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Dyslipidemia and its Correlation with Creatinine Clearence in Chronic Kidney Disease

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Abstract: ***Background: Dyslipidemia is recognized risk factors for progression of renal diseases. This altered lipid metabolism contribute to pathogenesis of cardiovascular disease as well as to the progression of renal disease. Aims: To measure the lipid profile in patients with Chronic kidney disease and to correlate HDL & TGL levels with creatinine clearance. Materials and Methods: The biochemical parameters Blood urea , Creatinine, Total Cholesterol, Triglycerides, HDL and LDL were measured in 50 cases & 50 controls. Results and Conclusion: There is significantly higher serum TGL and VLDL levels and lower HDL levels in the cases than controls (p<0.05). There is higher TGL/HDL and LDL/HDL ratio in cases than controls (p<0.05).There is a serial increase in serum TGL and VLDL levels and a serial decrease in HDL levels with declining renal function (p<0.05).***

Keywords: Lipid profile, Dyslipidemia, Chronic kidney disease

1. Background

Dyslipidemia is common but not universal in people with Chronic Kidney Disease. The major determinants of dyslipidemia in CKD patients are glomerular filtration rate (GFR), the presence of diabetes mellitus, severity of proteinuria, use of immunosuppressive agents, modality of renal replacement therapy such as treatment by HD, peritoneal dialysis, or transplantation, comorbidity and nutritional status.Initial evaluation of the lipid profile mainly serves to establish the diagnosis of severe hypercholesterolemia and/or hypertriglyceridemia and potentially rule out a remediable secondary cause if present

2. Aims and Objectives

1) To investigate the serum lipids in patients with Chronic Kidney Disease
2) To assess the levels of lipid parameters in relation to creatinine clerance in Chronic Kidney Disease

3. Introduction

The burden of chronic kidney disease is increasing rapidly worldwide. Studies have shown that more than 50% of deaths in CKD patients are attributable to cardiovascular events.{Couser, 2011 #1} Lipid disorders (Dyslipidemia) are recognized risk factors for CVD and progression of renal diseases of varied aetiologies. Dyslipidemia represents one of the major, potentially correctable risk factor{Duckworth, 2001 #2} Approximately 50% of patients with endstage renal disease (ESRD) die from cardiovascular events, which indicate that cardiovascular mortality is 30-times higher in dialysis patients {Covic, 2008 #3}
Measurement of the lipid profile at initial presentation with CKD will help the clinicians for effective management.

4. Definition of CKD

Kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney with or without decreased GFR, manifested by either pathological abnormalities or markers of kidney damage including abnormalities in composition of blood / urine or abnormalities in imaging tests, GFR < 60 mL / 1.73 square metre ≥ 3 months with or without kidney damage.

Dyslipidemia is a primary risk factor in the development of a number of disease multitudes ranging from atherosclerosis to stroke. The risk is substantially elevated in patients with end-stage renal disease (ESRD) (such patients show various abnormalities in plasma lipids and lipoproteins that are called uremic dyslipidemia.Disturbances of lipid transport and metabolism are common complications of chronic renal failure, regardless of the cause of renal disease, which may persist or deteriorate during renal replacement therapy. {Shiba, 2011 #4} Lipoprotein metabolism is altered in patients most with renal insufficiency. {Ray, 2014 #5}The altered lipid metabolism contribute to pathogenesis of atherosclerosis and cardiovascular disease as well as to the progression of renal disease. All these factors lead to increase in the morbidity and mortality in patients with CKD. Dyslipidemia develops early in renal failure and it becomes more pronounced as the renal disease progresses because of imbalance between lipoprotein synthesis and degradation due to impaired activity of lipoprotein lipase and direct inhibitory effect of various uremic toxins on the enzymes involved in lipid metabolism. The altered lipoproteins are in turn taken up by the scavenger receptors on macrophages and vascular smooth muscle cells, which are increased in uraemia, favouring the development of atherosclerotic plaques.

Dyslipidemia among CKD patients negatively impacts cardiovascular profiles, which in turn influence the frequency and/or duration of hospitalizations.{Wright, 2009 #6}

The most common dyslipidemia in CKD and dialysis is hypertriglyceridemia, whereas the total cholesterol concentration can be high, normal, or low, perhaps due in part to malnutrition .{Kwan, 2007 #7} Other abnormalities are reduced serum high density lipoprotein (HDL) cholesterol and elevated concentration of LDL cholesterol levels. High level of LDL-C and low level of HDL-C are the

major factors in the development of atherosclerosis which could result in cardiovascular disease . {Castelli, 1984 #8}.

Lipid ratios are also used to predict cardiovascular risks and the ratios might be the stronger predictors of heart disease. According to the NCEP , the optimal serum lipid profile is serum total TC level < 5.18 mmol/L, TG level < 1.7 mmol/L, LDL-C level < 3.37 mmol/L, and HDL-C level ≥ 1.04 mmol/L

Dyslipidemia is defined by the presence of at least one of the following: serum total TC level ≥ 5.18 mmol/L, TG level ≥ 1.7 mmol/L, LDL-C level ≥ 3.37 mmol/L, and HDL-C-cholesterol level < 1.04 mmol/L, and/or having received treatment for dyslipidemia during the previous 2 weeks

The pathogenesis of most lipid abnormalities in patients with CKD primarily involves defective removal from the circulation. The diminished clearance of triglycerides, which can lead to hypertriglyceridemia, stems both from an alteration in the composition of circulating triglycerides (which become enriched with apolipoprotein C-III) and, perhaps later, from reductions in the activity of lipoprotein lipase and hepatic triglyceride lipase, which are involved in triglyceride removal .{Miller, 2011 #10} The reduced lipoprotein lipase activity in CKD reflects increased inhibitor activity {Arnadottir, 1995 #11}. The associated secondary hyperparathyroidism , by increasing calcium accumulation within the cells in the liver and adipose tissue plays contributory role.{Hillgartner, 1995 #12}

Another possible mechanism for hypertriglyceridemia in CKD is retention of a circulating inhibitor of lipoprotein lipase, such as pre-beta-high density lipoprotein (HDL) {Thyagarajan, 2017 #13}. Pre-beta-HDL is a form of apolipoprotein A-I found in the non-lipoprotein fraction of normal plasma. Several previous studies showed that both a high level of cholesterol and triglyceride might play an important role in the pathogenesis and progression of kidney disease . It was found that hypercholesterolemia can induce a pro-inflammatory response and result macrophages recruitment . {Scarpioni, 2012 #14}

Both hyperlipidemia and macrophage influx appear to precede in the genesis of glomerulosclerosis .In type 2 diabetes, lipoxidation stress was also related to glomerulosclerosis and tubulointerstitial disease . Food restriction can prevent hypertriglyceridemia induced glomerular injury and macrophage influx. Both hypercholesterolemia and hypertriglyceridemia are associated with podocyte injury which might be accompanied by tubulointerstitial injury . There are numerous studies that indicate dyslipidemia can contribute to kidney damage. Dyslipidemia is an independent risk factor for progression of kidney disease in patients with diabetes Hyperlipidemia might be accompanied by coronary heart disease, diabetes and hypertension.

5. Materials and Methods

This cross-sectional observational study was conducted at K.A.P.V Govt. Medical College and MGMGH, Trichy, during the period of June 2015- October 2015

Hundred subjects were chosen for the study. Informed consent were obtained from all of the participants**.** Serum was used for the estimation of Glucose, Urea, Creatinine, Total cholesterol (TC), Triglycerides (TGL) and High Density Lipoprotein Cholesterol (HDL-C) immediately after the serum was separated. All the parameters were estimated using commercially available kits on semiautoanalyser . Glucose was estimated by Glucose-oxidase/ peroxidase method. Urea - Urease –Glutamate Dehydrogenase (GLDH) Method. Creatinine - Modified Jaffe's method,Total Cholesterol - Cholesterol Oxidase- PAP method ,Triglycerides - Glycerol Phosphate Oxidase –PAP method, HDL-C - Phosphotungstate /Magnesium precipitation Method. Creatinine clearance calculated by CKD-EPI.

Statistical analysis was done using SPSS version 21 software. All the Data for the statistical analysis were expressed as Mean ± SD. The p value < 0.05 was considered statistically significant.

Study Population
50 patients with CKD were considered as study group and 50 healthy volunteers were considered as control group .

Inclusion Criteria
Patients with established diagnosis of CKD of age between 30 – 60 years.

Exclusion Criteria
Acute infection, liver disease, previous history of Coronary Artery Bypass Graft surgery ,acute kidney injury,patients on immunotherapy,previous history of cerebrovascular diseases, patients who underwent renal transplantation

Sample Collection
Informed consent was obtained from all subjects prior to the study. Under aseptic precautions, 5ml of venous blood sample was collected after an overnight fasting of 12 hours from all subjects. After retraction of the clot, samples were centrifuged at 2000rpm for 15 minutes for separation of serum. The serum was used for the estimation of Glucose, Urea, Creatinine, Total cholesterol (TC), Triglycerides (TGL) and High Density Lipoprotein Cholesterol (HDL-C) immediately after the serum was separated. All these parameters were estimated using commercially available kits on semiautoanalyser LDL-C and VLDL-C were calculated using Fridewald's formula- **VLDL-C** = TAG/5 **LDL-C** = TC-{HDL+VLDL}

6. Results & Statistical Analysis

Data evaluation was done using SPSS Software programme. The results were expressed as Mean with standard deviation. Student's "*t"* test was performed to correlate the parameters between two normally distributed groups. For independent group analysis, paired *t* tests were done. A *P* value of less than 0.05 was considered significant

Table 1: Comparison of Lipid Parameters in the Study Group

Parameters	*Cases (Mean ± SD)*	*Controls (Mean ± SD)*	*Statistical Inference*
TC (mg/dl)	175.72 ± 16.49	173.00 ± 28.20	P > 0.05
TGL(mg/dl)	171.86 ± 23.005	133.54 ± 14.57	**P < 0.05**
HDL-C (mg/dl)	33.84 ± 7.061	42.52 ± 3.55	**P < 0.05**
VLDL-C (mg/dl)	34.37 ± 4.6	25.86 ± 5.59	**P < 0.05**
LDL-C (mg/dl)	107.50 ± 16.5	106.56 ± 16.71	P > 0.05

There is a significantly higher serum TGL and VLDL-C levels and a significantly lower HDL-C levels in the cases than controls ($p<0.05$). There is no significant difference in the serum TC and LDL-C levels between the two groups.

Table 2: Comparison of Lipid Ratios in the Study Group

Parameters	Controls	Cases	Statistical Inference
TGL /HDL	3.14	5.08	P < 0.05
TC/HDL	4.07	4.19	P > 0.05
LDL/HDL	2.51	3.18	P < 0.05

There is a significantly higher TGL /HDL and LDL/HDL ratio in the cases than the controls ($p<0.05$). There is no significant difference in the TC/HDL levels between the two groups.

Table 3: Comparison of Lipid Parameters in Relation to Creatinine Clearance In CKD

Parameters	Creatinine Clearance (ml/min)				Statistical Inference
	60-90	30-50	15-29	<15	
TC (Mean ± SD)	177.14 ±14.48	171.50 ± 13.96	172 ± 10.05	182.00 ± 24.24	P > 0.05
TGL(Mean ±SD)	144.07 ± 6.00	165.67 ± 8.60	180.50± 6.66	201.83±1 0.49	P < 0.05
HDL(Mean ±SD)	42.64 ± 1.73	35.92 ± 2.15	29.83±3. 76	25.50±1.7 3	P < 0.05
VLDL(Mean ± SD)	28.81 ± 1.20	33.13 ± 1.72	36.10±1. 33	40.36±2.0 9	P < 0.05
LDL(Mean ± SD)	105.68 ±14.21	102.45 ± 14.68	106.06± 9.00	116.13±2 3.84	P > 0.05

Serum TC levels were within the normal reference range in the cases irrespective of Creatinine clearance. There is a slight increase in Serum LDL levels with respect to decline in creatinine clearance. We observed a serial significant increase in the serum TGL and VLDL-C levels and a serial significant decrease in the HDL-C levels with declining renal function ($p<0.05$)

7. Discussion

In the present study serum triglyceride concentrations were found to be significantly increased in patients with CKD (mean 171.86 ± 23.005) when compared to the control group (mean 133.54 ± 14.57).

When patients in different stages of CKD were compared, serum TGL levels were found to be progressively increased from stage 2 to stage 5 in comparison with the control group. This observation shows that increase in serum TGL develops relatively in the early stages of CKD, and is further increased with the progression of renal dysfunction and inversely correlated with Creatinine clearance ($p < 0.05$ significant). These findings are in accordance with the study of Keane WF, Kasiske BL et al 1991

In the present study we observed a significantly higher levels of serum VLDL in CKD cases when compared to controls [mean value: cases 34.37 ± 4.6 controls 25.86 ± 5.59 , P value < 0.05]. As the renal function declined, we observed a progressive decrease in the serum HDL levels. These results of the present study are in accordance with that of the previous studies suggesting a global pro-atherogenic inflammatory activation occurs even in early stages of CKD.

Since lipid levels show considerable changes during the various stages of CKD, it might be interesting to see whether a data analysis considering all measured values during the entire observation period is more predictive than the classical analysis with one measurement at baseline of a certain CKD stage.

Female patients had higher cholesterol, triglycerides, and LDL levels than male patients. Factors such as hormones and individual's capability to degrade excess lipids may play a role. Dyslipidemia, an atherogenic risk factor contributes to the initiation and progression of CKD partly by stimulating and amplifying the effect of inflammatory mechanisms. In the present study we observed a significantly higher serum TGL and VLDL-C and decreased HDL in cases than controls ($p < 0.05$). There is no significant difference of TC and LDL between cases and controls. Inflammation and dyslipidemia are well known risk factors of atherosclerosis. The higher the ratio of LDL-C to HDL-C the higher the risk of developing cardiovascular disease (CVD). In the present study there is an increase in TGL /HDL and LDL/HDL ratio in cases when compared to controls. Hence serum lipid profile and lipid ratios could predict premature Atherosclerosis and Death in CKD patients.

8. Conclusion

There is alteration in lipid metabolism in patients with chronic kidney disease. Our results indicate that patients with chronic kidney disease show abnormalities of lipid metabolism such as hypertriglyceridemia, increased VLDL and low HDL cholesterol. This altered lipid metabolism contribute to pathogenesis of atherosclerosis and cardiovascular disease as well as to the progression of renal disease. All these factors lead to increase in the morbidity and mortality in patients with CKD. So early detection and treatment (diet /drug therapy) of this dyslipidemia may help in improving the clinical outcomes in patients with CKD. It also helps to assess the clinical effectiveness and economic merits of interventions.

9. Limitation of the Study

The cross-sectional design of our study and the smaller sample size

10. Conflicts of Interest

NIL

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