

Evaluation of Lipid Profile in Patients with Non-Diabetic Chronic Kidney Disease Stage 3, 4 And 5.

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Abstract

INTRODUCTION: Chronic kidney disease is a prevalent health problem worldwide, affecting millions of people. Dyslipidemia has been identified as an independent risk factor for the progression of renal disease. In chronic kidney disease, the most prevalent lipid abnormalities which have been noted are increased triglyceride levels and decreased HDL concentration. The LDL levels are usually normal or increased. **MATERIAL & METHODS:** The study was conducted at King George Hospital (KGH), Visakhapatnam from May 2018 to April 2019. It was an analytical, observational, cross-sectional study conducted in non-diabetic chronic kidney disease patients of age group 18 to 65 years admitted in medical and nephrology wards. A total of one hundred and twenty patients were enrolled in the study. A detailed medical history and clinical examination were performed in all patients. Demographic data like age sex were collected. An early morning venous sample was collected and sent for Fasting blood sugar, Hb A1C, Blood urea, serum creatinine, Serum electrolytes, Lipid profile (total cholesterol, triglycerides, HDL, LDL and VLDL).

RESULTS: Of 120 patients, 42 were on maintenance hemodialysis and 78 were on conservative management. The number of patients in stage 3 were 20 (16.6%), in stage 4 were 44 (36.6%) and 56 (46.6%) in stage 5. 33 patients have normal lipid profile, and 45 were abnormal in conservative management group and eight patients have normal lipid profile, and 34 have an abnormal lipid profile in hemodialysis group.

CONCLUSIONS: Prevalence of dyslipidemia in non-diabetic CKD and this problem of dyslipidemia increases as the severity of CKD increasing. A high degree of abnormality found in triglyceride levels in the form of hypertriglyceridemia in non-diabetic CKD patients.

Key Words: Chronic kidney disease, Dyslipidemia, non-diabetic

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I. Introduction

Chronic kidney disease is a prevalent health problem worldwide, affecting millions of people.^[1] CKD is known more for its morbidity than for its mortality. Since the advent of dialysis, the severity of the CKD consequences undergone profound changes. Chronic kidney disease represents a progressive, irreversible decline in the glomerular filtration rate (GFR). A common phenomenon in renal failure is progressive renal function loss, irrespective of the underlying cause of the kidney disease. Most chronic nephropathies lack a specific treatment and progress relentlessly to end-stage kidney disease (ESKD) with increasing prevalence worldwide.^[2]

It is characterized by a wide variety of biochemical disturbances and numerous clinical symptoms and signs.^[3] The alteration includes Hematologic abnormalities, cardiovascular problems, gastrointestinal disturbances, neurologic disorder, osteodystrophy, skin disorder and altered sexual function.^[4] Lipoprotein metabolism is also found to be altered in most patients with renal insufficiency.^[5]

Cardiovascular disease is one of the major cause of mortality in patients with mild to moderate Chronic Kidney Disease (CKD) and also End-Stage Renal Disease (ESRD).^[6] Irrespective of its agents, ultimately it leads to structural and functional hypertrophy of surviving nephrons. Clinically the patients are asymptomatic, with the progression of the disease process and with the increasing amount of nephron losses leads to the end stage of renal disease (ESRD) which depicts the prolonged signs and symptoms of uremia.

To reduce the burden of ESRD, the research area should focus on clinical trials to slow the progression of kidney disease. Besides, therapies directed towards slowing the progression of kidney disease via controlling hypertension by using angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARB's) are recommended management therapies.^[7]

Dyslipidemia has been identified as an independent risk factor for the progression of renal disease. The deleterious effects of hyperlipidemia on the progression of kidney disease is based on several lines of evidence. Hyperlipidemia has been shown to accelerate the progression of kidney disease. There is a shred of extensive evidence for the processes involved in lipid-induced kidney damage, where multiple mechanisms appear to be involved. In chronic kidney disease, the most prevalent lipid abnormalities which have been noted are increased triglyceride levels and decreased HDL concentration. The LDL levels are usually normal or increased.^[8]

There is lack of evidence about the prevalence of dyslipidemia in patients suffering from CKD in the Indian population and the type of cholesterol that is majorly affected owing to the variations in the dietary habits and lifestyle differences from the western counterparts. Emphasis must also be laid on the derangement of lipid profile in patients with CKD in the Indian reference population and the severity of dyslipidemia about the severity of CKD. This study is aimed at knowing the overall prevalence of dyslipidemia in hospitalized non-diabetic CKD patients and assess the derangement in lipid profile based on the severity of CKD.

II. Material & Methods

The study was conducted at King George Hospital(KGH), Visakhapatnam from May 2018 to April 2019. It was an analytical, observational, cross-sectional study conducted in non-diabetic chronic kidney disease patients of age group 18 to 65 years admitted in medical and nephrology wards. Hospital ethics committee clearance was taken before starting the study. Informed and written consent taken from all candidates who were included in the study.

Inclusion criteria:

1. Patients who are diagnosed as non-diabetic chronic kidney disease stage 3,4 and 5 (creatinine clearance < 60 ml/min/1.73m²) who were on conservative management or maintenance haemodialysis.
2. Age more than 18 years and less than 65 years.
3. Those who gave valid informed and written consent.

Exclusion criteria:

1. Patients with a BMI of more than 30.
2. Patients with Diabetes mellitus, history of ischemic heart disease.
3. Patients who are smokers and alcoholics.
4. Pregnant patients.
5. Patients who are taking Beta-blockers and OCPs

The patients who met all the inclusion criteria were selected randomly. No distinction is made between males and females. A total of one hundred and twenty patients were enrolled in the study. A detailed medical history and clinical examination were performed in all patients. Demographic data like age sex were collected. Height, weight, BMI was also collected. Blood pressure measurement in Right upper arm was taken in the supine position by using sphygmomanometer of all patients were recorded. An early morning venous sample was collected and sent for Fasting blood sugar, Hb A1C, Blood urea, serum creatinine, Serum electrolytes, Lipid profile (total cholesterol, triglycerides, HDL, LDL and VLDL). All these investigations were done in a commercially available automatic.

Estimated GFR was calculated for each patient based on MDRD formula

$$e\text{ GFR (ml/min per } 1.73\text{ m}^2) = 1.86 \times (\text{SCr})^{-1.154} \times (\text{age})^{0.203}.$$

The selected patients were divided into three different groups based on NKF KDOQI (National Kidney Foundation- Kidney Disease Outcomes Quality Initiative) staging system.

Stage 3 estimated GFR 30 to 59 ml/min/1.73m²

Stage 4 estimated GFR 15-29 ml/min/1.73m²

Group 2 with Stage 5 GFR <15 ml/min/1.73m²

To study the effect of hemodialysis on lipid levels, the study population is divided into two groups based on the management strategies. i.e. hemodialysis group and conservative management group. And the various levels of lipid studied in these groups.

Ultrasonogram of the abdomen done in all patients to know the size of the kidneys.

ECG: A standard 12 lead electrocardiogram was taken for all individuals in this study. Sokolow-Lyon Criteria (The sum of S wave in V1 and the R wave in V5 or V6 is > 35 mm, then LVH is present) was used to diagnose LVH in ECG.

Continuous variables expressed as a percentage and mean \pm SD. Independent sample t-test was applied after fulfilling the normality and equality of population variance assumption. Pearson's Chi-square test is used to

assess the association of different study parameters. To know the significance of the difference between two parameters in parametric data, Student's t-test was used. A P-Value of less than 0.05 was considered as statistically significant.

III. Results:

One hundred twenty patients took part in the study. Of these 42 were on maintenance hemodialysis and 78 were on conservative management. Among 78 in the conservative management group, 46 were males, and 32 were females. Among 42 in the hemodialysis group, 26 were males, and 16 were females. Age distribution showed that majority in both conservative management and hemodialysis group belonged to 41-50 years age group with mean age being 50.08 & 52.02 in each group respectively. The mean BMI among the two groups was 22.86 and 22.99 respectively.

In this study, patients with CKD stage 3,4 and 5 were enrolled. The number of patients in stage 3 were 20 (16.6%), in stage 4 were 44 (36.6%) and 56 (46.6%) in stage 5.

With regards to lipid profile, 33 patients have normal lipid profile, and 45 were abnormal in conservative management group and eight patients have normal lipid profile, and 34 have an abnormal lipid profile in hemodialysis group. Dyslipidemia vs stages of CKD showed that among 56 cases of stage 5, 41 had abnormal and 15 normal lipid profile. Among 44 cases of stage 4, 30 had abnormal and 14 normal lipid profile. Among 20 cases of stage 3, 7 had abnormal and 13 normal lipid profile.

Table no 1: Dyslipidemia vs stages of CKD

Lipid profile	Stages of chronic kidney disease		
	Stage 3	Stage 4	Stage 5
Normal	13	14	15
Abnormal	7	30	41
Total	20	44	56

Mean parameters in lipid metabolism and variation with management strategy:

Triglycerides: The mean triglyceride values in the total study population are 150.79mg/dl with a standard deviation of 39.41. In the HD group, the lowest value is 70 mg/dl. The highest value, 305 mg/dl. The mean value is 162.9, with a standard deviation of 41.5. In the conservative management group, the lowest value is 53 mg/dl. The highest value is 271. The mean value is 144.26 mg/dl with a standard deviation of ± 37.16 . The variation is statistically significant with $P= 0.0128$.

Total cholesterol: There is a rise in the total cholesterol values in patients under hemodialysis (150.07 ± 48.1) as compared those under conservative management (142.7 ± 46.5) with the mean value of the total study population is 145 ± 48.26 , but the rise is not statistically significant ($p = 0.425$).

HDL: There is statistically significant fall in the levels of HDL in the study population with the mean value at 45.45 ± 13.4 , and the extent of fall is greater in the hemodialysis group (42.1 ± 18.2) as compared to the conservative management group (49.5 ± 15.9) ($p = 0.022$).

LDL: The mean value in the study group is 99.16 ± 26.38 with a difference between patients under hemodialysis (102.1 ± 31.4) from those under conservative management (97 ± 25.8) ($p = 0.341$).

Table No 2: Mean parameters in lipid metabolism and variation with management strategy.

Type of lipid	Total population	On Hemodialysis	On conservative	p-value
Triglycerides	150.79 ± 39.41	162.9 ± 41.5	144.26 ± 37.16	0.0128
Total cholesterol	145.3 ± 48.2	150.07 ± 48.1	142.7 ± 46.5	0.425
HDL	45.45 ± 13.4	42.1 ± 18.2	49.5 ± 15.9	0.022
LDL	99.16 ± 26.38	102.1 ± 31.4	97 ± 25.8	0.341

IV. Discussion

The prevalence of dyslipidemia in non-diabetic CKD as calculated in this study is found to be 67.5% in patients with CKD without any prior history of diabetes. A study among Nepalese population with CKD recorded a higher prevalence of dyslipidemia among CKD patients when compared to the non-CKD control group, and the difference was statistically significant.^[9]

In the general study population, there is marked the elevation of triglycerides in 68 (48.57%) patients. A study by Saroj K et al. reported a prevalence of 36.6% and a study in Khatmandu, Nepal also showed a prevalence of 35.58% of hypertriglyceridemia in CKD.^[9,10]

The cause of hypertriglyceridemia in chronic kidney disease patients has not been delineated. Available data derived from kinetic studies with intralipid administration have demonstrated that in the reduced catabolism of triglycerides, the predominant defect may be due to deficiency of lipoprotein lipase or hepatic triglyceride lipase or both. These enzymes are the primary mediators of the process. Reasons for the decrease in the activity of these enzymes are not clear, possibly due to;

- Presence of circulatory inhibitor of lipolytic enzymes in the serum
- Changes in apoprotein concentrations which can affect lipoprotein lipase activity
- Insulin resistance was seen in renal insufficiency
- Alteration of lipoprotein substrate

Hypercholesteremia was found in 32 (22.86%) patients, and a decrease in HDL cholesterol was found in 30 (21.43%). Saroj K et al. found about 34.4% of the CKD study patients to have hypercholesteremia, and 34.1% had low levels of HDL cholesterol. The reports conducted in Kathmandu, Nepal by Poudel B et al. showed a prevalence of 33.75% of hypercholesteremia.^[9,10]

Anderson et al. found hypercholesteremia in 20% of the patients in their study.^[11] Hypercholesteremia is a significant risk factor for CAD. But, Gerald Appel found low values of cholesterol in CKD patients.^[12]

Goldberg et al. found a decrease in HDL concentrations in CKD patients as compared to controls in contrast to Rapoport and Aviram study showed no decrease in HDL concentrations in CKD patients.^[13,14]

The LDL cholesterol is abnormal is only observed in 18 (12.86%) of the study population whereas Saroj K et al. reported a larger figure of 35% of the study population to have undesirable LDL levels and Poudel et al. reported an even higher prevalence of 38.03%. But abnormality in uremia is mainly qualitative.^[9,10]

A total of 42 patients were on haemodialysis, and 78 patients were on conservative management. There was an increased incidence of dyslipidemia in patients under haemodialysis, 34 of the 42 patients, as compared to 45 out of 78 patients under conservative management ($P < 0.0001$; OR = 0.1765).

Kronberg F et al. found out that hypertriglyceridemia is more prevalent in the dialysis group than conservative management group and in the dialysis group more prevalent in the peritoneal dialysis patients may be owing to significant amounts of glucose being absorbed from the dialysis fluid.^[15]

The patients who were on hemodialysis were suffering from chronic kidney disease from a long time compared to patients on conservative management. Probably that might have contributed to the increasing number of lipid abnormalities in those patients.

There was a general worsening of lipid profile in patients as the severity of CKD increased as evidenced by the prevalence of dyslipidemia increases with increase in the grading of CKD.

In the present study, 20 patients (16.6%) were in stage 3, 44 (36.6%) patients belonged to stage 4 and 56 (46.6%) patients were categorized as stage 5 or end-stage renal disease. The prevalence of dyslipidemia increases as chronic kidney disease progresses. There is a statistically significant association between the parameters ($P = 0.009$).

According to Vaziri and Moradi, CKD causes profound dysregulation of lipoprotein metabolism, resulting in lipoprotein abnormalities. Dyslipidemias develop during the early stages of CKD but progress rapidly with the progression of CKD.^[16]

There is also an increased incidence of dyslipidemia in stage 5 CKD as most of the patients undergo regular hemodialysis. And this increased incidence of dyslipidemia in stage 5 CKD may also be due to the long duration of illness. This has to be confirmed by further studies.

No cases have been excluded from the study after enrolling due to complications or death during the study.

However, among patients with a baseline GFR less than 40 ml/min, statins administration was associated with a lower rate of decline in estimated GFR. The beneficial effects of statin have been attributed to both the lipid-lowering and lipid-independent anti-inflammatory (via interference with isoprenylation processes) action of these drugs.

Dyslipidemia represents an integral component of CKD. Disturbances in lipoprotein metabolism (mainly accumulation of intact or partially metabolized apolipoprotein B-containing particles as well as reduced concentrations of HDL-cholesterol) are evident even at the early stages of CKD and usually follow a downtrend course that parallels the deterioration in renal function. Since several intrinsic (genetic, primary kidney disease) or exogenous (drugs, method of renal replacement) factors can influence the phenotypic expression of these alterations, the precise knowledge of the pathophysiological mechanisms that underlie their development is of paramount importance.

Recently published studies suggest that dyslipidemia in these patients may actively participate in the pathogenesis of as well as in the deterioration of kidney function. Thus, we believe that the current evidence dictates the use of statins in patients with mild to moderate CKD.

Thus, in individuals with established CVD as well as in those who run a high risk for acute pancreatitis due to severe hypertriglyceridemia, the administration of hypolipidemic drugs (statins and gemfibrozil respectively) is a safe and reasonable approach.

Vaziri ND, Moradi H et al. study states that the most common quantitative lipid abnormalities in predialysis CKD patients are hypertriglyceridemia, increased concentrations of triglyceride-rich lipoprotein remnants, reduced high-density lipoprotein (HDL)-cholesterol levels as well as increased concentrations of lipoprotein(a) (Lp(a)).^[17] Notably, total and LDL-cholesterol levels are usually within normal limits or slightly reduced in these individuals.

Eustace JA et al., Liu Y, Coresh J et al. reported in their study that the typical profile of patients with chronic kidney disease, that is, the constellation of moderate elevation of plasma triglyceride concentrations, combined with low plasma HDL-cholesterol, corresponds to the pattern of dyslipidemia type IV.^[18] According to Frederickson et al. In CKD, total cholesterol is usually normal or even low. This may be the result of an additional micro inflammatory state and malnutrition.^[19]

In our study, lipid profile shows increased plasma triglyceride concentrations, combined with low plasma HDL-cholesterol as similar with that of Vaziri ND, Moradi H et al. and Liu Y, Coresh J, Eustace JA, et al. study but, total cholesterol and, LDL-cholesterol were increased.^[17,18]

The most common type of dyslipidemia observed in Liu Y, Coresh J, Eustace JA, et al. study was type IV according to Frederickson et al.³⁵ Similar reports were observed by Yee E, Bagdade JD, Wilson D, and Shafir E et al.^[20]

The most common lipid abnormality in the present study is decreased HDL in 74% of patients. A similar observation has been reported by Burrell et al. HDL – cholesterol was found to have a positive correlation with creatinine clearance by Grutzmacher et al. LCAT plays an important role in HDL-mediated cholesterol uptake from the extrahepatic tissues. LCAT deficiency can majorly account for diminished plasma HDL cholesterol and impaired HDL maturation in CRF.

CETP's role is to mediate the transfer of cholesterol ester from HDL to IDL in exchange for triglyceride. Thus an increase in plasma CETP can contribute to the CRF-associated reduction in HDL cholesterol ester and an increase of HDL triglycerides concentration. In fact, according to a recent study, more than 34% of hemodialysis-dependent patients were found to have high plasma CETP enzyme levels.

Hepatic lipase catalyses hydrolysis and removal of the triglyceride content of HDL. Thus hepatic lipase deficiency can potentially contribute to increased HDL triglyceride content. CRF results in pronounced hepatic lipase.

Hypertriglyceridemia is a common feature of CRF causes include increased synthesis and diminished clearance from the circulation. Because renal insufficiency causes insulin resistance, which can, in turn, promote hepatic VLDL production, it has been suggested that increased production maybe responsible, in part, for CRF-associated increase in plasma VLDL and triglycerides.

Several studies have shown that the concentrations of these particles (that are not captured by conventional LDL measurement) are elevated in patients with renal failure and may independently contribute to the determination of future cardiovascular risk.^[21,22] The National Kidney Foundation guidelines suggest non-HDL-cholesterol values of 130 mg/dl as a secondary target of therapy in individuals with triglyceride values of 1 200 mg/dl. Usually, a U- or J-shaped relationship was noted between plasma cholesterol concentration and cardiovascular mortality, i.e., higher mortality at low as well as high plasma cholesterol concentrations. The most suitable explanation for this paradox is this represents an example of reverse epidemiology^[23], i.e., a relationship, which is reversed by a confounding factor. The recent work of Liu et al.,^[24] is important in this respect. They identified microinflammation as a confounding factor.

Patients with chronic renal failure are at high risk of developing CVD. Most CKD patients have a ten-year risk of coronary heart disease events more than or equal to 20%. According to the National Cholesterol Education program, adult treatment panel 3 guidelines, these patients come under the highest risk category.^[25] A meta-analysis of 13 small prospective studies revealed a significant reduction in the rate of decline in the GFR and marginal reductions in proteinuria and progression toward ESRD with lipid-lowering therapy primarily with various statins.

Similarly, the Heart Protection Study showed a significantly lower rate of rising in serum creatinine levels in the statins-treated group compared with the placebo-treated group.^[26] Also, in a large published study of patients with coronary heart disease and dyslipidemia, statins administration for three years resulted in a significant improvement in creatinine clearance compared with a placebo group.

V. Conclusions:

An evaluation which was conducted in 120 patients in King George Hospital, Visakhapatnam on Non-diabetes kidney disease patients has revealed that the lipid abnormalities are found to occur in all stage 3,4 and 5 of non-diabetic chronic kidney disease. The study concludes that the prevalence of dyslipidemia in non-diabetic

CKD and this problem of dyslipidemia increases as the severity of CKD increasing. A high degree of abnormality found in triglyceride levels in the form of hypertriglyceridemia in non-diabetic CKD patients. Haemodialysis could be a potential risk factor for the development of dyslipidemia in non-diabetic CKD as the prevalence is high in the hemodialysis group of patients compared to the conservative management group.

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