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EVALUATION OF LIPID PROFILE IN NON-DIABETIC CHRONIC KIDNEY DISEASE STAGE 3 AND 4

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ABSTRACT: BACKGROUND: CVD are the major cause of mortality in patient with CKD. One of the established risk factor for cardiovascular disease is dyslipidemia. The pattern of dyslipidemia in CKD is entirely different from general population. So the study about the lipid pattern will be useful in early intervention and management of dyslipidemia in CKD. **AIM OF THE STUDY:** To estimate various levels of lipids in Non-Diabetic CKD stage 3 and 4. **METHODS:** The study was conducted in 50 patients of CKD in stage 3 and 4; 50 age and sex matched healthy individuals were selected as control. A detailed history and clinical examination were performed. Apart from routine investigations blood urea, creatinine, electrolytes and Creatinine clearance by using Cockcroft-Gault equation were measured. **RESULTS AND OBSERVATION:** Mean triglyceride of the study group was 197.26 mg/dl (178.18 mg/dl. control group). Statistical significance of these values was analyzed by finding out the standard error of difference between the two mean. It was 8.89. The actual difference of the mean between the two groups was 19.08, which is more than twice of standard error of difference between the two mean. So the difference in triglycerides values between the two groups is statistically significant. Similarly Mean HDL cholesterol of the study group was 34.18 mg/dl (39.48 mg/dl, Mean LDL cholesterol of the study group was 118.61(103.36) mg/dl, and mean total cholesterol of the study group was 192.24(178.48) mg/dl and all are statistically significant. **CONCLUSION:** Most common lipid abnormality in this study is statistically significant reduction of HDL-C level and elevation of serum triglycerides, TC and LDL-C level in patients with CKD Stage 3and 4. Most common hyperlipoproteinemia in this study is Type IV (Fredrickson classification).
KEYWORDS: chronic kidney disease, dyslipidemia.

INTRODUCTION: CVD as the major cause of mortality in patients with mild to moderate CKD and end-stage renal disease (ESRD).[1, 2] Approximately 50% of patients with ESRD die from a cardiovascular event,[3] which indicates a cardiovascular mortality that is 30 times higher in dialysis patients and 500 times higher in 25-34years old ESRD patients than in individuals from the general population of the same age and race. Numerous factors contribute to atherogenic diathesis and the high risk of cardiovascular disease in CKD. These include lipid disorders, oxidative stress, inflammation, physical inactivity, anemia, hypertension, vascular calcification, endothelial dysfunction, and depressed nitric oxide availability.[4-7] Dysregulation of lipid metabolism can contribute to atherogenic diathesis and possibly to progression of renal disease and impaired energy metabolism in CRF.

Dyslipidemia has been established as a well-known traditional risk factor for CVD in the general population and large-scale observational studies have shown that total and low-density

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lipoprotein (LDL)-cholesterol values are two of the most important independent predictors of cardiovascular morbidity and mortality.[8] Also, it is well known that patients with impaired renal function exhibit significant alterations in lipoprotein metabolism, which in their most advanced form may result in the development of severe dyslipidemia.

Although lipid abnormalities were originally considered as complications of ESRD, these changes can be present in early stages of CKD and may actively participate in the pathogenesis of serious complications such as atherosclerotic vascular disease. Although the nature of dyslipidemia can be significantly influenced by several intrinsic (nephrotic range proteinuria, concomitant diseases such as diabetes mellitus, hereditary disorders of lipid metabolism) or exogenous (epoietin administration, drugs such as steroids, calcineurin inhibitors, etc.) factors, 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). Notably, total and LDL-cholesterol levels are usually within normal limits or slightly reduced in these individuals.[9]

AIM OF THIS STUDY: Aim of this study is to estimate various levels of lipids in CKD patients, and to examine which type of hyperlipidemia predominates in these patients.

MATERIALS AND METHODS: The study was conducted in 50 patients of CKD in stage 3 and 4. This study also included 50 age and sex matched normal healthy individuals as control group.

Inclusion criteria:
1. Patients with chronic kidney disease stage 3 and 4.

Exclusion criteria:
1. Patients with diabetes mellitus.
2. Patients on maintenance haemodialysis.
3. Patients with proteinuria.
4. Patients with confounding factors like hypothyroidism, severe liver disease, estrogen and beta blockers therapy.

A detailed history and clinical examination were performed in all patients. Height, weight, Blood Pressure of all patients was recorded. Apart from routine investigations blood urea, creatinine, electrolytes, and Creatinine clearance by using Cockcroft-Gault equation were measured. Blood samples were obtained on one occasion from antecubital venepuncture after an overnight fast (12 hrs) from all patients.

Abdominal USG and ECG were taken for all patients.
LDL cholesterol was calculated by Friedewald`s equation

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LDL = TC - Triglycerides/5 - HDL

The VLDL was estimated by dividing the plasma Triglycerides by 5. This formula is used only on patients with fasting Triglycerides level of less than 350 mg/dl.

RESULTS AND OBSERVATION: One hundred patients took part in this study. Out of hundred patients fifty were known case of CKD stage 3 and 4 and the remaining fifty were control. Of the 50 CKD patients 18 were female and the remaining 32 were male. Their age varied from 28 to 52 yrs.

Total cholesterol was above 200 mg/dl in 13(26%) patients. Serum triglycerides were above the upper limit of normal (200 mg/dl) in 23 (46%) patients. HDL was less than 35 mg/dl in 37 (74%) patients. LDL cholesterol was above 130 mg/dl in 14(28%) patients and above 100 mg/dl in 42(84%) patients. Ratio between Total cholesterol and HDL cholesterol was above 6 in 20(40%) patients.

Mean triglycerides of the study group was 197.26 mg/dl(178.18 mg/dl in control group). The mean deviation was 45.51 mg/dl (17.20 mg/dl). The standard deviation was 59.75 mg/dl (21.52 mg/dl). The standard error of mean was 8.45(3.04). Statistical significance of these values was analyzed by finding out the standard error of difference between the two mean. The standard error of difference between the two mean was 8.89. The actual difference of the mean between the two groups was 19.08, which is more than twice of standard error of difference between the two mean. So the difference in serum triglycerides values between the two groups is statistically significant.

Mean HDL cholesterol of the study group was 34.18 mg/dl (39.48 mg/dl). The mean deviation was 3.46 mg/dl. (3.80 mg/dl).The standard deviation was 4.62mg/dl (4.98 mg/dl). The standard error of mean was 0.65(0.70). The standard error of difference between the two mean was 0.96. The actual difference of the mean between the two groups was 5.3 and it is statistically significant.

Mean LDL cholesterol of the study group was 118.61(103.36) mg/dl. The mean deviation was 14.72 (17.11) mg/dl. The standard deviation was 21.27(20.79) mg/dl. The standard error of mean was 3.01(2.94). The standard error of difference between the two mean was 4.21. The actual difference of the mean between the two groups was 15.25 and it is statistically significant.

Mean total cholesterol of the study group was 192.24(178.48) mg/dl. The mean deviation was 14.64(16.66) mg/dl. The standard deviation was 2.55mg/dl. The standard error of mean was 3.19(2.88). The standard error of difference between the two mean was 4.29. The actual difference of the mean between the two groups was 13.76 and it is statistically significant.

The ratio between total cholesterol and HDL cholesterol is considered as a risk factor for coronary artery disease, when the value exceeds 6. In this study 20 out of 50 patients were found to have more than 6. Mean ratio between total cholesterol and HDL cholesterol of the study group was 5.7(4.6). The mean deviation was 0.8(0.6).The standard deviation was 1.0(0.8).The standard error of mean was 0.1(0.1). The standard error of difference between the two mean was 0.18. The actual difference of the mean between the two groups was 1.1 and it is statistically significant.

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It was found that the serum concentration of increased triglycerides, decreased HDL cholesterol, increased LDL cholesterol, increased total cholesterol were statistically significant in CKD patients with stage 3 and 4.

DISCUSSION: The incidence and prevalence of chronic kidney disease (CKD) are increasing worldwide and are associated with poor outcomes. Patients with CKD are at high risk for developing CVD. Most CKD patients have a 10years risk of coronary heart disease events greater than or equal to 20%, placing them in the highest risk category according to the national cholesterol education program adult treatment panel 3 guidelines.[10]

Hyperlipidemia can potentially accelerate progression of renal disease by several mechanisms. First, reabsorption of fatty acids, phospholipids, and cholesterol contained in the filtered proteins (albumin and lipoproteins) by tubular epithelial cells can stimulate tubulointerstitial inflammation, foam cell formation, and tissue injury.[11,12] Second, accumulation of lipoproteins in glomerular mesangium can promote matrix production and glomerulosclerosis.[13-15] In this context, native and oxidized lipoproteins, particularly LDL, stimulate production of matrix proteins by cultured mesangial cells and promote generation of proinflammatory cytokines, which can lead to recruitment and activation of circulating and resident macrophages.[16,17,18]

In addition, impaired HDL-mediated reverse cholesterol transport can further contribute to tissue injury by limiting the unloading of the excess cellular cholesterol and phospholipid burden. In fact, low plasma HDL has been identified as an independent risk factor for progression of renal disease[19, 20] Moreover, hereditary LCAT deficiency, which is associated with a marked reduction in HDL cholesterol and impaired HDL-mediated reverse cholesterol transport, results in progressive renal disease.[21]

The most common lipid abnormality in our study is decreased HDL in 74% of patients. Similar observation has been reported by Burrell et al. HDL – cholesterol was found to have a positive correlation with creatinine clearance. LCAT plays an important role in HDL-mediated cholesterol uptake from the extrahepatic tissues. LCAT deficiency can potentially account for diminished plasma HDL cholesterol and impaired HDL maturation in CKD. Another possible mechanism for decreased HDL is CETP mediates transfer of cholesterol ester from HDL to IDL in exchange for triglycerides. Thus a potential increase in plasma CETP can contribute to the CKD associated reduction in HDL cholesterol ester and elevation of HDL triglycerides. Hepatic lipase catalyzes hydrolysis and removal of the triglyceride content of HDL. Thus hepatic lipase deficiency can potentially contribute to increased HDL triglyceride content.

Liu Y, Coresh J, Eustace JA et al, and Vaziri ND, Moradi H 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 according to Frederickson et al. Similarly in our study, lipid profile shows increased plasma triglyceride concentrations, combined with low plasma HDL-cholesterol and also the same pattern were observed by Bagdade JD, Yee E, Wilson D and Shafrir E et al.[22]

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Elevation of plasma triglycerides in ESRD patients is accompanied by increased production VLDL and impaired clearance of VLDL. Because renal insufficiency causes insulin resistance, which can, promote hepatic VLDL production. Similarly, clearance of chylomicrons is impaired and plasma concentration of chylomicron remnants is elevated in CKD patient. The above compositional abnormalities are present in nearly all patients with mild to severe renal insufficiency.

Chronic kidney disease in the absence of heavy proteinuria does not significantly affect gene expressions of either hydroxyl-3-methylglutaryl-CoA reductase (HMG-CoA reductase) which is the rate-limiting enzyme for cholesterol biosynthesis, or that of cholesterol 7a-hydroxylase which is the rate-limiting enzyme for cholesterol catabolism and conversion to bileacids.[23] So CKD in the absence of heavy proteinuria does not alter hepatic LDL receptor gene expression, thereby LDL levels are not elevated. But in our study LDL levels were significantly elevated even though we eliminated proteinuric patients.

Usually a U- or J-shaped relationship was noted between plasma cholesterol concentration and cardiovascular mortality, a higher mortality at low as well as high plasma cholesterol concentrations. The most plausible explanation for this paradox is that this represents an example of reverse epidemiology[24,25] i.e, a relationship, which is reversed by a confounding factor. Liu et al,[26] Degoulet et al[27] identified micro inflammation and malnutrition were the confounding factors.

Observational studies by Ziad A Massy and Dick de Zeeuw among apparently healthy individuals or patients with preexisting CVD have repeatedly demonstrated a roughly linear relationship between serum total and LDL cholesterol and risk of death from CVD.[28,29] Among patients with CKD, however, this relationship is much less obvious. As we included only stage 3 and 4 CKD in our study, we did not get low total cholesterol and low LDL, rather there were elevated levels.

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 downhill 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 indicate that dyslipidemia in these patients may actively participate in the pathogenesis of CVD as well as in the deterioration of renal function. Thus, we believe that the current evidence dictates the use of statins in patients with mild to moderate CKD and it should be individualized. The beneficial effects of statins have been attributed to both the lipid-lowering and lipid-independent anti-inflammatory (via interference with isoprenylation processes) action of these drugs.

CONCLUSIONS:

1. Most common hyperlipoproteinemia in this study is Type IV (Fredrickson classification)

2. Most common lipid abnormality in this study is statistically significant reduction of HDL-C level in patients with CKD stage 3 and 4.

3. There is a statistically significant increase in serum triglycerides, TC and LDL-Cholesterol level in patients with CKD stage 3 and 4.

4. There is a negative correlation between the ratio of TC to HDL-C and severity of CKD.

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Lipid Disorder	Both Male and Female in % (No of Patients)	Among the 32 Males in % (No of Patients)	Among the 18 Females in % (No of Patients)
Increased TC	26 (13)	28.1(9)	22.2(4)
Increased TGL	46(23)	46.9(15)	44.4(8)
Decreased HDL	74(37)	71.9 (23)	77.8(14)
Increased HDL	28(14)	25(8)	33.3(6)
Table 1: Lipid abnormality in study group			

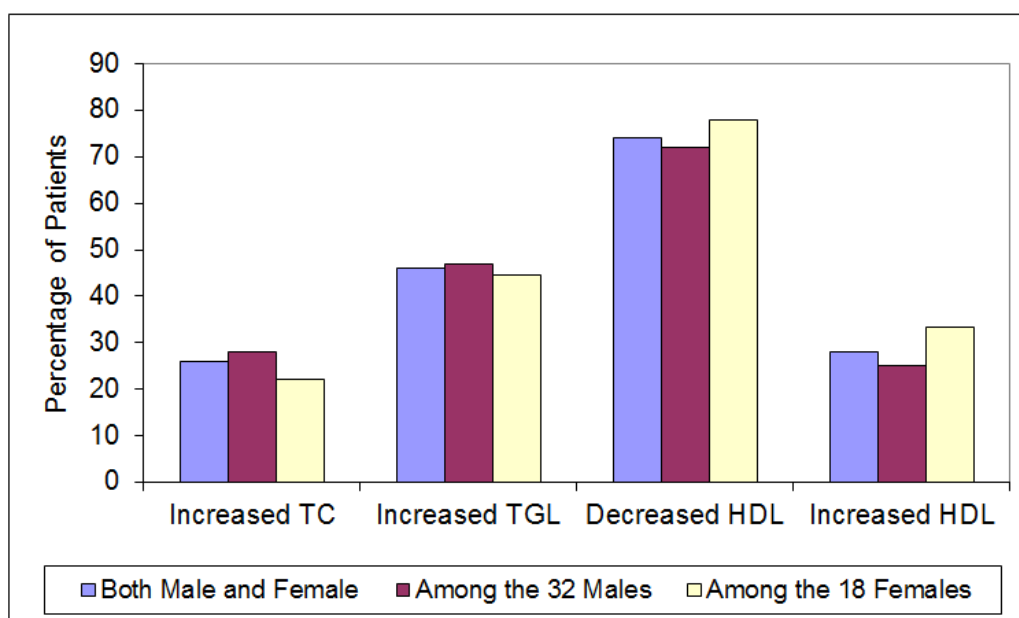|	TC	TGL	HDL-C	LDL-C	Ratio
Mean	192.24	197.26	34.18	118.61	5.7
Mean Deviation	14.64	45.51	3.46	14.72	0.8
std deviation	22.55	59.75	4.62	21.27	1.0
std error of mean	3.19	8.45	0.65	3.01	0.1
std error of dif bet 2 mean	4.29	8.89	0.96	4.21	0.18
Table 2: Lipid abnormality in study group – Statistical analysis					

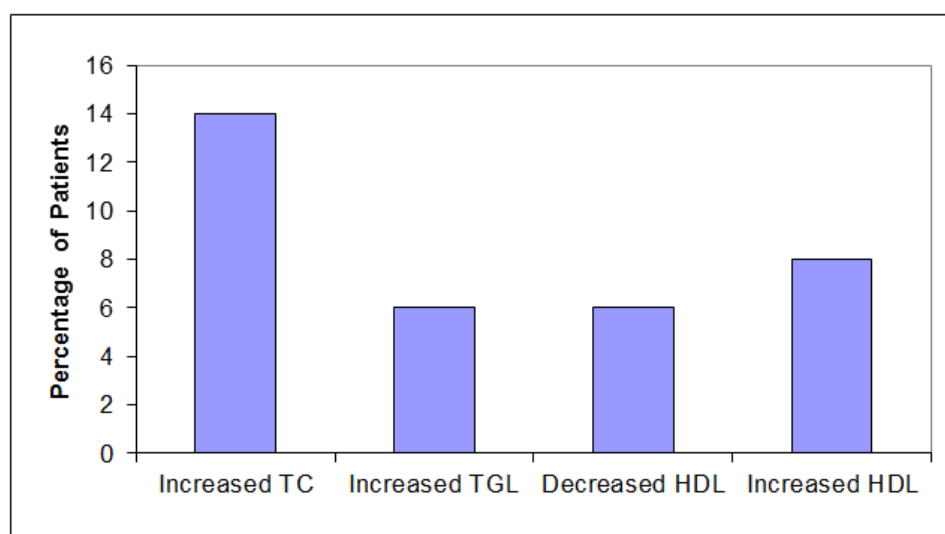**Chart 1: Lipid abnormality in study group – sex difference**

Chart 2: Lipid abnormality in study group

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Date of Submission: 28/06/2014.
Date of Peer Review: 30/06/2014.
Date of Acceptance: 28/07/2014.
Date of Publishing: 02/08/2014.