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Original Research Article

Correlation of Lipoprotein(a) in normal individuals and in Chronic kidney disease patients with Diabetes Mellitus

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Keywords

Lipoprotein(a), Chronic kidney disease, Diabetes mellitus, low density Lipoprotein, apolipoprotein (a)

A B S T R A C T

To estimate and correlate Lipoprotein (a) levels in normal individuals and in Chronic kidney disease patients with diabetes mellitus and without diabetes mellitus. Introduction - Lipoprotein(a), is a low density lipoprotein (LDL) like particle in which highly polymorphic glycosylated apolipoprotein(a) is covalently linked to apolipoprotein B-100 by a single disulfide bridge .In recent years , several reports have indicated that Lipoprotein(a) is markedly high in patients with end stage renal disease. Methods and Materials-The study was conducted over a period of six months. The study includes 60 subjects in the age group of 40 to 60 years. They were divided into 3 groups.Each group had 10 males and 10 females. All the parameters were analysed in kone lab 60 automated systems using commercially available kits. Results- Data evaluation was done using SPSS programme. The results were expressed as Mean with standard deviation. The P value was used to compare the different groups. The P value < 0.05 was considered significant. Conclusion - In this study, Serum Lipoprotein(a) levels was significantly higher in Chronic kidney disease patients with Diabetes mellitus than Chronic kidney disease patients without Diabetes mellitus.

Introduction

Lipoprotein(a), is a low density lipoprotein (LDL) like particle in which highly polymorphic glycosylated apolipoprotein (a) is covalently linked to apolipoprotein B-100 by a single disulfide bridge(Berg K et al 1994). High plasma levels of Lp(a) are associated with increase risk for atherosclerotic cardiovascular disease (Desmarais RL , Sarebock JJ , et al ,1995) .The link between atherosclerosis and lipoprotein(a) is due to its structural similarity to plasminogen which impairs

the binding of plasminogen to fibrin, leading to inhibition of fibrinolysis. The presence of lipoprotein(a) in atherosclerotic plaques is further evidence of its potential role in atherogenesis (Lawn RM , Wade DP, ,et al,1992) .

In recent years, several reports have indicated that Lipoprotein(a) is markedly high in patients with end stage renal disease. Lipoprotein(a) concentration is an independent factor contributing to the risk of atherosclerotic disease in both hemodialysis and continuous ambulatory peritoneal dialysis patients which is the major cause of morbidity and mortality in these groups .(Florian Kronenberg ,Paul Konig , et al, 1995). Renal failure is inherently associated with specific alterations of lipoprotein metabolism (Florian Kronenberg, Paul Konig, et al, 1995). The diabetic state is by itself characterized by abnormal lipoprotein metabolism (Fruchart JD, Shepherd J, et al, 1989). These two factors may contribute to the dyslipoproteinaemia in diabetic renal failure, with the development of atherosclerosis and progressive renal failure as possible clinical consequences (Alaupovic P, 1991).

Patients with diabetic nephropathy constitute a major proportion of patients with chronic kidney disease treated with dialysis and transplantation (Brunner FP, Brynger H, et al, 1988 & United States Renal Data System USRDS. 1996). During the course of the disease, these patients frequently develop severe atherosclerotic complications and vascular disease resulting in a significantly higher morbidity and mortality rate than in their nondiabetic counterparts (Brunner FP, Brynger H, et al, 1988& Larsson O, atman P-O et al, 1987). In diabetes, conflicting reports are available regarding prognostic significance of lipoprotein (a) levels. A few studies suggest that there may be elevation of Lipoprotein (a) in insulin dependent diabetes mellitus; particularly patients with microalbuminuria and proliferative retinopathy (Haffer, S.M, 1993). Similarly, Lipoprotein(a) has been correlated to coronary artery disease in diabetics in some studies , while other trials do not show any such correlation Mohan .V , Rema . M , et al,1998). The main aim of this study to estimate and correlate Lipoprotein (a) levels in normal individuals and in Chronic kidney disease patients with diabetes mellitus and without diabetes mellitus.

Materials and Methods

The study was conducted over a period of six months. The study was conducted among subjects attending Nephrology Department, SRMC & RI as inpatients. The study includes 60 subjects in the age group of 40 to 60 years. They were divided into 3 groups. Group 1 composed of normal healthy controls. Group 2 consisted of subjects with Chronic kidney disease with type 2 Diabetes mellitus. Group 3 consisted of subjects with Chronic kidney disease without Diabetes mellitus. Each group had 10 males and 10 females. All patients underwent a full medical history that included age, family history of diabetes, hypertension, coronary artery disease , Chronic kidney disease, duration of Chronic kidney disease, type of dialysis (Peritoneal or Hemodialysis), duration of Diabetes, treatment history for diabetes, smoking and alcohol, Drug history and treatment history for any other disease was collected through a standard questionnaire.

Blood samples were collected after 12

hours of fasting in the vacutainers for estimation of glucose, lipoprotein (a), lipid profile, Bun and creatinine. Blood samples were collected in the morning after 12 hours of overnight fasting. The samples were separated by centrifugation at 2400 rpm. Plain vacutainer is used for serum and for plasma, sodium fluoride vacutainers were used. Lipoprotein (a) was analysed in kone lab 60 automated systems using commercially available kit by LATEX DAIICHI. Lipid profile was analysed in kone lab 60 using commercially available kit by RANDOX. Glucose was analysed in konelab 60 automated systems using commercially available kit by ACCUREX. Bun and creatinine were analyzed in Kone lab 60 automated systems using commercially available kit by TRACE.

Results and Discussion

A total number of 60 samples were selected to study the level of Lipoprotein(a) in normal individuals and in Chronic kidney disease patients with and without diabetes mellitus. The subjects were divided into 3 groups. Each group had 20 individuals aged between 40 to 60 years, out of which 10 were males and 10 females. Group 1 composed of 20 healthy controls (without chronic kidney disease and Diabetes mellitus), Group 2 consisted of 20 subjects with Chronic kidney disease with diabetes mellitus, Group 3 consisted of 20 subjects with Chronic kidney disease without diabetes mellitus. Data evaluation was done using SPSS programme. The results were expressed as Mean with standard deviation. The P value was used to compare the different groups. The P value < 0.05 was considered significant. The mean and standard deviation of biochemical parameters of the three groups was calculated.

In this study as per table 1 , the mean value of Lp(a) 76.8 ± 6.3 is increased in Chronic kidney disease patients with Diabetes mellitus , compared to Chronic kidney disease patients without Diabetes mellitus 69.4 ± 4.7 and general control group 19.6 ± 6.4. Previous studies have shown that Lipoprotein(a) concentration are increased in subjects with renal failure, regardless of ethnic group or diabetic status (Steven M. Haffner, Katherine K. Gruber, et al, 1992).

Framingham heart study correlates with this study, which states that sex has no significant influence on Lp(a) concentration (Leo J Seman, Carl Deluca , et at 1999). According to Kronenberg et al, the mechanism of elevation of Lp(a) in patients with renal failure is undetermined. It is possible that kidney has a metabolic role in the breakdown of Lp(a), a theory which is supported by arteriovenous difference by some and by findings of apo(a) fragments in the urine, the excretion of which is reduced in renal failure**(** Kronenberg F, Trenkwalder E, Lingenhel A et al, 1997).

Several studies have reported higher concentration of Lp(a) in diabetic patients, which has lead to the speculation that Lp(a) may contribute to the greatly increased incidence of vascular disease associated with diabetes (Per-Ola Atteman, Carolyn Knight-Gibson, et al 1998). The diabetic subjects included in this study had type 2 Diabetes mellitus who were on regular treatment . In a study by Boemi et al,1999 , macroalbuminuria in both type 1 and type 2 diabetic patients is

Table.1 Comparison of Lipoprotein(a) between General controls ,chronic kidney disease with Diabetes mellitus and chronic kidney disease without Diabetes mellitus

Parameters	Control (n-20)	CKD with DM (n-20)	CKD without DM (n-20)
Lipoprotein (a) (mg/dL)	19.6 ± 6.4	76.8 ± 6.3	69.4 ± 4.7

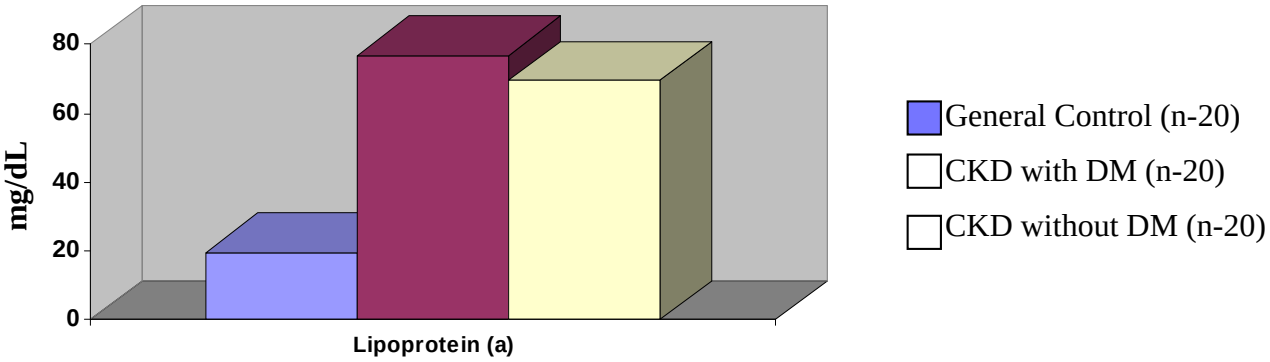
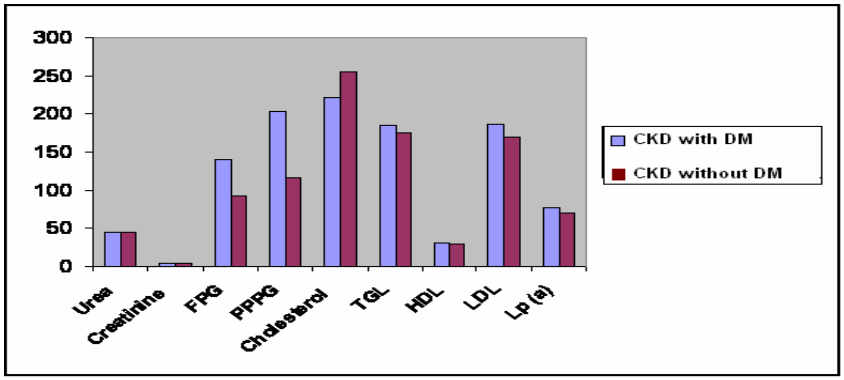


Table.2 Comparison of biochemical parameters between Chronic kidney disease with Diabetes mellitus and Chronic kidney disease without Diabetes mellitus

Parameters	CKD with DM (n-20)	CKD without DM (n-20)	P Value
Bun	44.4 ± 14.2	44.5 ± 12.5	0.972
Creatinine	4.2 ± 1.3	4 ± 0.9	0.616
FPG	140.5 ± 51.6	92.9 ± 6.6	0.001
PPPG	203.1 ± 55.8	116.4 ± 10.05	0.001
Cholesterol	255.8 ± 7.4	234.3 ± 6.8	0.001
Triglycerides	184.9 ± 6.8	175.6 ± 4.7	0.001
HDL	31.4 ± 4.8	29.2 ± 3.7	0.118
LDL	186.9 ± 7.4	169.9 ± 5.3	0.001
Lipoprotein (a)	76.8 ± 6.3	69.4 ± 4.7	0.001

Biochemical Parameters of CKD with DM and CKD without DM



associated with significantly increased plasma concentration of Lp(a) regardless of kidney dysfunction, as determined by creatinine clearance rates or serum creatinine.

In a study by Jenkins et al 1992, Renal disease is a frequent complication of Diabetes that has prompted speculation that kidney dysfunction is the principal cause of raised Lp(a) in type 1 and type 2 diabetic patients . In this study as per table 2, there is no significant difference in bun and creatinine values between Chronic kidney disease patients with Diabetes mellitus Vs Chronic kidney disease patients without Diabetes mellitus. Comparing the lipid profile, the mean value of Total cholesterol 255.8 ± 7.4, triglycerides 184.9 ± 6.8, HDL 31.4 ± 4.8, LDL 186.9 ± 7.4, Lipoprotein (a) 76.8 ± 6.3 were increased and highly significant in Chronic kidney disease patients with Diabetes mellitus compared to Chronic kidney disease patients without Diabetes mellitus.

It is well known that chronic kidney disease patients have a characteristic dyslipidemia, which may be influenced by other factors like nutritional status, Diabetes and presence of proteinuria. The most important abnormalities are increased serum level of triglyceride (elevated VLDL – remnants / IDL). The concentration of HDL is decreased with reduced concentration of free and esterified cholesterol and increased TGL content. The concentration of HDL 2 subfraction is low while HDL 3 is normal.The concentration of LDL is not generally increased; the small dense LDL particles which are susceptible to oxidation bind weakly to LDL receptors and are cleared from plasma. These small LDL particles are more artherogenic. The apolipoprotein composition is also altered. The early change is increased apo C III in VLDL and LDL and a decrease in apo AI content of HDL. These apoliporotein abnormalities coupled with changes in the concentration of the particles lead to a decrease in apo A: apo C III ratio, which is a hallmark of uraemia dyslipidaemia. This change is noted when the GFR is moderately reduced and the triglyceride is still normal. The ratio of apo AI : apo B is also reduced. Lipoprotein (a) is consistently elevated in considerable of patients with ESRD (Bonnie C.H.Kwan, Florian Kronenberg, et al 2007).

In a study by Kronenberg et al, the pathogenic mechanism for the elevation of Lp(a) in End stage renal disease is only speculative. Besides a decreased catabolism, an increased synthesis or both are conceivable failure (Kronenberg F, Trenkwalder E, Lingenhel A et al, 1997). This study indicates that Lioprotein(a) concentration is increased in Chronic kidney disease group, especially in Chronic kidney disease patients with Diabetes mellitus.

The present study concludes that the Serum level of Lipoprotein (a) which is considered as a risk factor for atherosclerotic disease was significantly high in chronic kidney disease patients with Diabetes mellitus than Chronic kidney disease patients without Diabetes mellitus. Lipid profile parameters in Chronic kidney disease patients with Diabetes mellitus were also significantly high. The increase in Total cholesterol was 50 % and increase in Triglycerides was 25 %, compared to general control group.

As small group was included in this study, the study can be extended to a larger group to see the correlation of Lipoprotein(a)

and the rate of progression of renal disease and the use of predictive value of Lipoprotein(a) and apo (a) phenotypes in hyperlipidaemic patients to detect early renal dysfunction in diabetic individuals.

Patients with Chronic kidney disease have reduced plasma HDL cholesterol compared with nonuremic individuals. Because of the low apo-AI level and decreased Lecithin cholesterol acyl transferase activity esterification offree cholesterol and hence the conversion of HDL_3 to HDL_2 arediminished in uremia. This decreased ability of the HDL particlesto carry cholesterol leads to an impairment in the reverse cholesteroltransport from peripheral cells to the liver, thereby burdeningthe vasculature with cholesterol and promoting atherosclerosis. In uremia, there is decreased catabolism of IDL and LDL leading to their increased plasma residence time and further modification of the apo B contained in these lipoproteins by oxidation, carbamylation, and glycation.

These modifications lead to the reduced recognition and binding of these lipoproteins to LDL receptors and LRP in the liverand hence further reduction in plasma clearance by this physiologic pathway. In contrast to the decreased clearance by the liver, there is an increased clearance of these altered lipoproteinsvia the scavenger pathway. Modified LDL particles, such as ox-LDLand malondialdehyde-modified LDL, are taken up by macrophages via binding to several cell surface scavenger receptors. The accumulation of cholesterol leads to the transformation of macrophages in to foam cells in the vascular wall and contributes to atherogenesis (Bonnie C.H.Kwan, Florian Kronenberg, et al 2007).

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