed that serum HDL-C was significantly decreased in CKD patients both in non dialysis and haemodialysis groups when compared with controls [25].

Total cholesterol:

In the present study, total cholesterol levels were lower in CKD patients, though the results were not statistically significant when compared with controls (p-value 0.09).

Several other studies observed hypercholesterolemia in CKD patients. The difference of observations between the studies could be due to racial variation of the study group, differences of dietary habit that varies depending upon the geographical variation and culture. Malnutrition and associated infection which is very common particularly in the patient population in the hospitals may also lead to decreased cholesterol level.

Balode AA et al., observed significant hypercholesterolemia in CKD patients as compared to the controls [10]. Sumathi ME et al., studied serum total cholesterol, TGL, HDLc, LDLc, and VLDLc in 60 chronic renal failure patients. They observed a significant increase in serum total cholesterol, LDLc, VLDLc and significant decrease in HDLc in the patient group as compared to their controls [11].

VLDL:

There was significant raise in VLDL levels in CKD patients compared to controls ($p<0.001$). Increase in VLDL cholesterol in CKD are mainly due to their reduced clearance as well as insulin resistance driven overproduction of VLDL [2,26].

LDL:

There was no significant difference in LDL levels observed in patients as compared to controls, (p-value 0.059) but the value of LDL was found to be lower in the CKD group as compared to the controls.

In CKD patients, the hepatic LDL receptor gene expression is not altered until there is significant glomerulosclerosis or heavy proteinuria [9]. There is alteration of metabolism of LDL particles in CKD patients leading to formation of sdLDL. The sdLDL is a subfraction of LDL which is formed in presence of hypertriglyceridemia. It has increased atherogenic potential, gets oxidized and accelerates atherogenesis [6,9,27].

Comparison of lipid profile in chronic kidney disease patients on conservative management and haemodialysis:

Total cholesterol levels were decreased in patients on haemodialysis as compared to patients treated by conservative line but this difference was statistically not significant. HDL levels were lower in patients of conservative management compared to haemodialysis patients but this was also statistically not significant. VLDL in conservatively treated group was marginally increased compared to haemodialysis group but this was also statistically not significant ($p>0.05$).

LDL values were lower in patient treated with haemodialysis as compared to patients treated conservatively however, this difference was statistically not significant. There was increase in triglycerides in patients treated with conservative treatment compared to patients on haemodialysis, but the difference was statistically not significant ($p>0.05$).

Sumathi ME et al., studied serum lipid profile in 30 conservatively treated and 30 haemodialyzed Chronic Renal Failure (CRF) patients. They found higher total cholesterol, TGL, HDLc, and VLDLc and LDLc in conservatively treated CRF patients as compared with the haemodialyzed patients and the difference was statistically significant except LDLc which was not significant [11].

LIMITATION

A more extensive study including large patient population and for longer duration; with proper clinical trial is required to achieve a firm conclusion. Study to detect hypertriglyceridemia induced qualitative alteration of HDL and LDL particles will provide additional information on the development of cardiovascular complications in CKD patients. Evaluation of predialysis and postdialysis lipid profile in the same patient and follow up lipid profile estimation after repeated haemodialysis will provide more reliable information on the effect of haemodialysis on lipid profile in CKD patients.

CONCLUSION

Increased triglycerides, increased VLDL and reduced HDL; rather than increased total cholesterol and LDL are responsible for increased cardiovascular complications in patients with CKD. Use of hypolipidemic drugs aimed at lowering triglycerides and consumption of low fat diet may be helpful for impeding the progression of renal disease as well as in lowering the cardiovascular complications observed in CKD patients which will increase the survivability and decrease morbidity and mortality in CKD patients.

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