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Original Research Article

A Study of Dyslipidemia in Patients of Chronic Kidney Disease of Rural Population of Eastern Bihar- A Cross Sectional Observational Study Based on a Tertiary Care Hospital Set-Up

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Introduction

Chronic kidney disease (CKD) is a significant health problem. It was estimated that the prevalence of CKD is 8-16% worldwide[1]. On the other hand, it is well documented that cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with CKD[2-6]. Thus, although some patients with CKD will ultimately develop end stage renal disease (ESRD), most patients with CKD will die of CVD before dialysis becomes necessary[7]. Mild chronic impaired renal function contributes actively to the development of CVD, so the American Heart Association has recommended that these patients should be classified in the highest risk group for developing cardiovascular events[5]. Even microalbuminuria in the absence of apparent deterioration in renal function or diabetes predicts more CVD and deaths[8]. In patients who finally advance to ESRD and especially dialysis patients, the prevalence of clinical coronary heart disease is 40% and CVD mortality is 10 to 30 times higher than in the general population of the same gender, age and race[5,9,10].

Several factors contribute to atherogenesis and CVD in patients with CKD[11]. Although most of the cases of coronary heart disease in the general population can be explained by traditional, Framingham risk factors, in patients with CKD, uremia related, non -traditional risk factors, such as, inflammation, oxidative stress, anemia, malnutrition, vascular calcification and endothelial dysfunction have been proposed to play a central role.

Notable among the traditional risk factors for CVD in the general population is dyslipidemia. Several observational studies have shown that total and LDL-cholesterol values are two of the

most important independent predictors of cardiovascular morbidity and mortality

Aims & Objectives

- To estimate various lipid profile abnormalities in Chronic Kidney Disease patients.
- To identify the predominant Lipid pattern in Chronic Kidney Disease patients.
- To study the correlation between the Serum creatinine levels and Lipid abnormalities in Chronic Kidney Disease

Study Design

Cross Sectional Observational Study

Study Place

The study was conducted at Dept. of General Medicine, M.G.M. Medical College & L.S.K. Hospital, Kishanganj, Bihar

Study Population

The target population consisted of patients diagnosed to have Chronic Kidney Disease , either admitted as In-patient (IPD) or visiting the Out Patient Department (OPD) between December 2018 and November 2020. 110 consecutive patients fulfilling all inclusion and exclusion criteria were included in the study as cases.

110 healthy age and sex-matched controls, fulfilling the exclusion criteria were included as controls in the study.

Inclusion Criteria

.Patients with Chronic Kidney Disease:

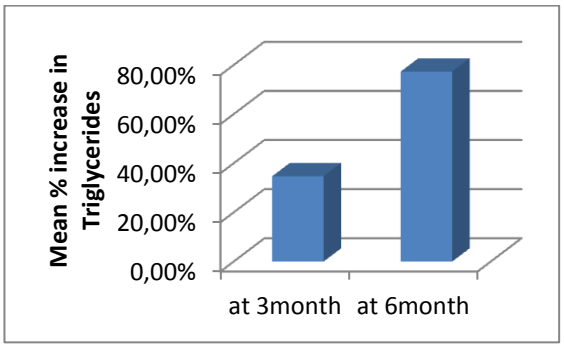
- Between age group of 15 to 80 years.
- With established CKD irrespective of etiology.
- On conservative or dialysis treatment for CKD.
- As evidenced by imaging or biochemical evidence for more than 3 months.

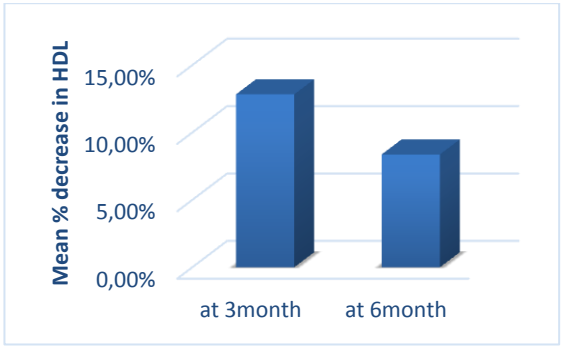
Exclusion Criteria

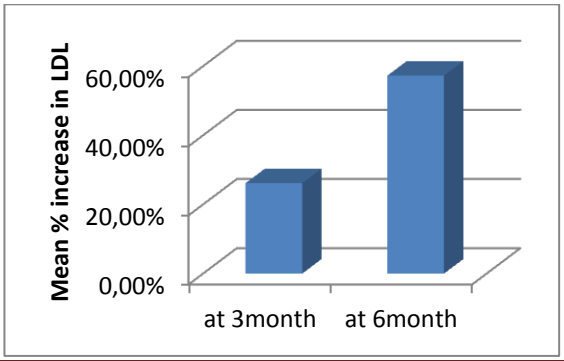
Patients with Acute Renal failure and Nephrotic Syndrome. Patients who are taking drugs affecting lipid metabolism like beta blockers, statins, fibrates, niacin, oral contraceptive pills, progestogens, growth hormone and valproic acid. Female patients who are pregnant.

Results

110 patients who were admitted in MGM MEDICAL COLLEGE with Chronic Kidney Disease were selected after taking in consideration of all the parameters in inclusion and exclusion criteria. This study group was explained about the study and consent was taken from them in the language they understand, and then after taking detailed history and physical examination, further investigations were done which were required for the study. These patients were closely observed for 6 months during this study period, and the 3 monthly lipid profile were compared with first reading in follow up







Among 110 patients selected, 59 were female and 51 were male, out of which female patients aged between 30-40 yrs of age and male patients aged between 50- 60 yrs of age were more common. Irrespective of etiology almost all these patients were having creatinine clearance <15ml/mg/1.73m^2, and on radiological imaging most of these patients had shrunken kidney.63 patients had hemoglobin<10 gm/dl and 47 patients had >10 gm/dl, still all these patients were receiving regular blood transfusions and Erythropoiesis Stimulating Agents.

Out of 110 patients, all these had creatinine levels more than 5 mg/dl and these were receiving hemodialysis, hence in follow up creatinine and urea levels were not following a pattern, still in this study it is noted that in CKD with creatinine more than 5 mg/dl dyslipidemia may be associated. In this three readings of fasting lipid profile was obtained in regular intervals of three months and these patients were not put on lipid lowering drugs for the study.

Abnormalities noted in lipid profile

The mean triglyceride levels that were observed in the first reading was 127.48 ± 52.41,whereas after 3 months it is 170 ± 71.82 and further after 3 more months is 220.28 ± 89.79, which indicates 34.74 % ± 26.77% and 77.34% ± 50.70% percent raise respectively. The P value is <0.001 in both, hence indicating there is significant raise in triglyceride levels in CKD patients.

The mean HDL that were observed in the first reading was 42.52 ± 8.67 whereas after 3months and 6 months, it is 37.75 ± 6.31 and 35.18 ± 8.40 respectively .The percentage decline in HDL levels at 3rd and 6th months are 8.37% ± 22.08% and 12.83% ± 33.39% respectively. The p value is < 0.001 for both. Hence there is significant decline in the levels of HDL .

The mean LDL levels that were observed in the first reading were 84.37 ± 26.62, whereas after 3 and 6 months ,it is 104.25 ± 33.66 and 127.59 ± 47.52 respectively. The percentage raise in LDL levels after 3 and 6 months are 26.16% ± 31.12% and 57.27% ± 56.27% respectively. The p value in both is <0.001.Hence there is significant raise in LDL levels in CKD.

In the study correlation between serum creatinine levels with triglycerides, HDL and LDL have been traced using unpaired t test ,the results were as shown above. Serum creatinine levels are not correlated with triglyceride, LDL and HDL levels in 3monthly interval follow up , where in P value is >0.01 implying correlation being statistically insignificant. Hence there is no significant correlation between serum creatinine levels and lipid abnormalities

Hence in this study, it can be concluded that "In CKD patients, there is significant raise in triglycerides, decrease in HDL levels and raise in LDL levels". So dyslipidemia can be seen associated with CKD which again predisposes to CVD.

Review of Literature

CKD is a heterogeneous group of disorders characterized by alterations in kidney structure and function, which manifest in various ways depending upon the underlying cause or causes and the severity of disease. Risk factors for CKD include genetic or sociodemographic predisposition, or the presence of diseases which can initiate and propagate kidney disease.

Normal Physiology of Lipoproteins

Lipoproteins are macromolecular particles composed of characteristic lipids and proteins that serve to transport the otherwise insoluble triglycerides and cholesterol molecules. Lipoproteins consist of a coat composed of a monolayer of amphipathic lipids and apo-lipoproteins (synonym: apoproteins) that surround a core composed of hydrophobic lipids. Since they both have hydrophobic and hydrophilic parts, they can inter-act with both the aqueous environment of the plasma and the hydrophobic core lipids. Circulating lipoproteins range in size from 5 to >1,000 nm, and can be separated according to density. HDL is small, containing the least lipid

and the most protein, whereas chylomicrons are large and lipid-rich. Lipoproteins are also distinguished by their apolipoprotein contents. Lipoproteins have mainly 2 major functions: One is the delivery of choles-terol and triglyceride molecules from the liver and intes-tine to muscle and fat tissue via mainly very low-density lipoprotein (VLDL) particles that contain apoB48 and apoB100 or LDL particles. The other function is to assist the transport of excess cholesterol from extrahepatic tis-sues to the liver for elimination via the bile, which is me-diated primarily by HDL particles[11].

Renal dysfunction is also associated with many perturbations in lipoprotein metabolism leading to dyslipidemia and accumulation of atherogenic particles[12]. CKD is associated with dyslipidemia associating hy-pertriglyceridemia, elevated LDL cholesterol, an accumu-lation of apolipoprotein B (Apo B) containing lipopro-teins, increased concentrations of lipoprotein(a) parti-cles, and low HDL levels [12]. In CKD, HDL metabolism is impaired and HDL-3 are not maturated into HDL-2 due to a lecithin-cholesterol acyl-transferase (LCAT) deficiency[13,14]. In CKD, there is substantial evidence that those oxLDL accumulate, especially in HD patients[15]. All these changes relate to oxidative stress and in-creased cardiovascular mortality in CKD patients.

HDL in CKD

HDL cholesterol deficiency and dysfunction in CKD patients play a significant effect on the formation of atherosclerosis through various mechanisms. HDL cholesterol shows anti-oxidant and anti-inflammatory characteristics, and also hinders the formation of atherosclerosis by decreasing the monocyte infiltration in artery intimal walls[12]. However, HDL cholesterol maturation is impeded due to LCAT deficiency, so that apoprotein (Apo) A-1 level decreases. Furthermore, the release of intracellular cholesterol is limited due to the upregulation of the acylCoA cholesterol acyltransferase, and the HDL cholesterol ability to decrease formed oxidized LDL cholesterol levels is restricted due topara-oxonase and glutathione peroxidase deficiency in CKD patients[12]. HDL cholesterol carries the peripheral cholesterol to the liver, which is called reverse cholesterol transport and prevents the cholesterol from being taken up by the macrophages and formation of foamy cells[16]. ApoA-1 deficiency can impair the binding of HDL to ATP binding cassette transporter A-1 and this impaired step causes a dysfunction in free cholesterol efflux from macrophages to HDL cholesterol[16]. The accumulation of free cholesterol in macrophages produces foamy cells in vessels and causes formation of atherosclerotic plaques.

Lipoprotein Abnormality in Nephrotic Syndrome

Dysregulated lipid metabolism leading to dyslipidemia is an often under-recognized, but a nearly universal, complication of persistent nephrotic syndrome[17]. Lipid and lipoprotein metabolism is altered in nephrotic syndrome even without CKD, and the extent of altered lipid metabolism in nephrotic syndrome correlates with the magnitude of proteinuria[18]. The extent of altered lipid metabolism in nephrotic syndrome correlates with the magnitude of proteinuria. In nephrotic syndrome, cholesterol, triglycerides, and Apo B-containing lipoproteins (including VLDL, intermediate-density lipoprotein (IDL) and lipoprotein (a)) are elevated, whereas the concentra-tion of HDL cholesterol and the content of Apo A-I and Apo A-II apolipoproteins are very similar in healthy in-dividuals[18-19]. Thus, lipoprotein abnormalities, although are similar with CKD and nephritic syndrome, may also have some differences.

LDL Cholesterol, Intermediate Density Lipoprotein, and Very Low-Density Lipoprotein Cholesterol Dysfunctions in CKD

In patients with nephrotic syndrome, serum VLDL cholesterol, IDL cholesterol, and triglyceride levels are increased due to impaired urinary clearance, LCAT enzyme, and acquired hepatic

LDL receptor dysfunction[20]. Since hepatic lipase has an important function in the removal of the triglyceride content of the IDL cholesterol and conversion of IDL cholesterol to LDL cholesterol, hepatic lipase deficiency in nephrotic syndrome leads to increased serum levels of atherogenic IDL cholesterol and triglyceride enrichment of the LDL cholesterol[18] . Increased apoB100 levels due to impaired clearance and increased production also result in high LDL cholesterol levels in patients with nephrotic syndrome[18]. HDL cholesterol dysfunction with LDL receptor-related protein (LRP) deficiency increases the chylomicron remnant and IDL cholesterol levels and is another factor underlying the formation of small dense LDL (sdLDL) in CKD patients[12]. Although serum LDL cholesterol levels can be normal ranges, sdLDL level – a highly atherogenic subtype of LDL that can be easily oxidized – increases in serum as kidney function worsens[21]. There-fore, both the IDL cholesterol and sdLDL cholesterol can trigger the formation of atherosclerotic plaques even when LDL cholesterol levels are in normal range[21,22]. This also shows the importance of the analysis of detailed lipid profile in patients with CKD. Serum triglyceride is one of the most valuable lipid types altered in kidney diseases. Hypertriglyceridemia mostly occurs in early stages of CKD[22]. The most dramatic increase in triglyceride levels usually occurs in patients with nephrotic syndrome, but it also increases in other kidney diseases due to both abnormal production and reduced catabolism of triglycerides[22]. Reduced catabolism of triglycerides occurs due to the inactivation of the lipoprotein lipase (LPL). Increased apolipoprotein C-III/C-II ratio precipitates the inactivation of the LPL, since apolipoprotein C-III is an inactivator for LPL, whereas apolipoprotein C-II is an activator for LPL[23]. Chylomicron remnants and IDL cholesterol accumulate because of the decrease in the catabolism of triglycerides[22]. Low serum cholesterol levels are associated with high mortality in CKD patients due to cardiovascular complications, which can be explained only by increased systemic inflammation and oxidative stress, which may increase oxidized LDL cholesterol level without an increase in LDL cholesterol level in CKD patients[12,22]. Therefore, lipid profile, especially LDL cholesterol levels with detailed analysis is particularly important to determine the patients' risk for atherosclerosis and other cardio-vascular complications due to the capability of the oxidized saddle for accumulation on vessel walls. Cholesterol levels also have an inverse relationship with mortality and needs to be followed up carefully (and triglyceride levels could be used as a biomarker in nephrotic syndrome).

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