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A STUDY ON LIPOPROTEINS IN CHRONIC KIDNEY DISEASE

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ABSTRACT

Chronic kidney disease (CKD) is defined as either kidney damage or decreased kidney function for three or more months. Decreased kidney function is defined by GFR below 60mL/min/1.73m^2. Lipoprotein abnormalities are considered to accelerate glomerular injury in various forms of renal diseases. Recent studies have also shown a strong genetic basis for the increase in serum Lipoprotein (a) levels in chronic kidney disease. Therefore in our study we have analysed the levels of Lp(a) and lipid profile parameters in patients with Chronic Kidney Disease. 50 patients with chronic kidney disease (GFR <60 mL /min/1.73m^2 for >3 months) in the age group of 30-65 years were selected and the study included both male and female patients. 50 healthy individuals were selected for the study and they formed the control group. Measurement of serum urea, creatinine, total cholesterol, triglycerides, HDL-C and LDL-C by using standard enzymatic kits and lipoprotein (a) by immunoturbidimetric method were carried out using Beckmann Coulter auto analyzer. Patients with chronic kidney disease showed a significant increase in Lp(a) levels when compared to the control group. Lp(a) levels in CKD patients were found to correlate negatively with eGFR. It can be speculated that the atherogenic effect of Lp(a) leads to renal ischemia because of increased atherosclerotic renal artery stenosis. The variation in the Lp(a) levels in different ethnic groups, should also be considered during analysis of risk factors for nephropathy.

KEY WORDS: **Chronic kidney disease, Lipoproteins, Lipoprotein (a)**

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INTRODUCTION

Chronic kidney disease (CKD) is a progressive condition marked by deteriorating kidney function over a period of time. Kidney function is quantified by glomerular filtration rate (GFR) with GFR most frequently estimated using equations that incorporate serum creatinine along with demographic data[1]. The early stages of CKD (stages 1 and 2) are manifested by kidney damage and are generally asymptomatic. As kidney disease worsens, kidney function begins to deteriorate, stage 3 & 4 of CKD ensues and kidney replacement therapy is required[2]. CKD is defined as either kidney damage or decreased kidney function for three or more months. Decreased kidney function is defined by GFR below 60mL/min/1.73m^2. CKD is generally associated with old age, diabetes, hypertension, obesity and cardiovascular disease, with diabetic glomerulosclerosis and hypertensive nephrosclerosis as the presumed pathological entities[3]. Alterations in lipid metabolism resulting in abnormal lipoprotein composition have been noticed in chronic renal insufficiency[4]. Lipoprotein abnormalities are considered to accelerate glomerular injury in various forms of renal diseases. Several mechanisms are proposed to be responsible for lipoprotein-induced glomerular pathophysiology, including mesangial proliferation, production of extracellular matrix proteins and expression of leukocyte chemo attractants. Recent studies have also shown a strong genetic basis for the increase in serum Lipoprotein (a) levels in chronic kidney disease. Lipoprotein (a) is considered to accelerate glomerular injury in various forms of renal diseases[5]. Lp(a) is an LDL like lipoprotein consisting of apo(a) which shows a strong homology with plasminogen, competing with it for binding to fibrin[6]. Lipoprotein (a), an independent risk factor for atherosclerotic disease, is also considered to accelerate progression of renal disease. Serum levels of Lp(a) are found to be elevated in patients with nephrotic syndrome and glomerular Lp(a) deposits correlate with a more severe course of renal disease, independent of the underlying form of glomerular pathology. Several lines of evidence suggest that biological effects of Lp(a) are at least partially mediated by Reactive Oxygen Metabolites (ROM). Several studies have shown Lp(a) levels to be increased in non diabetic subjects with treated and untreated chronic renal failure[7,8]. A number of studies have shown increased Lp(a) concentration in diabetic patients with proteinuria[9,10]. Hyperlipedemia could cause renal injury and lipid abnormalities might contribute to the progression of renal disease. Lipid reduction may preserve glomerular filtration rate and may decrease proteinuria in patients with renal disease. The majority of studies show that Lp(a) levels vary in different ethnic populations. Therefore in our study we have analysed the levels of Lp(a) and lipid profile parameters in patients with Chronic Kidney Disease, as Lp(a) may cause renal damage through atherosclerotic renal artery stenosis and glomerular injury. This may help us to identify the high risk group and to plan effective treatment strategies.

MATERIALS AND METHODS

The study protocol was performed in accordance with the approval of the Institutional ethics committee (ECN: 606/ICE/2014) and informed written consent was taken from all subjects.

Patient selection

Inclusion criteria

50 patients with chronic kidney disease (GFR <60 mL /min/1.73m^2 for >3 months) in the age group of 30-65 years were selected and the study included both male and female patients.

Exclusion criteria

Patients on dialysis, those with hematuria and pyuria. 50 healthy individuals without diabetes, hypertension, renal disease and any other systemic illness were selected for the study and they formed the control group. Venous blood was collected from all the participants after an overnight 12 hours fast. 2 ml of the blood sample was collected in an oxalate fluoride vacutainer for estimation of fasting plasma glucose. 3ml of blood collected in a plain vacutainer, was allowed to clot and serum was separated by centrifugation at 3000 RPM for 10 minutes. Serum urea, creatinine, total cholesterol, triglycerides, High Density Lipoprotein- Cholesterol (HDL-C) and Low Density Lipoprotein- Cholesterol (LDL-C) were measured by using standard enzymatic kits in Beckmann Coulter auto analyzer on the same day of sample collection. The remaining serum was stored at -20^{0}C and lipoprotein (a) was analyzed by immunoturbidimetric method using the Beckmann Coulter auto analyzer.

RESULTS

The study included 50 patients with chronic kidney disease and 50 healthy controls. Comparison was made between the two groups using a student ‘t’ test. The mean levels of fasting plasma glucose (FPG), urea, creatinine and eGFR were found to be significantly altered in the CKD group compared to controls. Among the lipid profile parameters, the mean levels of TGL and VLDL cholesterol were found to be significantly altered between the two study groups. Patients with chronic kidney disease showed a significant increase in Lp(a) levels (68.07±40.174 Vs 32.576±28.737; p= 0.0001) when compared to the control group. Lp(a) levels in CKD patients was found to correlate negatively with eGFR (r= -0.111, p=0.0123).

Table 1
Comparison of mean ± SD of the measured biochemical parameters between the control and CKD groups and the statistical significance of the differences

Parameters	Control (n=50)	CKD patients (n=50)	'p` value
Fasting Plasma Glucose (mg/dl)	91.60±7.55	154.24±86.99	0.0001
Urea(mg/dl)	19.66±4.32	96.02±60.50	0.0001
Creatinine(mg/dl)	0.792±0.118	4.371±2.560	0.0001
eGFR(mL/min/1.73m^2)	107.58±28.24	22.58±15.05	0.0001
Lp(a) (mg/dl)	32.576±28.737	65.154±40.714	0.0001
Total cholesterol(mg/dl)	156.42±28.50	160.86±47.89	0.5757
Triglycerides(mg/dl)	99.08±30.12	129.71±60.28	0.0018
HDL-C(mg/dl)	43.78±19.56	43.92±18.94	0.3209
LDL-C(mg/dl)	115.04±27.54	96.16±42.00	0.0009
VLDL-C(mg/dl)	19.798±6.027	25.962±11.623	0.0012

Values are expressed in mean ±standard deviation.
The values are statistically significant if the 'p' value is less 0.05.

Table 2
Shows the Pearson's correlation analysis between Lp (a) levels and eGFR in patients with CKD

Parameters	Mean ± SD	r-value(p-value)
Lp(a) (mg/dl)	68.154±40.714	r= -0.111(0.0123)
eGFR(mL/min/1.73m^2)	22.58±15.05	

The values are statistically significant if the 'p' value is less 0.05

DISCUSSION

Hyperglycemia, hypertension, hypercholesterolemia and proteinuria are the most significant risk factors or markers for the development and progression of diabetic nephropathy in type 2 diabetic patients[11]. In both type 1 and type 2 diabetes, an unfavorable lipid profile is present at a very early stage of albuminuria, when GFR is normal or elevated. Several studies have shown Lp(a) levels to be increased in non diabetic subjects with treated and untreated chronic renal failure. In our study, the mean levels of TGL and VLDL-C are found to be significantly elevated. Muntner et al. reported that people with hypertriglyceridemia and low HDL cholesterol at baseline have a higher risk for having a loss of renal function[12]. High triglycerides levels as an independent predictor of renal disease was confirmed in a prospective study of 297 patients with type 1 diabetes[13]. There is evidence that circulating lipids bind to and become trapped by extracellular matrix molecules, where they undergo oxidation thereby increasing the formation of reactive oxygen species such as superoxide anion and hydrogen peroxide[14]. The resultant reduction in the actions of endothelium-derived vasodilators/growth inhibitors, such as prostacyclin and nitric oxide, with maintenance or increased formation of endothelium-derived vasoconstrictors/ growthpromoters, such as angiotensin II, endothelin-1, and plasminogen activator inhibitor-1, has significant vascular and renal pathophysiology consequences[15]. Macrophages phagocytose oxidized lipids and undergo a transition to foam cells which release cytokines that recruit more macrophages to the lesion and influence lipid deposition, endothelial cell function and vascular smooth muscle cell proliferation[16]. Glomerular cells mimic some of the characteristics of cells in the atherosclerotic vessel wall. Therefore, similar pathogenetic mechanisms may contribute to the progression of atherosclerosis and chronic kidney disease. Renal dysfunction in particular has been associated with elevated Lp(a) levels. Patients with chronic kidney disease in our study have shown a significant increase in Lp(a) levels when compared to the control group. The 2-year prospective Study by Ki Ho Song et al has stated that an elevated Lp(a) level is an independent risk factor for the progression of diabetic nephropathy in type 2 diabetic patients with overt proteinuria. This association was independent of proteinuria, hyperglycemia, or hypertension. Several studies have shown Lp (a) levels to be increased in non diabetic subjects with treated and untreated chronic renal failure. A number of studies have shown increased Lp(a) concentration in type 1 diabetic patients with proteinuria. On the contrary, other studies found no such association. In three studies of subjects with type 2 diabetes, one study found that microalbuminuria was associated with increased Lp(a) concentrations while the remaining two studies reported the opposite finding. Another study reported significant reduction of Lp(a) concentrations in a patient with nephrotic syndrome after remission. The majority of the studies did not control for ethnicity. Boemi et al also reported that macroalbuminuria in both type 1 and type 2 diabetic patients is associated with significantly increased plasma concentrations of Lp(a) regardless of kidney dysfunction, as determined by creatinine clearance rates or serum creatinine[16]. In patients with end stage renal disease, Lp(a) was found to be significantly elevated. Most of the studies however share a similar finding that both diabetic and non diabetic patients with proteinuria have higher levels of Lp(a) compared to those without proteinuria. This may

suggest that metabolic conditions in patients with renal disease and proteinuria may cause plasma Lp(a) to rise. The observation of arteriovenous differences of Lp(a) between the aorta and renal vein, with lower concentration in the renal vein, suggest that the kidney is involved in the catabolism of Lp(a)[17]. It can be speculated that the atherogenic effect of Lp (a) leads to renal ischemia because of increased atherosclerotic renal artery stenosis. In addition to vascular injury, Lp(a) might be implicated in glomerular injury. Lp(a) and oxidized Lp(a) have been shown to induce activation of reactive oxygen metabolites in isolated rat glomeruli . We have found the Lp(a) levels in CKD patients to correlate negatively with eGFR (r= -0.05, p<0.0001). Ki Ho Song et al has demonstrated that CKD patients, who had elevated Lp(a) levels at baseline, showed more rapid deterioration of renal function as determined by serum creatinine and calculated GFR over the 2-year follow-up. The limitation of the study includes the fact that 35 numbers of patients with CKD were on lipid lowering drugs. The presence of lower LDL-C in patients with CKD compared with control group may indicate the presence of small dense LDL particles. Estimation of apolipoprotein-B levels may provide additional information regarding the presence of the atherogenic small dense LDL particles[18]. The effect of lipid reduction by lipid lowering agents on the progression of diabetic nephropathy is still unknown. There have been no large trials analyzing whether the treatment of dyslipidemia could prevent the development of nephropathy or the decline of renal function. However there is some evidence that lipid reduction by antilipemic agents might preserve GFR and decrease proteinuria in diabetic patients. The levels of Lp(a) are not very much affected by statins. At the same time lifestyle change have very little effect on Lp(a) concentrations. Aspirin, estrogen, CETP and nicotinic acid have been shown to decrease Lp(a) levels[19]. The variation in the Lp(a) levels in different ethnic groups, should also be considered during analysis of risk factors for nephropathy[20].

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