



COMPARISON OF DIURNAL INDEX AND LIPID PARAMETERS FROM NORMAL INDIVIDUALS AND PATIENTS OF DIABETIS WITH CHRONIC KIDNEY DISEASE

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Abstract

Chronic kidney disease (CKD) heightens the risk of cardiovascular complications and often linked with a non-dipping blood pressure (BP) pattern. We assessed 24 hour ambulatory blood pressure, and lipid profile of diabetic patients suffering from CKD. To determine the frequency of associated risk factors in diabetic CKD patients, A cross-sectional research design was employed at ERA's Lucknow Medical College and Hospital for this study. We recruited 184 patients with diabetic CKD Patients (mean age, 60.9±12.0 years). After adjusting for age and sex, hypertension and lipid profile showed a significant association with CKD. Levels of triglycerides (TG), very-low-density lipoprotein (VLDL), total cholesterol, and low-density lipoprotein (LDL) were elevated in CKD cases in comparison to normal individuals, whereas high-density lipoprotein (HDL) and estimated glomerular filtration rate (eGFR) were notably lower in the cases. On analysis of data, HDL level was decreased in CKD patients and correlation was statistically significant ($p<0.001$). LDL level was found to be higher in cases than in CKD patients, this correlation was also significant with p value less than 0.001. In the cases total cholesterol level was found to be elevated that is in CKD patients and the association was scientifically significant ($p<0.001$). In cases the level of triglyceride was also more that are in CKD patients and the association was significantly correlated ($p<0.001$). In addition, Dipping was maximum in control groups (70.7%) while non-dipping was maximum in the case group (75%). A significant association of dipping was found with the case ($p<0.001$).

Keywords: CKD, Dyslipidemia, CVD, Ambulatory blood pressure monitoring.

Introduction

Chronic kidney disease (CKD) has now become a major worldwide health concern, contributing extensively to increased morbidity and mortality. Alterations in lipid profile are closely connected with the advancement of CKD, ultimately elevating the chances of cardiovascular problems and death [1] The functional unit of the kidney which is known as nephron, consists of Bowman's

capsule and glomerulus and plays a vital role in eliminating metabolic waste products from the human body.[2-4] Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF), chronic kidney disease (CKD) is defined as either structural renal injury or a reduced glomerular filtration rate (GFR), with a GFR level below 15 ml/min.[5,6] Different types of etiological profiles which is involved in pathogenesis which lead to the progression of a uremic condition in CKD.[7,8] Diabetic kidney disease (DKD) progresses in about 40% of diabetic patients and is a primary cause of global prevalence of CKD .[9] Diabetic kidney disease, also known as chronic kidney disease caused by diabetes, occurs in both type 1 and type 2 diabetes. It is characterized by persistently elevated albuminuria levels exceeding 300 mg per 24 hours or a urinary albumin-to-creatinine ratio (ACR) greater than 300 mg/g, accompanied by diabetic retinopathy and no clinical evidence of other kidney diseases.[10] The National Cholesterol Education Program (NCEP) defines dyslipidemia as the presence of one or more lipid abnormalities, including total cholesterol (TC) levels ≥ 200 mg/dl, triglycerides (TG) ≥ 150 mg/dl, low HDL-C levels (< 40 mg/dl in men and < 50 mg/dl in women), elevated LDL-C ≥ 130 mg/dl, and a total cholesterol to HDL-C ratio of ≥ 4.5 . [11]. Healthy lipid and lipoprotein levels in the blood are essential for maintaining the right amount of cholesterol within cells and protecting against conditions like atherosclerosis, kidney disease and other complications.[12] In individuals with chronic kidney disease (CKD), end-stage renal disease (ESRD) causes significant disturbances in the regulation of key enzymes and receptors responsible for lipoprotein metabolism, particularly affecting high-density lipoprotein cholesterol (HDL-C) and triglyceride-rich lipoproteins [13,14] Key changes observed include a decrease in the activity of enzymes like lecithin cholesterol acyltransferase (LCAT), lipoprotein lipase (LPL), hepatic lipase, acyl-CoA diacylglycerol acyltransferase (DGAT), and LDL receptor-related protein (LRP). In contrast, there is an increase in the activity of cholesterol ester transfer protein (CETP) and acyl-CoA cholesterol acyltransferase (ACAT). Studies have demonstrated that non-diabetic patients with chronic kidney disease undergoing hemodialysis often suffer from significant dyslipidemia [15-17]

According to Rifai et al., patients with chronic kidney disease (CKD) undergoing hemodialysis exhibited higher levels of triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and total cholesterol to HDL-C ratio, along with decreased levels of high-density lipoprotein cholesterol (HDL-C), compared to healthy controls [15] Mekki et al. observed that both intermittent and long-term dialysis were ineffective in correcting the dyslipidemia associated with chronic renal failure (CRF).[16] An Indian study reported the presence of hypertriglyceridemia, elevated levels of very low-density lipoprotein cholesterol (VLDL-C) and lipoprotein(a), along with reduced high-density lipoprotein cholesterol (HDL-C) levels.[17] In patients with chronic kidney disease (CKD) undergoing hemodialysis, increased levels of reactive oxygen species (ROS) and reduced activity of the antioxidant enzyme superoxide dismutase (SOD) contribute to heightened lipid peroxidation and oxidative stress.[18] Ashish et al found significantly higher dyslipidemia in peritoneal dialysis (PD) than in hemodialysis.[19] Herzog et al. reported poor survival outcomes following acute myocardial infarction (MI), while Karnik et al. documented a higher incidence of cardiac arrest and sudden cardiac death among CKD patients undergoing hemodialysis .[20,21] Ganta et al. reported that dyslipidemia in chronic kidney disease (CKD) contributes to the accelerated progression of cardiovascular disease and is associated with increased mortality.[22] In chronic kidney disease (CKD), both traditional and nontraditional risk factors, along with hypertriglyceridemia as an independent risk factor, are strong predictors of coronary heart disease.[23,24] Several studies recommend early initiation of statin therapy to manage dyslipidemia in CKD patients, aiming to reduce cardiovascular mortality.[25-27] Rhee et al. emphasized the importance of adhering to guidelines and conducting a thorough risk assessment prior to initiating treatment for dyslipidemia .[28] Multiple studies have identified significant dyslipidemia as a major risk factor for cardiovascular disease (CVD) in non-diabetic chronic kidney disease (CKD) patients undergoing hemodialysis and conservative therapy. Our study aims to examine dyslipidemia in both diabetic kidney disease (DKD) and non-diabetic CKD patients on hemodialysis, with a particular focus on

its higher incidence and prevalence, especially in DKD

Methodology

This cross-sectional study was conducted on both inpatient (IPD) and outpatient (OPD) patients in collaboration with the Department of Physiology and the Department of Medicine at Era's Lucknow Medical College and Hospital, Lucknow

Distribution of Subjects

In this study total of 184 patients in the age group of 20 to 70 years of both gender were selected and made two groups ,each having 92 patients. One group had 92 individuals with normal kidney function (control) the second group had 92 diabetic patients with chronic kidney Disease (case).

Sample collection

Appropriate and applying the correct technique blood samples were collected from the patients for lipid profile estimation and blood sugar analysis. Samples were collected from both cases (CKD) and in controls (normal kidney function). We had taken consent from all the patients who were enrolled in this study. All the participants were clinically evaluated and their clinical and medical history was recorded on pre-designed proforma. Blood samples of 6 ml (1.5 ml EDTA,1.5 ml fluoride,3 ml plain) were drawn from the antecubital vein between 8 am to 9 am after an overnight fast. Triglycerides and Total Cholesterol and HDL, determined by enzymatic method. Hexokinase method was used to measure fasting glucose All diagnostic tests were performed in the laboratory of Era's Lucknow Medical College and Hospital, Lucknow. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI creatinine equation (2009)

$$eGFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age}$$

❖ Multiply by 1.018 for women and by 1.159 for African ancestry

ABP monitoring:

Twenty four hour ABPM was completed with an oscillometric device (Meditech Ambulatory Blood Pressure Monitor -ABPM-05) with a cuff of appropriate size based on the arm circumference and applied to the non-dominant arm of the patient who visited medicine cardiology OPD and IPD of Era Medical College, Era University, Lucknow.

During ACTIVE TIME (06:00 AM–10:00 PM), measurements were taken in 15-minutes intervals. During the PASSIVE TIME (10PM:00–06:00 AM), measurements were taken in 30- minute intervals.

Results:

Table1: Distribution of Subjects according to Age & Sex (N=184)

Variable		Control = 92		Case =92		Total =184		Chi sq	P value
Age		No	%	No	%	No	%	2.35	0.672
	20-29	12	13.0%	9	9.8%	21	11.4%		
	yr.								
	30-39	7	7.6%	4	4.3%	11	6.0%		
	yr.								
	40-49	17	18.5%	23	25.0%	40	21.7%		
	yr.								
	50-59	44	47.8%	42	45.7%	86	46.7%		
	yr.								
	>6 0 years	12	13.0%	14	15.2%	26	14.1%		
Sex	Male	64	69.6%	66	71.7%	130	70.7%	0.11	0.746
	Female	28	30.4%	26	28.3%	54	29.3%		

The distribution of age showed that the subjects of the age range 50-59 years were in majority (46.7%) followed by the age range 40-49 years (21.7%). Further males were in majority (70.7%) while females contributed only 29.3% in the study. There was no statistically significant difference in the gender distribution between both the group, case and control groups ($p > 0.05$)

Table 2: Descriptive summary of subjects according to body mass index (N=184)

Group		Mean \pm SD	t-value	p-value
Body mass index	Case	21.32 \pm 3.77	-9.42	<0.001
	Control	26.27 \pm 3.35		

The mean body mass index of the case group was 21.32 \pm 3.77 while in the control group it was 26.27 \pm 3.35. Between both the groups, a statistically significant difference in mean Body Mass Index was discovered ($p < 0.001$).

Table 3: Intergroup Comparison of lipid parameters (N=184).

Parameter	Group	Mean \pm SD	t-value	p-value
HDL	Case	23.00 \pm 10.54	-16.28	<0.001
	Control	65.24 \pm 22.54		
LDL	Case	148.73 \pm 22.75	11.28	<0.001
	Control	117.13 \pm 14.12		
Cholesterol	Case	187.75 \pm 37.76	3.36	0.001
	Control	169.82 \pm 34.53		
VLDL	Case	48.66 \pm 19.64	3.95	<0.001
	Control	38.99 \pm 12.81		
TG	Case	214.41 \pm 81.29	8.06	<0.001
	Control	136.71 \pm 44.06		

Very-low-density lipoprotein (VLDL), Low-density lipoprotein (LDL), Triglycerides (TG) and Cholesterol had raised levels in cases as compared to control, while high-density lipoprotein (HDL) and Estimated glomerular filtration rate (EGFR) had a lower level in cases compared to control. On analysis of data, HDL level was decreased in CKD patients and correlation was statistically significant ($p < 0.001$). LDL level was found to be more in cases than in control group, this correlation was also statistically significant ($p < 0.001$).

It was also observed that total cholesterol level was more in the case that is in control group patients and the association was statistically significant ($p < 0.001$). The triglyceride level was also more in case group and the association was significantly correlated ($p < 0.001$).

Table 4: Association of Diurnal index with case and control group (N=184)

Diurnal index	Group				Total		Chi sq	P value
	Total							
	Control		Case					
	No	%	No	%	No	%	87.37	<0.001
Extreme dipping	19	20.7%	0	0.0%	19	10.3%		
Dipping	65	70.7%	23	25.0%	88	47.8%		
Nondipping	08	8.7%	69	75.0%	77	41.8%		
Reverse dipping	0	0.0%	0	0.0%	0	0.0%		
Total	92	100.0%	92	100.0%	184	100.0%		

After analyzing the result it was seen that Dipping was maximum in control groups (70.7%) while non-dipping was maximum in the case group (75%). A significant association of dipping was found

with the case ($p < 0.001$).

Discussion

Individuals with diabetes commonly experience dyslipidemia, which is typically characterized by an increase in small, dense low-density lipoprotein (LDL) particles, reduced levels of high-density lipoprotein cholesterol (HDL-C), elevated fasting and postprandial triglyceride levels, and higher concentrations of apolipoprotein B (ApoB). [18-20]. These all contribute significantly to atherosclerosis and are causes of cardiovascular disease. Patients with CKD brought on by problems in lipid metabolism are found to have a higher prevalence of dyslipidemia. A separate predictor of cardiac disease and death risk is impaired renal function. [21]. According to the World Health Organization Multinational Study of Vascular Disease in Diabetes, both elevated serum cholesterol levels and proteinuria were recognized as important risk factors for fatal and non-fatal stroke, myocardial infarction, and cardiovascular disease-related mortality [22].

The atherogenic lipoprotein changes associated with kidney failure may contribute to a heightened risk of cardiovascular disease in individuals with diabetic nephropathy. Dyslipidemia not only has detrimental effects on the cardiovascular system but also accelerates the progression of diabetic nephropathy. In this study, lipid profiles and the diurnal index were compared between healthy individuals and patients with diabetic chronic kidney disease. Results obtained from the study inferred that Low-density lipoprotein (LDL) (148.73 ± 22.75), Cholesterol (187.75 ± 37.76), Very-low-density lipoprotein (VLDL) (48.66 ± 19.64), and Triglycerides (TG) (214.41 ± 81.29) had raised level in cases compared to control, while high-density lipoprotein (HDL) (23.00 ± 10.54) and Estimated glomerular filtration rate (EGFR) had a lower level in cases compared to control. On analysis of data, HDL level was decreased in CKD patients and correlation was statistically significant ($p < 0.001$). LDL level was found to be elevated in cases than in control group patients, this correlation was also statistically significant ($p < 0.001$). Total cholesterol levels were significantly higher in chronic kidney disease (CKD) patients compared to the control group, with a statistically significant association ($p < 0.001$). Similarly, triglyceride levels were elevated in the CKD patients, and this difference was also significantly correlated ($p < 0.001$). The reason that association may be observed is that, in diabetic with chronic kidney disease (CKD), dyslipidemia may be worsened by continuous hyperglycemia and insulin resistance [23]. Patients with CKD also show reduced endothelial cell LPL expression and activity. [24]. These anomalies may result in a delayed degradation of triglyceride-rich lipoproteins that include ApoB. Increased Apo-CIII levels, which are frequently reported in microalbuminuric patients, would impede LPL function and stifle the elimination of ApoB [25]. Chylomicron remnants and HDL can contain triglycerides and phospholipids that can be hydrolyzed by hepatic lipase [26]. In models of animal, chronic kidney disease (CKD) has been associated with reduced hepatic lipase expression and activity. [27]. In animals with CKD, messenger RNA for the VLDL-C receptor and LDL receptor-related protein is downregulated. [28]. The aggregation of atherogenic chylomicrons and very-low-density lipoprotein cholesterol (VLDL-C) remnants can result from any of these metabolic disturbances. In patients with chronic kidney disease (CKD), apolipoprotein AI (Apo-AI) concentrations are decreased due to reduced hepatic synthesis and increased catabolism. Additionally, decreased activity of lecithin-cholesterol acyltransferase (LCAT), impaired binding with the adenosine triphosphate-binding cassette transporter 1 (ABCA1), and low Apo-AI levels collectively contribute to diminished high-density lipoprotein (HDL) production [29]. LDL-C and total cholesterol readings are often within acceptable ranges. Additionally, several cross-sectional and prospective investigations utilizing 24-hour ABPM have shown that individuals with diabetic CKD had altered BP variability and circadian BP rhythms. **Rohatgi et al.** [29] demonstrated that patients with reduced kidney function (estimated glomerular filtration rate [$eGFR$] ≤ 60 ml/min/1.73 m²) exhibited significantly higher 24-hour systolic blood pressure (BP) variability compared to those with $eGFR > 60$ ml/min/1.73 m², indicating increased short-term BP variation. This study included 803 untreated hypertensive individuals, all physicians, with varying degrees of kidney function.

In a large study of 10,271 Spanish patients with hypertension, including those with and without diabetes or chronic kidney disease (CKD), Mojón et al. [30] found that individuals with CKD had higher systolic ambulatory blood pressure (ABP), especially at night, and lower diastolic BP compared to those without CKD (eGFR > 60 ml/min/1.73 m²). Additionally, as CKD severity increased, there was a higher prevalence of abnormal nocturnal blood pressure patterns, such as non-dipping and rising BP profiles [30] prospectively evaluated 47 patients with essential hypertension without renal disease, 28 matched healthy participants, 27 normotensives, and 41 hypertensive patients with stable CKD. Following a 24-month follow-up, both normotensive and hypertensive patients with CKD displayed changes in their 24-hour ABP with noticeably lessened nocturnal blood pressure reductions than their respective control groups. The same researchers expanded their findings to 48 hypertensive patients with chronic renal failure who were monitored for 3 years, and they discovered that the non-dippers experienced a higher rate of reduction in creatinine clearance than the dippers. [31] Moreover, the non-dipper group showed a greater increase in urine protein excretion compared to the dipper group, indicating that the non-dipping pattern may be associated with a faster progression of renal insufficiency in patients with renal hypertension. Omboni et al. [32] also found significant positive correlations between urinary albumin excretion rate and 24-hour, daytime, and nighttime ambulatory systolic blood pressure (SBP)

Kario et al.[33] have demonstrated that decreased diurnal BP variation is linked to a future impairment in renal function impartial of SBP load and other recognized danger variables. Weber et al.[34] also confirmed that 24-hour systolic blood pressure predicts both renal and cardiovascular outcomes. Further research showed that SBP levels during the day and at night could predict results for the kidneys and the cardiovascular system. Loss of nocturnal BP lowering, not morning BP spike, is related with a risk of chronic kidney disease, according to prospective research comprising 603 African. Further research showed that SBP levels during the day and at night could predict results for the kidneys and the cardiovascular system. Loss of nocturnal BP lowering, not morning BP spike, is associated with a risk of chronic kidney disease, according to prospective research comprising 603 African Americans who were enrolled in the Jackson Heart Study and had normal baseline renal function [34].

Conclusion:

Several studies have identified high-risk patients displaying abnormal blood pressure variability and disrupted circadian BP patterns, which are associated with target organ damage and poor renal outcomes in individuals with hypertension, including those with both diabetic and non-diabetic chronic kidney disease. Among these patterns, the most prominent is the diminished nocturnal blood pressure drop, commonly known as the non-dipping pattern, which has been closely linked to target organ damage. Another commonly observed abnormal ambulatory blood pressure pattern in patients with diabetic CKD is masked hypertension, a condition that often goes undetected during routine clinical assessments but is significantly associated with organ damage as well.

In this context, our assessment highlights the clinical importance of lipid profiling and ambulatory blood pressure monitoring in the thorough evaluation of patients with diabetic chronic kidney disease. These methods enhance the accuracy of diagnosing and classifying hypertension, assessing target organ damage, stratifying risk, predicting clinical outcomes, and monitoring treatment responses, particularly in a population where achieving optimal blood pressure control is a significant challenge

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