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A study of dyslipidemias in patients with non-dialysis chronic kidney disease patients in a tertiary care centre of Kumaon region

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Abstract

Background: CKD is a worldwide public health issue and has been identified as a major risk factor for atherosclerotic CVD.

Objectives: the primary aim of this study was to evaluate KFT and lipid profile parameters including LP(a) in different grades of chronic kidney disease to find correlation between Lp (a) and lipid profile and KFT

Material and methods: Present study was conducted on 185 total subjects, of which 85 were CKD patients and 100 were age, sex and BMI matched healthy controls we defined CKD as < 60 mL/min/1.73 m2 estimated glomerular filtration rate (eGFR) for three or more consecutive months. KFT and Lipid profile parameters were performed on Roche Cobas 501 autoanalyser. Serum Lp(a) was done on semiautoanalyser (MERCK) based on immunoturbidimetric principle.GFR was calculated by Cockcroft-Gault formula

Results- Significantly raised levels (p< 0.001) of urea (101.41 ± 36.36 vs 20.32 ± 4.78), creatinine (5.67±2.24 vs 0.68 ± 0.12), GFR (12.89± 5.67 vs 106.6 ± 21.24) was observed in CKD patients when compared with the controls. No statistically significant difference was observed in mean total cholesterol level of the CRF cases and control group (215.46 ± 29.45 and 202.64 ± 46.52 respectively ; p value = 0.41) . Triglycerides in cases was 196.84 ± 67.34 when compared with controls 121.34 ± 70.73 with p value < 0.0001. LDLc in cases and controls was 116.46 ± 31.76 vs91.76 ± 33.49; p value <0.05. Significant decrease in HDL in CKD cases when compared with controls (39.34 ± 10.89 vs 56.76 ± 12.56; pvalue < 0.001) . LDLC/HDL-C ratio was statistically significantly raised in CKD cases than the controls (3.71± 0.98 vs 2.61 ± 1.09;p<0.05) .Lp (a) in the CRF cases was 29.87 ± 24.98 and that of the controls was 21.89 ± 17.76 (p value <0.05).

Conclusion: CKD is characterized by dyslipidemias increasing progressively with the severity of declining glomerular functions which predisposes these patients to cardiovascular risk. So concerted lifestyle modifications and medical management can interrupt the pathophysiological cascade of events induced by dyslipidemia.

Keywords: CKD, Dyslipidemias, Serum, Patients.

Introduction

Chronic kidney disease (CKD) is a significant public health problem with a profound impact on quality of life and cost burden all over the world[1]. CKD is a condition of decreased kidney function represented by glomerular filtration rate(GFR) less than 60ml/min/1.73m2 for at least 3 months. It is classified into stage I-V on the basis of glomerular filtration rate, where stage V (GFR under 15 mL/min/1.73 m2) represents, the irreversible end stage renal disease (ESRD)[2,3]. Dyslipidemia characterized by atherogenic profile i.e. elevated triglyceride levels, low high-density lipoprotein cholesterol levels, and increased small, dense, low-density lipoprotein particles, is a common complication of progressive kidney disease and contributes to the high cardiovascular morbidity and mortality of chronic kidney disease (CKD) patients[4,5]. Numerous factors influence the nature of lipid disorders in patients with kidney disease, including the presence and severity of proteinuria and renal failure, dietary and drug regimens, pre-existing genetic disorders (cholesterol metabolic signature genes) of lipid metabolism, and renal replacement therapies (haemodialysis, peritoneal dialysis, and renal transplantation [6-10]. Recent studies also suggests that dyslipidemia in turn can activate monocytes, degrade glycocalyx, and increase permeability of the glomerular filtration barrier, which may contribute to the progression of renal disease[11-12]. In an evaluation of 2001-2010 National Health and Nutrition Examination Survey (NHANES), the prevalence of dyslipidemia increased from 45.5% in CKD stage 1 to 67.8% in CKD stage 4[13]. It is important to recognize concordance of these two chronic diseases because of the increased risk of morbidity and mortality. Several studies conducted worldwide [4,5,10,12,14-16] have reported an association between CKD and dyslipidemias increasing cardiovascular mortality, yet in kumaon region no study to our knowledge, reported this association. The primary aim of this study was to examine the dyslipidemia including Lp (a) levels in CKD participants and to find if there is any correlation among KFT parameters, lipid profile parameters and LP (a).

Material and methods

This study was conducted after approval from Institutional Ethical Committee of GMC Haldwani and this study was conducted Dr. Susheela Tiwari Government Hospital, Haldwani, Nainital, Uttarakhand, India, tertiary care referral center in Kamoun region during the period august 2018 to Jan 2020. Out of total 185 subjects enrolled, 85 were chronic kidney disease patients attending nephrology clinic and 100 were age, sex, BMI matched subjects who fulfilled the inclusion and exclusion criteria were taken as controls 5 ml of venous blood was collected from each study subject in vacutainer plain tube and was left for some time for coagulation, then centrifuged at 3000 rpm for 10 minutes to obtain serum. Biochemical analysis of serum for urea, creatinine, total cholesterol, triglycerides high density lipoprotein cholesterol was performed on Roche /Hitachi Cobas 501c autoanalyser Very low density lipoprotein cholesterol values were calculated using the formula Triglycerides/5 and Low density lipoprotein cholesterol was calculated using Freidwalds equation. Serum sample for Lp (a) estimation was stored in Eppendorf tube at 4^0c for batch analysis. Lp (a) estimation was based on the principle of immunoturbidemetery and was done on semiautoanalyser (MERCK). GFR was

calculated using GFR can be estimated using the cockcroft – Gault formula (17) CrCL (ml/mt) =140-age x weight (kg)/72 x S. creatinine (mg/dl) x 0.85 (for women).

The following cut points were used to define the presence of dyslipidemia: TG-130 mg/dl, HDL–C -40 mg/dl, and nonHDLc-160 mg/dl. These cut points were based on normative NHANES data (18).

Statistical analysis

Data analysis was done with the help of computer. Using the software SPSSV27, range, frequencies, percentages, means, standard deviations and 'p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables. A 'p' value less than 0.05 is taken to denote significant relationship**.**

Results

Table 1 shows the base line demographic parameters of the study subjects. Of the total 85 CKD patients 61.18% were males and 38.82% were females with the mean age of 53.72 ± 8.79 years. Subjects attending medicine OPD for some other minor illness matched in age, sex and BMI were included as controls.

Parameters	Cases (n=85)	Controls (n=100)
AGE (years) 31-40 41-50 51-60 61-70 Mean age	6 (7.05%) 28 (32.94%) 32 (37.64%) 19 (22.35%) 53.72 ± 8.79	9 (9%) 36 (36%) 40 (40%) 15 (15%) 56.92±7.99
No. of Males No. of Females	52 (61.18%) 33 (38.82%)	68(68%) 32(32%)
Height (in cms)	92.45 ± 3.74	91.87±4.89
Weight (kgs)	72.89 ± 5.78	74.32 ± 8.99
BMI (kg/m^2)	26.12 ± 3.32	25.67±3.31

Table 1: Baseline characteristics of study population

Table 2 illustrates the mean ± SD values of KFT, lipid profile and Lp (a) values of CKD cases and controls. A significantly raised levels (p< 0.001) of urea (101.41 ± 36.36 vs 20.32 ± 4.78), creatinine (5.67±2.24 vs 0.68 ± 0.12), GFR (12.89± 5.67 vs 106.6 ± 21.24) was observed in CKD patients when compared with the controls. No statistically significant difference was observed in mean total cholesterol level of the CRF cases and control group (215.46 ± 29.45 and 202.64 ± 46.52 respectively; p value = 0.41). Significant increase in serum triglycerides was seen in cases (196.84 ± 67.34) when compared with controls (121.34 ± 70.73 p value < 0.0001. We observed an increase in LDL cholesterol between cases and controls (116.46 ± 31.76 vs91.76 ± 33.49). This was significant statistically p value (<0.05). This study demonstrated a significant decrease in HDL in CKD cases when compared with controls (39.34 ± 10.89 vs 56.76 ± 12.56 (P value< 0.001). TG/HDL-C ratio was calculated by dividing serum concentration of TG by HDL-C measured in mg/dl and was found to be significantly raised in CKD cases as compared to controls(p<0.05). LDLC/HDL-C ratio calculated by dividing serum LDL-C by HDL-C

values was also statistically significantly raised in CKD cases than the controls (3.71± 0.98 vs 2.61 ± 1.09; p<0.05). The mean Lp (a) in the CRF cases was 29.87 ± 24.98 and that of the controls was21.89 ± 17.76. There was statistically significant difference in this parameter. (p value <0.05).

Parameters	Cases (n=85) Mean ± SD	Controls (n=100)Mean ± SD	P value
Urea (mg%)	101.41 ± 36.36	20.32 ± 4.78	<0.0001
Creatinine (mg%)	5.67±2.24	0.68 ± 0.12	<0.0001
GFR (ml/min/1.73m2)	12.89± 5.67	106.6 ± 21.24	<0.0001
Total cholesterol (mg%)	215.46 ± 29.45	202.64 ± 46.52	0.41
Triglycerides (mg%)	196.84 ± 67.34	121.34 ± 70.73	<0.001
LDLc (mg%)	116.46 ± 31.76	91.76 ± 33.49	<0.05
HDLc (mg%)	39.34 ± 10.89	56.76 ± 12.56	<0.001
Tg/HDLc	5.165 ± 2.44	2.835± 1.15	<0.05
LDLc/HDLc	3.71± 0.98	2.61 ± 1.09	<0.05
Lp(a) (mg%)	29.87 ± 24.98	21.89 ± 17.76	<0.05

Table 2: Biochemical Parameters of the study subjects

Table 3 shows the baseline kidney function tests parameters and lipid profile tests in different CKD groups divided according to their GFRs in ml/min/1.73m2; group I (GFR≥30), group II (GFR =15-30), group III(GFR<15). In this study, serum Lp (a) levels were raised in group II (23.92±22.64) as compared to group I (22.67±19.42) but was found to be statistically non-significant (p=0.15). However, Lp (a) levels were significantly raised when group III was compared with group I (32.87±27.47 vs 22.67±19.42; p<0.001) and with group II (32.87±27.47 vs 23.92±22.64; p<0.001). No significant difference was observed in total cholesterol level of group II CKD cases as compared to group I (170.84± 56.88 vs 164.87± 49.98; p = 0.68) but the difference was statistically significant when group III was compared with group I (221.21± 65.76 vs 164.87± 49.98; p < 0.05) and group II (221.21± 65.76 vs 170.84± 56.88; p < 0.001). The level of serum triglyceride was significantly higher in group II when compared with group I (156.67± 42.55 vs 132.87± 58.87; p < 0.05) and in group III in comparison with group I (224.89 ± 62.73 vs 132.87 ± 58.87; p < 0.001) and group II (224.89 ± 62.73 vs 156.67 ± 42.55; p < 0.001). In this study serum LDL-C level levels in group I, II, III were 98.49 ± 32.63, 109.89 ± 46.98 and 130.54 ± 42.54 respectively and the p value was significant when group II was compared with group I (p < 0.05) and when group III was compared with group I (p < 0.001) and group II (p < 0.001)

We observed HDL-C level in group III cases was significantly reduced as compared to group I (54.56±8.94; p<0.001) and group II (36.34±10.65 vs 47.76 ± 9.87; p < 0.05). HDL-C value of group I was also significantly reduced than group II (p value <0.05).

Biochemical Parameters	Group I GFR ≥30	Group II GFR=15-29	Group III GFR<15	GI vs GII	GI Vs GIII	GII Vs GIII
Lp (a)	22.67±19.42	23.92±22.64	32.87±27.47	=0.154	<0.001	<0.001
Total Cholesterol	164.87±49.98	170.84± 56.88	221.21± 65.76	= 0.689	<0.05	<0.001
Triglycerides	132.87± 58.87	156.67± 42.55	224.89±62.73	<0.05	<0.001	<0.001
LDLc	98.49±32.63	109.89±46.98	130.54±42.54	>0.05	<0.001	<0.001
HDLc	54.56±8.94	47.76±9.87	36.34±10.65	<0.05	<0.05	<0.001
Urea	67.87 ± 9.87	81.72 ±11.54	129.42 ±34.45	<0.001	<0.001	<0.001
Creatinine	1.31 ± 0.31	2.01 ± 0.98	5.64 ± 3.02	<0.001	<0.001	<0.001
TG/HDLc	2.452±1.098	3.319±1.248	5.264±1.924	<0.05	<0.01	<0.001

Table 3: Biochemical tests in CKD patients divided according to GFR

Table 4 shows the correlation of Lp (a) with lipid profile parameters including total cholesterol, triglycerides, LDL-C, HDL-C and with serum creatinine. There was no significant correlation (p=0.545) between LP(a) and total cholesterol. However, a positive and significant association of Lp (a) with triglycerides, LDL-c with p value of < 0.001 and < 0.0001 was observed. We found a significant but negative correlation of Lp (a) and HDL-C parameter. The p value (<0.05) between serum creatinine and LP(a) was also significant.

Biochemical Parameters	Lp (a)
Total cholesterol	r=0.456 p=.545
Triglycerides	r =0.069 p<0.001
LDLc	r =0.0506 P< 0.0001
HDLc	r= - 0.045 P< 0.05
Creatinine	r=0.068 p<0.05

Table 4: Correlation between Lp (a) and total cholesterol, HDLc, TG, LDLc and creatinine in CKD patients

Discussion

We observed that majority (61.18%) of cases were males in the mean age group of 53.72 ± 8.79 years. A meta-analysis also revealed that due to several protective factor's women had lower prevalence of CKD[19]. In present study we observed the high levels of LDLc, triglyceride and Lp(a) in chronic kidney disease patients .However we found no difference in total cholesterol level in grade I patients as compared to healthy controls ,but the level of TC was found be raised in grade II and grade III CKD subjects. The data of this study also revealed the raised level of Lp(a) in CKD patients of grade II and III. The level of LP(a) showed positively correlation with TC, TG, LDLc and creatinine level but a significant negative correlation with HDLc

The lipid profile data of present study revealed no significant alterations in total cholesterol in early stage (GFR ≥ 30ml/min) in CKD cases. However higher levels were observed in group III (< 15ml/ min). The earlier experimental studies by Pandak and associates done on rats, examined 3 week after 5⁄6 nephrectomy demonstrated post transcriptional upregulation of HMG CoA reductase, a regulatory enzyme of cholesterol synthesis. They concluded that heavy proteinuria in animals and humans with chronic renal insufficiency modify HMG-CoA reductase expression which may be responsible for pathogenesis of hypercholesterolemia observed in ESRD patients[20]. In our earlier study we observed hypothyroidism in 48% CKD subjects which may contribute to hyperholestrolemia seen in these patients[21].We observed hypertriglyceridemia in CKD patients increasing progressively with declining renal functions. This finding supports many earlier studies[6,9,14-16]. The study of a research team associates found no such increase in triglyceride[22,23]. Other workers in the experimental CRF rats reported the increased expression of enzymes involved in fatty acid synthesis[24]. A study by Vaziri et al suggested that the upregulation of hepatic diacylglycerol acyl transferase (DGAT) can contribute to enhanced triglyceride synthesis in experimental nephrectomised rats and humans as well[25]. In their another study they observed the decreased apoC II (lipoprotein lipase activator)/apoC III (lipoprotein lipase inhibitor) ratio CKD may also be responsible for elevated triglyceride levels as observed in this study[26] Clement et al in a study identified upregulation of angiopoietin like protein 4 (ANGPTL4), an inhibitor of lipoprotein lipase as an important cause of hypertriglyceridemia observed in kidney disease patients [27]. In general population, low density lipoprotein cholesterol (LDL-C) is independently associated with the risk of atherosclerotic events. In this study we observed raised LDL-c in CKD patients. This finding is in accordance with many studies in which qualitative changes with elevated LDLc level was demonstrated. The proportion of small density LDLc (sdLDL), a subtype of LDL that is considered to be highly atherogenic was found to be raised[28-30]. Experimental studies by Vaziri et al demonstrated the downregulation of hepatic LDL receptor expression in liver explained the elevated LDLc levels in patients of CKD[31]. As demonstrated by Kosenko et al a proprotein convertase subtilisin kexin type 9 degrades LDLR[32]. The plasma of CKD patients demonstrated the increased expression of PCSK9 mediated LDLR degradation that may be responsible for increased LDLc in these patients[32]. Recently in experimental studies by Thakore et al found CRISPR/cas9 mediated genome editing can effectively reduce hepatic PCSK9 expression with marked increase in LDLR along with reduction of LDLc[33]. Lipoprotein (a) is an atherogenic and prothrombotic factor that promotes LDL oxidation and facilitates monocyte adhesion thereby is a powerful risk factor for cardiovascular diseases[32-37].

In present study we observed increase in level of Lp (a) with declining glomerular functions. This result is in this study accordance with Kuboyama et al which demonstrated the acquired increase in Lp (a) levels in CKD patients as a consequence of its high rate of synthesis in liver independent of its isoform [34]. Moreover Gasevoort The reduction in plasma LP (a) upon antiproteinuric therapy in CKD patients[35]. *In vivo* turnover studies using stable-isotope techniques elucidated the significantly reduced fractional catabolic rate of apolipoprotein(a), as mechanism for the increased plasma Lp (a) levels which resulted in a much longer residence time in plasma of almost 9 days, compared with only 4.4 days in control subjects[36]. Thus, in CKD patients with elevated levels of Lp (a), increased CVD risk may be there[37]. High density lipoprotein cholestrol (HDLc) are known to be inversely related with cardiovascular disease risk in patients with CKD. Reverse cholesterol transport is a critical mechanism by which HDL particles exert a protective effect on the development of atherosclerosis, HDL also has antioxidative, anti-thrombotic and anti-inflammatory properties which significantly contribute to overall cardiovascular protection[38-41]. We observed the significant reduction in HDLc values with declining glomerular filtration rate in CKD subjects. This finding can be explained in this study can be explained by Okubo et al study that observed the increased fractional catabolic rate of apoA1, principal apolipoprotein of HDL responsible for reverse cholesterol transport function with impaired renal function in CKD[38].Ooi et al reported the inverse correlation of apo A1 fractional catabolic rate with HDLc particle size responsible for increased small dense HDLc yield and low HDLc levels[39]. Calabnesi et al demonstated the elevated plasma level of Lecithin cholesterol acyl transferase (LCAT) and cholesterol ester transfer protein (CETP) in patients of glomerulopathy conciding with cholesterol ester depletion in HDL indicating their role in this lipoprotein abnormality[40]. Recently Milijkovic et al found that altered HDL subclasses distribution, changed paraxonase1 activities on different HDL subclasses as well as diminished anti-oxidative protection could be important factors in atherosclerosis development in CKD and ESRD patients[41]. In this study we also found the high ratio of TG/HDL with declining renal functions in CKD patients. This finding is in accordance with studies in Korean adults and Japanese population, where it was also shown to be the unique lipid-related ratio independently associated with CKD stage 3 or more[42,43]. High triglyceride (TG) levels and/or low high-density lipoprotein cholesterol (HDL-C) levels were illustrated to predict an increased risk of renal dysfunction in many studies. Recently, the ratio of TG/HDL, a more reasonable indicator of insulin resistance and cardiovascular events in renal dysfunction patients[44].

Strength and Limitation

This study was done on 185 subjects in kumaon region of uttrakand demonstrates that patients of chronic kidney disease presents with dyslipidemia.No such data is available of this population of this area.

However the limitation of this study is that we have not divided the patients on the basis of etiology of CKD.

Conclusion

In conclusion, this study demonstrates that chronic kidney disease is characterized by derangement in lipid profile parameters, increasing progressively with the severity of declining glomerular functions. These dyslipidemias have substantial risk of mortality and cardiovascular risk in these patients. So correct preventive measure including lifestyle modification and treatment strategies if explored for management of lipid disorders can increase the quality

as well as the life expectancy of the patients with chronic kidney disease.

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