REVIEW ARTICLE

DYSLIPIDEMIA IN CHRONIC KIDNEY DISEASE

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ABSTRACT

Globally chronic kidney (CKD) disease is one of the major health problems. Global prevalence of CKD is 8−16%. Prevalence of chronic kidney disease in Bangladesh is 26%. Patients with chronic kidney disease (CKD) exhibit significant alterations in lipoprotein metabolism. In this review different lipid parameters are shown from different studies and the pathogenesis of CKD induced dyslipidemia is discussed.

Key words: Chronic kidney disease, Renal failure, Dyslipidemia, Hypertriglyceridemia, Hemodialysis, Peritoneal dialysis

Introduction

The incidence and prevalence of chronic kidney disease (CKD) are increasing worldwide and are associated with poor outcomes.The global prevalence of CKD is 8−16% whereas in Bangladesh it is 26%[1,2]. It is well known that patients with impaired renal function exhibit significant alterations in lipoprotein metabolism, which is their most advanced form may result in the development of severe dyslipidemia. Among human studies relating dyslipidemia to renal outcome, one study found that higher total cholesterol (TC), higher non-HDL cholesterol, lower HDL-cholesterol and higher triglyceride (TG) were significantly associated with an increased risk of developing renal dysfunction[3]. According to the Kidney Disease Outcomes Quality Initiative (K/DOQI), CKD is defined as kidney damage or a decreased kidney glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2 for at least 3 months[4,5]. In the general population, high total cholesterol (TC), high low-density lipoprotein (LDL) cholesterol, high triglyceride, and low high-density lipoprotein (HDL) cholesterol are all well-established risk factors for CVD development. However, CKD, with both dialysis and transplantation, is associated with specific qualitative and quantitative lipid abnormalities, resulting in specific dyslipidemia (Table I)[6,7].

Dyslipidemia is a common complication of CKD and lipoprotein metabolism alteration and is associated with the decline in GFR; hence, lipid profile depends on the level of kidney function and the degree of proteinuria (Table II).

A study has been made to find out the association of dyslipidemia in patients of CKD and to correlate findings of dyslipidemia with severity of the disease(Table III)[9].

Table I: Trend of changes in lipids, lipoproteins and apo-proteins in various stages of CKD[7]

Parameter	CKD 1-5	Nephrotic Syndrome	Hemodialysis	Peritoneal Dialysis
Total Cholesterol	↗	↑↑	↔↓	↑
LDL - Cholesterol	↗	↑↑	↔↓	↑
HDL - Cholesterol	↓	↓	↓	↓
Non HDL Cholesterol	↗	↑↑	↔↓	↑
Triglyceride	↗	↑↑	↑	↑
Lp(a)	↗	↑↑	↑	↑↑
Apo -I	↘	↗	↓	↓
Apo - IV	↗	↑↘	↑	↑
Apo B	↗	↑↑	↔↓	↑

Notes: *Non-HDL cholesterol includes cholesterol in LDL, VLDL, IDL, and chylomicron and its remnant. Explanation of arrows: normal (↔), increased (↑), markedly increased (↑↑), and decreased (↓) plasma levels compared with non-uremic individuals; increasing (↗) and decreasing (↘) plasma levels with decreasing GFR. Abbreviations: apoA-IV, apolipoprotein A-IV; CKD, chronic kidney disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; Lp (a), lipoprotein (a); ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; VLDL, very low-density lipoprotein; IDL, intermediate-density lipoprotein; GFR, glomerular filtration rate.*

(Copyright ©2007 American Society of Nephrology. Kwan BCH, Kronenberg F, Beddhu S, Cheung AK. Lipoprotein Metabolism and lipid management in chronic kidney disease. J Am Soc Nephrol. 2007; 18:1246–1261.)

Table II: Lipid abnormalities by target population (approximate percentage)[8]

		Total Cholesterol >240 mg/dL	LDL Cholesterol >130 mg/dL	HDL Cholesterol <35 mg/dL	Triglyceride >200 mg/dL
General population		20	40	15	15
CKD Stage 1– 4	With Nephrotic syndrome*	90	85	50	60
	Without Nephrotic syndrome*	30	10	35	40
CKD Stage-5	Hemodialysis	20	30	50	45
	Peritoneal dialysis	25	45	20	50

**Nephrotic syndrome was defined as >3 g of total protein excretion in 24 h.*

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Abbreviations: CKD, chronic kidney disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table III: Characteristics of study patients according to CKD stage[9]

	eGFR (mL/min per 1.73 m^2)					
	<30	30–59	60–90	>90	Total patient	p value
Age	49.18 ± 13.81	47.06 ± 11.68	48.56 ± 11.59	42.54 ± 11.53	47.62 ± 12.67	0.430
BMI	20.44 ± 2.49	22.88 ± 2.40	21.65 ± 2.39	20.76 ± 3.29	21.21 ± 2.72	0.014
Creatinine	7.59 ± 3.66	1.56 ± 0.28	1.00 ± 0.17	0.81 ± 0.11	4.11 ± 4.06	<o.ooo1
Total Cholesterol	224.64 ± 36.13	174.76 ± 44.78	184.18 ± 58.34	176.92 ± 48.13	199.75 ± 49.52	<o.ooo1
LDL–C	147.34 ± 38.67	103.47 ± 28.16	101.51 ± 36.21	100.86 ± 19.09	122.83 ±40.37	<o.ooo1
HDL–C	39.41 ± 3.82	37.41 ± 4.74	37.00 ± 4.27	41.23 ± 5.80	38.83 ± 4.58	<0.036
TG	252.92 ± 67.78	215.32 ± 51.86	204.76 ± 75.44	204.37 ± 55.95	228.91 ± 67.5	<0.022

The mean value of total cholesterol was found to be 224.64 ± 36.13 in stages 4 & 5, 174.76 ± 44.78 in stage 3, 184.18 ± 58.34 in stage 2 and 176.92 ± 48.13 in stage 1 of CKD. The mean value of total cholesterol in total patients was 199.75 ± 49.52, which is statistically highly significant (p value <0.0001). The mean value of serum triglyceride in total patients of CKD is 228.91 ± 67.55 across all stages and is statistically highly significant (p value< 0.022). The mean LDL-C in total patients of all stages of CKD was 122.83 ±40.37 which is statistically highly significant (p value <0.0001). The mean HDL-C in total patients was 38.83 ± 4.58 which is also statistically highly significant (p value <0.036)

Abbreviations: eGFR, estimated glomerular filtration rate, BMI, body mass index, LDL, low-density lipoprotein; HDL, high-density lipoprotein, TG, Triglyceride

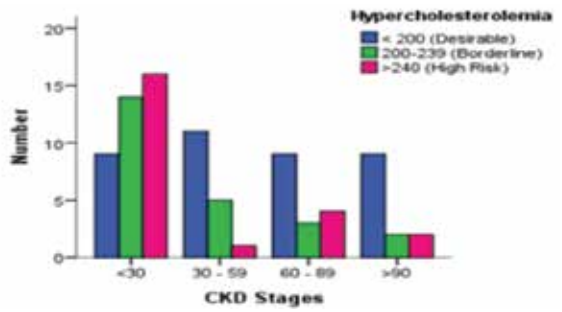

Fig 1. Serum cholesterol level among patients in different stages of CKD[9]

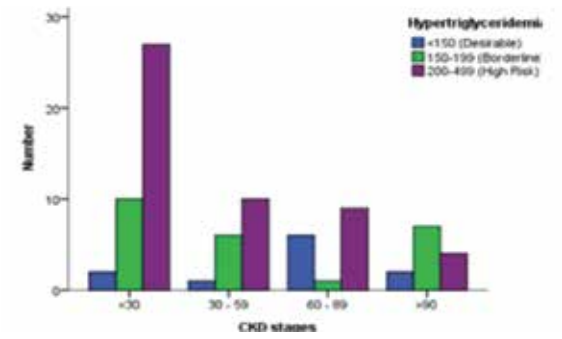

Fig 2. Serum triglyceride level among patients in different stages of CKD[9]

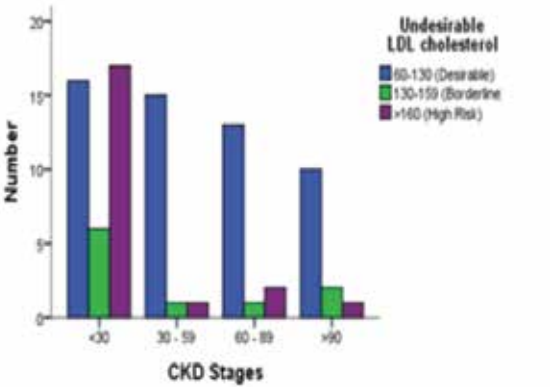

Fig 3. Serum undesirable LDL-C level among patients in different stages of CKD[9]

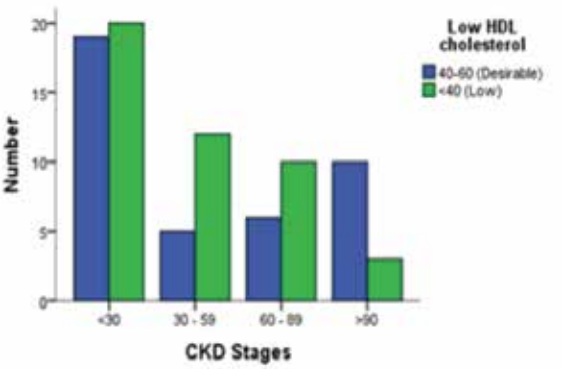

Fig 4. Serum low HDL-C level among patients in different stages of CKD[9]

Pathophysiology of CKD–induced dyslipidemia[10]

CKD is characterized by specific metabolic abnormalities of plasma lipoproteins. These abnormalities involve all lipoprotein classes and shows variations depending on the degree of renal impairment, the etiology of primary disease, the presence of nephrotic syndrome (NS) and the method of dialysis [hemodialysis (HD) or peritoneal dialysis (PD)] for patients undergoing renal replacement therapy.

Pathogenesis of dyslipidemia

Dyslipidemia in CKD (G1–4)[8]

Patients with non-dialysis-dependent CKD and without nephrotic syndrome have low HDL and high triglycerides and normal or even low TC

and LDL cholesterol, but more atherogenic profile is hidden behind this spectrum. This profile includes increased apolipoprotein B (apoB), lipoprotein (a) (Lp a), intermediate- and very-low-density lipoprotein (IDL cholesterol, VLDL cholesterol; "remnant particles"), and small dense LDL particles. Also, in patients with more severe CKD, LDL, and HDL particles are often modified by the oxidative process, that leads into the formation of small lipoproteins and increased formation of oxidized LDL[11].

Patients with CKD usually have hypertriglyceridemia due to an increased concentration of triglyceride-rich lipoproteins (VLDL, chylomicrons, and their remnants). Hypertriglyceridemia occurs because of both the delayed catabolism and the increased hepatic production of triglyceride-rich lipoproteins. Delayed catabolism is the most prevalent mechanism responsible for an elevated triglyceride-rich lipoprotein concentration in CKD patients and occurs probably because of a decreased activity of hepatic triglyceride lipase and peripheral lipoprotein lipase. Also, the presence of lipase inhibitors may contribute to delayed triglyceride-rich lipoprotein catabolism. Apolipoprotein C-III (apoC-III) is a direct lipoprotein lipase inhibitor, and its levels are elevated in uremia which further contributes to hypertriglyceridemia. It is also possible that secondary hyperparathyroidism plays an additional role in triglyceride-rich lipoprotein catabolism impairment, resulting in raised plasma triglyceride concentrations associated with CKD. Besides low catabolic activity, increased hepatic production of triglyceride-rich lipoproteins contributes to increased levels of triglycerides in CKD patients. Insulin resistance, often associated with CKD, seems to be responsible for a hepatic VLDL overproduction[10].

Although LDL is not usually elevated in patients with CKD, LDL particles tend to be smaller, denser, and more atherogenic in their form. Oxidized LDL and IDL, which are considered to be highly atherogenic, are increased. Various studies have shown increased levels of small dense LDL in non-dialysis-dependent CKD patients in comparison with the healthy controls and have indicated small dense LDL as a risk factor for CVD development. Because of the significantly modified lipid subfraction turnover, residence time of lipoproteins in the circulation is prolonged. Thus, lipoproteins are at risk of post-ribosomal modification which includes glycation, oxidation, and carbamylation. These modified lipoproteins have reduced affinity for the classic LDL receptors and are taken up by the scavenger receptors, increased in uremia, on the surface of the macrophages. High affinity for macrophages results in the accumulation of cholesterol and the formation of foam cells in the vascular walls, finally resulting in the development of accelerated atherosclerotic plaques[7]. Lp (a) is an LDL-like lipoprotein which contains covalently bounded apolipoprotein (a) (apo (a)) that distinguishes it from the LDL. Various studies, in both healthy individuals and CKD patients, have shown strong and negative association between apo (a) isoform size and the serum Lp (a) levels. Thus, serum Lp (a) levels depend on apo (a) isoform size and are highly genetically determined by the apo (a) gene. As mentioned earlier, individuals with predominantly low molecular weight apo (a) isoforms have on average, higher Lp (a) plasma concentrations. In patients with CKD, Lp (a) concentration is as well influenced by GFR; hence, patients with large apo (a) isoforms, and not those with small isoforms, tend to have increased Lp (a) levels early in CKD stage 1, even before GFR is significantly decreased.

Patients with CKD have decreased HDL in comparison with individuals with preserved kidney function. This state places them at higher risk for atherosclerosis development, especially considering the results of various epidemiological

studies that presented HDL as a negative risk factor for atherosclerosis. The main function of HDL is reverse cholesterol transport, a process that includes cholesterol transport from the arterial wall to the liver for further excretion. This together with HDL-mediated inhibition of inflammation, platelet adhesion, and LDL oxidation serves in normal circumstances against atherosclerosis, but in CKD patients, protective function of HDL is diminished because of several mechanisms. First, patients who have impaired kidney function often have decreased levels of apolipoproteins AI and AII, the main components of HDL. Furthermore, in CKD patients, the activity of lecithin–cholesterol acyltransferase, the enzyme important for the esterification of free cholesterol in HDL, is impaired. On the other hand, the activity of cholesterol ester transfer protein (CETP), which supports the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins, is increased. All these processes are responsible for the decreased serum level of HDL. Besides its impaired function as the cholesterol carrier, patients with CKD have reduced activity of the HDL associated enzymes, such as paraoxonase, which may be responsible for impaired antioxidative and anti-inflammatory function of HDL. All these factors can contribute to accelerated atherogenesis in this specific population[7,10,12].

Dyslipidemia in nephrotic syndrome

There is an important difference in lipid profile between patients with and without nephrotic syndrome. In nephrotic syndrome, lipid profile is significantly atherogenic with increased TC and LDL, which is crucial for the diagnosis of nephrotic syndrome. In patients with CKD stage 1–4 with nephrotic syndrome, hypercholesterolemia occurs because LDL production is increased and catabolism is decreased. LDL clearance is slower because of the decreased function of hepatic LDL receptors. The mechanism of this insufficiency of receptor function is not completely known; however, studies on experimental animals have shown that an ineffective translation and/or an increased LDL-receptor protein turnover could be the main processes behind these changes. Also, an inverse correlation between serum albumin levels and TC and LDL levels is presented[10,11]. Besides hypercholesterolemia, hypertriglyceridemia often occurs in nephrotic syndrome, and it seems to be caused mostly by the decreased catabolism of triglycerides. Delipidation from triglyceride-rich lipoproteins, which is mediated by lipoprotein lipase and hepatic lipase, is impaired resulting in the accumulation of VLDL and remnant lipoproteins such as IDL. Impaired function of these enzymes may be caused by the loss of their activator cofactor in the urine. In addition, it seems that expression of these enzyme genes is downregulated in patients with nephrotic syndrome[10]. HDL levels are normal or even low in patients with nephrotic range proteinuria because of the mechanism similar to one described in the pathogenesis of the CKD without proteinuria. CKD patients with nephrotic range proteinuria have severely increased Lp (a) levels regardless of their apo (a) isoforms. This is probably due to heavy protein loss and consequent increased production of Lp (a) in the liver[10,13].

Dyslipidemia in patients on dialysis - HD

CKD patients who are on HD usually have similar lipid profile to those with non-dialysis-dependent CKD. TC and LDL levels are generally relatively normal, triglyceride levels are elevated, and HDL is low. In these patients, LDL is rarely markedly elevated. However, the K/DOQI guideline on dyslipidemias in CKD patients has reported that 55.7% of patients on HD have LDL levels >100 mg/dL. These quantitative lipid abnormalities, as

well as those qualitative hidden behind, play a role in atherosclerosis and cardiovascular mortality in HD patients. Approximately 50% of ESRD patients die because of CVD, and cardiovascular mortality is 30 times higher in dialysis patients[13-15]. HD patients have moderately increased apoB and significantly increased apoC-III. Triglyceride-rich apoB contain lipoproteins (VLDL and IDL) are elevated because of decreased activities of lipoprotein lipase and hepatic lipase, resulting in hypertriglyceridemia. The same mechanism occurs in non-dialysis-dependent CKD patients. Besides this mechanism, some factors related to the process of HD itself may contribute to the increase of triglyceride levels in HD patients. It is possible that low molecular weight heparin used for anticoagulation in this patients group may potentate triglyceride elevation. It is believed that heparin releases lipoprotein lipase from the endothelial surface; hence, its prolonged use may cause depletion in lipoprotein lipase and thus reduce triglyceride-rich lipoproteins catabolism. However, controversy surrounds the association between heparin use and HD-induced dyslipidemia because some studies have reported and others have not revealed any such association. Also, it is not so clear whether the type of the membrane used in HD has any influence on serum triglyceride levels. Some studies have shown the use of high flux polysulfone or cellulose triacetate membranes to be associated with a significant reduction in serum triglyceride levels. The reason for this reduction may be due to increased apoC-II/C-III ratio, resulting in increased lipoprotein lipase activity and improvement in lipolysis of the intravascular triglyceriderich lipoproteins[10,13]. HD patients also have increased plasma Lp (a), which is isoform specific. Malnutrition and inflammation are usually present in this group of patients and together with the impaired clearance of apo (a) may be responsible for these alterations[10]. In HD patients, HDL levels are reduced. A study of 183 patients treated with HD15 without cholesterol medications has shown increased plasma levels of CETP in approximately one-third of the patients, which can be one of the factors responsible for these changes[10]. In addition, HDL levels may be affected by the type of membrane or dialysate that is used in HD procedure. Thus, the use of high-flux membrane in comparison with low-flux membrane can increase HDL levels. Also, the use of bicarbonate dialysate results in elevated HDL levels more often than the use of acetate dialysate[10]. As mentioned earlier, behind the absence of hyperlipidemia, more atherogenic lipid profile in HD patients is usually presented. Shoji et al[16] have compared 210 chronic HD patients and 223 age- and sex-matched healthy controls. The patients treated with HD had lower TC and higher triglyceride than the controls. Also, HD patients had higher VLDL and IDL but lower HDL and LDL in comparison with the controls. Despite lower mean LDL levels, HD patients had significantly decreased cholesterol/ triglyceride ratio, reflecting the domination of more atherogenic small dense LDL. Finally, other studies have also shown that HD patients have elevated Lp (a) and oxidized LDL forms even in cases in which LDL levels are mainly normal[8,13]. Various clinical trials have shown reduction of LDL levels to be associated with CVD mortality reduction in the general population. However, it is obvious that in HD patients association between dyslipidemia and CVD mortality is not that simple as in the general population. Observational studies have noted the term “reverse epidemiology” between TC levels and risk of all-cause mortality. In other words, lower TC levels are associated with a higher mortality rate. Malnutrition/ inflammation could be responsible for these observations[13,16].

One 10-year prospective study followed 1,167 Japanese HD patients[17]. This study has shown low TC to be independently associated with higher C-reactive protein (CRP) and mortality in patients with low albumin[10]. Another prospective study followed 823 dialyzed patients for a median of 2.4 years and classified them due to presence or absence of inflammation and/or malnutrition at baseline. Inflammation and/or malnutrition were defined by albumin serum levels, CRP or interleukin-6. An increase in baseline TC of 1 mmol/L was associated with a reduction of all-cause mortality in the presence of inflammation/malnutrition.[10] These studies results reveal that low serum TC levels are associated with increased mortality in HD patients, suggesting hypocholesterolemia as a surrogate for malnutrition or inflammation[13,16].

Dyslipidemia in patients on dialysis - PD

Patients on PD have some form of "uremic dyslipidemia" just like those on HD, but their lipid profile is more atherogenic in nature with more altered dyslipidemia when compared with those on HD[6,10,13]. PD patients show increased levels of triglyceride, apoB containing VLDL and IDL, TC and LDL, as well as small dense LDL and Lp (a) while HDL levels are low. These differences may be attributed to PD per se, but may also be associated with the selection of dialytic modality. One cross sectional study compared 31 patients on continuous ambulatory peritoneal dialysis (CAPD), 30 patients treated with HD, and 27 healthy controls. Patients on CAPD had significantly higher mean TC (6.8 vs 5.1 mmol/L, $p < 0.001$), LDL (4.6 vs 3.2 mmol/L, $p < 0.001$), VLDL (1 vs 0.7 mmol/L, $p < 0.05$), and triglyceride (2.3 vs 1.5 mmol/L, $p < 0.01$) than patients on HD. Also, there was no significant difference in HDL (1.1 vs 1.3 mmol/L in HD, p=NS) in patients on CAPD[13].

Hypertriglyceridemia is predominantly present in patients on PD. The exact mechanism is not completely understood, but it is believed that a significant absorption of glucose from the dialysis fluid may induce hepatic lipoprotein synthesis or may cause an increase in insulin levels resulting in the enhanced hepatic VLDL synthesis and secretion. Recent studies have shown an improvement in lipid profile when the overnight dwell has been switched from a dextrose-based solution to icodextrin, because of the reduced glucose overload[10,13]. Higher TC, LDL and small dense LDL can be explained by several mechanisms similar to those in nephrotic syndrome and those related to the protein loss. In PD patients, great amounts of plasma proteins are lost into the peritoneal dialysate, which stimulates the liver to produce albumin and other proteins, including cholesterol-enriched lipoproteins in an attempt to compensate for the protein loss. Also, various lipoproteins, such as HDL, are lost through the peritoneal cavity which may contribute to its decreased levels[10,13]. Compared to HD, patients on PD have increased Lp (a) plasma levels which are not isoform specific. Also, Lp (a) levels are usually more elevated in patients on PD than those on HD[13]. This may be due to enhanced Lp (a) synthesis in the liver as a result of the increased protein loss[10]. In their large multicenter cross-sectional study, Kronenberg et al[18] have shown that 34% of HD patients and 42% of CAPD patients had serum Lp (a) greater than the 75th percentile of the healthy control group (>0.92 mmol/L, $p < 0.005$ for HD vs PD)[13].

Conclusions

Dyslipidemia is often present in patients with renal impairment and differs quantitatively and qualitatively in non-dialyses-dependent patients, patients with nephrotic range proteinuria, ESRD patients, and renal transplant recipients. It can affect kidney function and significantly increase the risk of CVD development. Thus, diagnosis and management of these patients are important to potentially improve their clinical outcome.

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