ORIGINAL ARTICLE

LIPID ABNORMALITIES, LIPOPROTEIN (a) AND APOPROTEIN PATTERN IN NON-DIALYZED PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

The present study was carried out to explore the altered lipid, lipoprotein and apoprotein abnormalities along with lipoprotein (a) in chronic kidney disease patients with stage I to V which were further divided into group 1 (stage I and II), group 2 (stage III and IV) and group 3 (stage V). 50 chronic kidney disease patients with stage I to V and 20 healthy normal subjects as controls were recruited for this study. Among the various parameters tested triglyceride levels were high in group 1 and 2, whereas VLDL cholesterol, Lp (a) and apo B levels were significantly high in all the groups when compared to controls ($P < 0.05$). However, LDL cholesterol level was significantly low in group 3 only as compared to control group ($P < 0.05$). Apoprotein AI values also showed significant decrease in all groups as compared to controls ($P < 0.05$). Though total cholesterol levels in group 1 and LDL levels in group 1 and 2 were higher than controls, but the values attained not statistically significant ($P > 0.05$). In conclusion high levels of VLDL cholesterol, Lp (a), apo B and low levels of apoprotein AI as reported in this study are the major lipid disorders in the development of cardiovascular complications at all the stages in these patients.

KEY WORDS

Chronic Kidney Disease, End stage renal disease, Lipid Profile, Lp(a), Lipoprotein Metabolism.

INTRODUCTION

Chronic Kidney disease (CKD) is a progressive loss of renal function over a period of months. All individuals with a glomerular filtration rate (GFR) $< 60 \text{ ml/min/1.73m}^2$ with proteinuria for 3 months are classified as having chronic kidney disease (1). Cardiovascular disease (CVD) is a major cause of mortality in patients with mild to moderate CKD and end stage renal disease (ESRD) (2). Dyslipidemia has been established as a well-known traditional risk factor for CVD in CKD and large-scale observational studies have shown that

total and low-density lipoprotein (LDL) cholesterol are most important independent predictors of cardiovascular morbidity and mortality (3).

CKD reflects most quantitative abnormalities in predialysis patients and the incidence of CVD becomes substantially elevated when CKD progresses (4). Abnormal lipid and lipoprotein concentrations in patients with CKD may be cause of their high-risk of atherosclerosis and lipoprotein (a) [Lp(a)], lipoproteins and apolipoproteins composition which would be an index of increased atherogenic status (5).

There is no consistency on lipid profile especially on total cholesterol in CKD among Western and Indian studies. There are western studies that showed hypercholesteremia (6) no hypercholesteremia (7) in CKD. However, there are only a few Indian studies (8,9,10) which have explored the atherogenic lipid profile at all the stages of CKD. The present study was undertaken to explore the altered lipid, lipoprotein and apoprotein abnormalities along with Lp(a) in CKD from stage I to stage V (ESRD) classified as per National Kidney

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Foundation Kidney Disease Outcomes Quality Initiative (NKFK/DOQI) guidelines (1) which plays a vital role in development of atherosclerotic cardiovascular disease.

MATERIALS AND METHODS

The study was conducted on successive patients after informed consent was obtained from them and approved by the ethical committee of the institution. A total of fifty CKD patients (32male and 18 female, aged 19-50 years) with stage I to stage V who were attending nephrology department were recruited for this study. Subjects were further divided into three groups based on stages of the disease, classified as per (NKFK/DOQI) guidelines (1). Group 1, 2 and 3 included patients with CKD. Group 1 consisted of (n=15) stage I and II patients with a GFR between 60 and 119 ml/min/1.73m². Group 2 (n=20) had stage III and IV patients with a GFR between 15 and 59 ml/min/1.73m² while, group 3 (n=15) had stage V i.e., (ESRD) patients with a GFR < 15 ml/min/1.73m². 20 age and sex matched healthy subjects who were nonsmokers, nondiabetic and nonhypertensive served as controls. 5 ml of venous blood samples were collected in plain tubes after an overnight fast. The samples were allowed to clot for half an hour following which the samples were centrifuged for 15 min at 2000rpm and serum was stored immediately at -80°C until analysis.

Serum total cholesterol, triglycerides, HDL cholesterol, urea and creatinine, were measured using commercially available kits in Beckman Synchron CX9 auto analyzer. LDL cholesterol and VLDL cholesterol concentration was calculated using Friedewalds Formula (11). Lp (a) concentration was measured by ELISA using commercially available kit of (Daiichi Pure Chemicals, Japan). Apoproteins apo AI and apo B were measured by immuno turbidimetric method using commercially

available kit (APTEC diagnostics, Belgium).

Analysis was carried out in SPSS, Version 11.5. All the values obtained were expressed as mean and standard errors of mean (SEM). "Mann Whitney U test" was applied to compare the difference in the means between controls and study group. The differences were considered as significant if P value was <0.05.

RESULTS

A case control study was taken to determine lipid profile along with Lp (a) and apoproteins apoA and apoB changes in patients with CKD from stage I to stage V. Clinical details of controls and CKD patients were shown in Table 1. Table 2 shows mean and standard error of mean of total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, VLDL cholesterol, Lp (a), apoA, apoB, urea and creatinine of controls and group 1, 2, 3

Table 1: Clinical details of Controls and Chronic kidney disease patients

Characteristic	Controls	CKD Patients
Age	4.2 ± 8.6	49.41 ± 13.66
Causes of CKD		
1. Diabetes mellitus (n=15)		47.45 ± 18.64
2. Hypertension (n=17)		56.50 ± 15.91
3. Lupus nephritis (n=02)		39.63 ± 11.43
4. Chronic pyelonephritis (n=03)		60.32 ± 13.57
5. Membranous nephropathy (n=05)		44.40 ± 15.19
6. Nephrotic Syndrome (n=08)		48.20 ± 7.34
Urea	21.7 ± 1.22	110.19 ± 20.07
Creatinine	0.65 ± 0.04	5.09 ± 1.24

Values are mean ± SD; n= number of patients

Table 2: Mean and Standard Error Mean for the Biochemical parameters among Control and CKD Patients

Parameter (mg/dL)	Controls (n=20)	Group-I (n=15)	Group-II (n=20)	Group-III (n=15)
Total C	155.10 ± 6.10	223.42 ± 32.96	145.55 ± 15.75	138.90 ± 11.68
TGL	91.25 ± 6.20	223.42 ± 31.65*	142.1 ± 15.56*	137.40 ± 24.30
HDL-C	50.55 ± 8.23	50.40 ± 4.04	50.20 ± 4.25	48.33 ± 5.06
LDL-C	86.35 ± 5.50	154.66 ± 29.14	142.1 ± 15.56	61.3 ± 9.96*
VLDL-C	18.09 ± 1.18	46.71 ± 6.51*	31.58 ± 4.09*	27.4 ± 4.84*
Lp (a)	12.5 ± 2.0	18.34 ± 2.99	27.21 ± 5.23 *	39.9 ± 7.12*
ApoAI	185.05 ± 7.57	46.63 ± 7.33*	50.0 ± 7.79 *	41.22 ± 7.59*
ApoB	85.45 ± 3.85	174.28 ± 10.56*	183.05 ± 6.65*	174.66 ± 9.14*

* Statistically significant; p value <0.05 is considered as significant; Figures in parentheses indicate the number of patients.

patients. In group 1 patients ApoAI levels were significantly low when compared to controls, whereas triglycerides, VLDL cholesterol and apo B levels were significantly high when compared with controls. Total cholesterol and LDL cholesterol and Lp (a) levels were higher than controls but the values attained not statistically significant ($P < 0.05$).

In group 2 patients ApoAI levels were significantly lower than controls whereas triglycerides, VLDL cholesterol, LDL cholesterol, Lp (a) and apoB levels were significantly higher than controls. Total cholesterol and HDL cholesterol levels were not significantly different with control group. In group 3 patients apoAI and LDL cholesterol levels were significantly low whereas levels of VLDL cholesterol, Lp(a) and apo B were significantly high when compared with controls. Total cholesterol and HDL cholesterol levels were low and triglyceride levels were high but, the values attained statistically not significant.

DISCUSSION

Several prospective studies suggest that lipid abnormalities principally present in CKD is hypertriglyceridemia. In the present study, we find hypertriglyceridemia in group 1 and group 2 patients when compared to controls. Elevated triglyceride levels are due to impaired activity lipoprotein lipase (LPL) (12) and direct inhibitory effect of various uremic 'toxins' on the enzymes involved in lipid metabolism (13), represent the most important pathophysiological mechanisms underlying the development of hypertriglyceridemia in renal failure.

In Indian studies, there is no evidence of hypercholesteremia in earlier stages but in ESRD, cholesterol is either normal or reduced whereas western studies have reported hypercholesteremia to be present predominantly in all CKD groups. This could be due to difference in dietary habits (6). We did not find hypercholesteremia in any of the CKD groups, but cholesterol levels were low in ESRD patient group, though the results were not statistically significant when compared with controls. Similarly Michael et al (7) found no evidence of hypercholesteremia instead, level of total cholesterol was significantly lowered in ESRD patients.

It is well known that patients with impaired renal function exhibit significant alterations in lipoprotein metabolism, which in their most advanced form may result in the development of severe dyslipidaemia (14). VLDL cholesterol levels were significantly high in group 1, 2 and 3 when compared with controls in this study and increase in VLDL cholesterol and their remnants in CKD are mainly due to their reduced clearance as well as

insulin resistance driven overproduction of VLDL (15).

LDL cholesterol is usually normal or slightly reduced in CKD and exhibit important disturbances in density distribution of LDL subfractions that is characterized by a predominance of small, dense LDL particles which are susceptible factors for atherogenesis (16). In the present study we find high levels of LDL cholesterol in group 1 and 2 which were not statistically significant when compared to controls. Similar results are forwarded by Bhagwat et al (10). However, levels were significantly low in group 3 when compared to controls.

Apo AI, which is the activator of lecithin cholesterol acyl transferase (LACT), is reduced in CKD due to down regulation of hepatic apoAI genes leads to decline in the activity of LACT, which causes reduced cholesterol esterification and impairment of HDL maturation. The activity of LACT is consistently diminished in CKD, so there is decrease in HDL levels (17). HDL cholesterol levels in group 2 and group 3 were lower than controls in the present study also, though the values attained were not statistically significant.

The characteristic apoprotein profile is marked increase in the concentration of apo CIII, apo B and relatively smaller increase in the concentration of apo E in chronic renal failure (9). We measured only apoAI and apoB in this study. ApoAI was found to be reduced in all the groups in our study when compared with controls. A decrease in the HDL, which contains the apoAI the major antiatherogenic contributing factor of HDL is decreased as the renal function, deteriorates, suggesting that decrease in apoAI is the main contributing factor for CVD in CKD patients (17). Apo B is the protein component of LDL and major atherogenic factor of CVD, which was found to be significantly elevated in all the groups in the present study when compared with controls. Increase in apoB level is mainly due to partially catabolized apoB containing, triglyceride-rich, particles of the VLDL and IDL classes and defect in the removal of apo B rich remnants (15).

Lp (a) is another atherogenic factor of importance in the pathogenesis of CVD. Elevated Lp (a) levels in subjects with early impairment of renal function are associated with greater prevalence of CVD (18). Lp (a) levels were higher than controls in all the groups in this study, which is in agreement with Kalra et al reported that Lp(a) levels starts increasing early during the course of CKD and becomes pronounced with increasing severity of disease (19).

In conclusion, abnormal lipid, lipoprotein and apoprotein pattern in non-dialyzed patients with CKD is significantly high

in triglycerides, VLDL cholesterol, Lp(a), apo B and low in apo A at all the stages. However, HDL cholesterol level was reduced in all the groups but statistically not significant. There is no hypercholesteremia, though total cholesterol level in group 1 and group 2 was higher than the control which was not statistically significant. Together, these abnormalities enhance the risk of atherosclerotic cardiovascular disease in these patients. A prospective study with larger sample size including dialysis patients (hemodialysis and peritoneal dialysis patients) is planned to establish the observations made in this study.

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