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Key Words

Hemodialysis, malondialdehyde, triglycerides and decreased

Corresponding Author

R. Felix Nitin,
Department of General Medicine
Sree Mookambika Institute of
Medical Sciences College
Kanyakumari, Tamil Nadu, India

Author Designation

¹Professor
²Junior Resident

Received: 15th February 2025

Accepted: 15th March 2025

Published: 21st May 2025

Citation: R.V. Mookambika and R. Felix Nitin, 2025. A Retrospective Study on Lipid Profile and Lipid Peroxidation in Chronic Kidney Disease, Focus- Ing on Hemodialysis. Res. J. Med. Sci., 19: 18-24, doi: 10.36478/makrjms.2025.4.18.24

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A Retrospective Study on Lipid Profile and Lipid Peroxidation in Chronic Kidney Disease, Focus- Ing on Hemodialysis

¹R.V. Mookambika and ²R. Felix Nitin

Department of General Medicine, Sree Mookambika Institute of Medical Sciences Kanyakumari, Tamil Nadu, India

Department of General Medicine Sree Mookambika Institute of Medical Sciences College Kanyakumari, Tamil Nadu, India

Abstract

This retrospective study aims to evaluate the alterations in lipid profile and the extent of lipid peroxidation in patients with chronic kidney disease (CKD), particularly those undergoing hemodialysis (HD) and to assess their potential contribution to increased cardiovascular risk. Data were collected retrospectively from 60 CKD patients undergoing hemodialysis. Parameters assessed included total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and lipid peroxidation markers such as malondialdehyde (MDA) and thiobarbituric acid reactive substances (TBARS). Statistical analyses were conducted to evaluate the correlation between lipid profile abnormalities and markers of oxidative stress. CKD patients undergoing HD exhibited dyslipidemia characterized by elevated triglycerides and decreased HDL levels. Lipid peroxidation markers, including MDA and TBARS, were significantly elevated and negatively correlated with glomerular filtration rate (GFR), suggesting increased oxidative stress. Additionally, antioxidant enzyme activity, particularly superoxide dismutase (SOD), was found to be reduced in these patients. No significant variation was noted in total antioxidant activity during HD. The study highlights that CKD patients on hemodialysis are prone to atherogenic lipid profiles and elevated oxidative stress. These findings underscore the importance of regular monitoring of lipid parameters and oxidative markers in HD patients to mitigate cardiovascular risk. The influence of factors such as dialysate composition and heparin usage on lipid metabolism warrants further investigation

INTRODUCTION

Chronic Kidney Disease (CKD) is a pervasive health issue affecting approximately 8%-16% of the global population, with its prevalence notably increasing among older adults^[1,2]. This progressive condition is characterized by the gradual loss of kidney function, leading to an array of complications, including cardiovascular disease, which remains the leading cause of mortality in CKD patients. A significant aspect of managing CKD involves understanding its impact on lipid metabolism, as dyslipidemia—a condition marked by abnormal lipid levels—is common among those undergoing hemodialysis (HD) treatment. This condition exacerbates the cardiovascular risks faced by CKD patients, necessitating a closer examination of lipid profiles and associated oxidative stress levels. Research has highlighted the crucial relationship between lipid profile abnormalities and lipid peroxidation in CKD patients undergoing HD. Dyslipidemia in this population is often characterized by increased triglycerides, elevated low-density lipoprotein (LDL) cholesterol and reduced high-density lipoprotein (HDL) cholesterol levels, which collectively contribute to atherogenic profiles and the progression of cardiovascular diseases^[3,4]. Additionally, the process of lipid peroxidation—an oxidative degradation of lipids—occurs at heightened rates in CKD, generating by-products such as malondialdehyde (MDA) that negatively correlate with kidney function and are linked to increased oxidative stress^[5,6]. This oxidative stress is critical, as it not only intensifies lipid abnormalities but also triggers inflammatory responses that further complicate the health status of hemodialysis patients. The implications of these findings are significant, underscoring the need for targeted interventions to manage lipid levels and oxidative stress in CKD patients undergoing HD. Emerging studies suggest that addressing these factors may lead to improved outcomes and reduced mortality rates, highlighting a shift in focus from traditional risk factor management to a more nuanced understanding of the metabolic and inflammatory pathways involved in CKD. Controversies remain regarding the effects of treatment modalities, such as the use of heparin during HD, which can influence lipid metabolism and may complicate the management of dyslipidemia in these patients^[7,8,9]. As research progresses, understanding the interplay between lipid profiles and lipid peroxidation will be vital in developing effective strategies to mitigate cardiovascular risks and enhance the quality of care for individuals with CKD.

Chronic Kidney Disease: Chronic kidney disease (CKD) has emerged as a significant public health concern, with a global prevalence estimated to be between 8% and 16%^[1]. The increasing prevalence of CKD is particularly pronounced among older adults, with data

indicating that the rate of CKD among individuals aged 60 and above rose from 18.8% during 1988-1994-24.5% in 2003-2006^[2].

Mortality Trends in Dialysis Patients: Mortality rates among patients undergoing dialysis have shown a consistent decline, averaging a reduction of 2-3% per year since 2001, culminating in a 28% decrease by 2012. This decline has brought mortality rates among these patients in line with those recorded in 1982^[10]. The improvements in survival rates may be attributed to advancements in dialysis technology, patient management and increased awareness of CKD.

Risk Factors and Epidemiology: The risk factors associated with CKD can be categorized into traditional and non-traditional factors. Traditional risk factors include advanced age, diabetes mellitus, hypertension, family history of kidney disease, smoking, male gender, obesity, and a sedentary lifestyle^[11]. Recent studies suggest that the relationship between certain traditional risk factors and mortality in hemodialysis (HD) patients does not follow the expected linear correlation. Specifically, hypertension and hyperlipidemia exhibit a U-shaped relationship with mortality in this population, indicating a more complex interaction than previously understood^[12].

Malnutrition-Inflammation Syndrome: In the context of CKD, a phenomenon known as malnutrition-inflammation (MIA) syndrome has been observed, which is correlated with increased atherosclerosis and mortality among HD patients^[13]. This syndrome suggests that the presence of hypercholesterolemia, high body mass index (BMI) and hyperhomocysteinemia may reflect a paradoxical nutritional status that could contribute to improved outcomes if properly managed. Therefore, addressing MIA in HD patients could potentially lead to a decrease in mortality rates, warranting a reassessment of traditional risk factors and the establishment of new treatment objectives^[14].

Lipid Profile: Chronic Kidney Disease (CKD) significantly alters the composition and quality of blood lipids, leading to a highly atherogenic lipid profile. Patients with CKD commonly exhibit dyslipidemia characterized by hypertriglyceridemia, an increase in triglyceride remnant-rich lipoproteins and elevated lipoprotein(a) levels, alongside a decrease in high-density lipoprotein (HDL) cholesterol levels^[15,16]. Interestingly, the total cholesterol and low-density lipoprotein (LDL) cholesterol levels typically remain within normal limits in stages 1-4 of CKD, except in cases of nephrotic syndrome, where a rise in LDL cholesterol has been observed^[16].

Hemodialysis and Lipid Metabolism: The lipid profile in patients undergoing hemodialysis (HD) can be influenced by various factors, including the composition of the dialysate and the use of anticoagulants such as heparin. Studies indicate that bicarbonate dialysate may have positive effects on lipid profiles, potentially improving lipid metabolism during HD^[7,8]. Conversely, the use of heparin has a more complex relationship with lipid metabolism. Heparin is known to cause the release of lipoprotein lipase from the endothelial surface; chronic administration of heparin leads to a decrease in lipoprotein lipase levels, impairing the catabolism of triglyceride-rich lipoproteins such as chylomicrons and very-low-density lipoproteins (VLDL)^[7,17,8]. The effects of unfractionated heparin on lipoprotein metabolism have yielded controversial results. While some studies suggest that heparin usage during HD does not significantly alter lipoprotein lipase levels^[7,18], others highlight the potential negative impact of chronic heparin use on lipid metabolism^[15,16].

Non-Traditional Risk Factors: In addition to traditional lipid abnormalities, factors such as oxidative stress and inflammation contribute to the risk profile of HD patients. Uremia-associated factors, including anemia and imbalances in calcium-phosphorus metabolism, further complicate the lipid metabolism landscape in these patients^[18,19]. Dyslipidemia in the context of CKD is often termed uremic dyslipidemia, reflecting the distinct alterations in lipid metabolism that occur in patients with compromised renal function^[18].

Lipid Peroxidation: Lipid peroxidation refers to the oxidative degradation of lipids, a process primarily driven by reactive oxygen species (ROS) such as free radicals that attack lipids containing carbon-carbon double bonds^[5]. This phenomenon is particularly significant in the context of chronic kidney disease (CKD) and hemodialysis (HD), where it has been shown to elevate levels of certain biomarkers, indicating an increased state of oxidative stress among affected patients^[6,20].

Mechanisms and Effects: The lipid peroxidation process initiates when free radicals react with polyunsaturated fatty acids, leading to the formation of lipid peroxidation by-products, such as malondialdehyde (MDA). In CKD patients, elevated MDA levels have been observed and negatively correlate with glomerular filtration rate, suggesting a direct relationship between kidney function and oxidative stress^[20]. This oxidative stress is a critical factor in the pathogenesis of various complications associated with CKD, including atherosclerosis, anemia and malnutrition^[21,22].

Biomarkers of Lipid Peroxidation: In clinical studies, markers such as thiobarbituric acid reactive substances (TBARS) have been utilized to assess lipid peroxidation. Elevated TBARS levels in erythrocytes indicate increased oxidative stress, while a concomitant decrease in total antioxidant capacity (TAC) further underscores the imbalance between pro-oxidants and antioxidants in CKD patients^[21,2].

Chronic Inflammation and Lipid Peroxidation: Patients with CKD often exhibit a state of chronic inflammation, which can exacerbate oxidative stress. This chronic inflammatory response triggers the production of inflammatory cells, such as polymorphonuclear cells (PMNs) and monocytes, which contribute to further oxidative damage^[22,23]. The interplay between lipid peroxidation and inflammation is a complex and ongoing area of research, as it appears to significantly influence the overall health outcomes for patients undergoing hemodialysis.

Hemodialysis: Hemodialysis (HD) is a medical procedure used to treat patients with chronic kidney disease (CKD) by removing waste products and excess fluids from the blood. Research has demonstrated that HD is associated with various biochemical changes, particularly concerning lipid metabolism and oxidative stress.

Lipid Peroxidation and Antioxidant Activity: Studies have shown that hemodialysis can lead to increased lipid peroxidation, a process where free radicals damage lipids in cell membranes, which can contribute to cardiovascular complications in CKD patients^[24,25]. Concurrently, there is a noted decrease in superoxide dismutase (SOD) activity, an important antioxidant enzyme, which may further exacerbate oxidative stress in these patients^[24,25]. Despite these changes, serum antioxidant activity (AOA) and erythrocyte levels have not shown significant variations during HD^[24].

Effects of Dialysate Composition: The composition of the dialysate, specifically whether acetate or bicarbonate is used, has been found to influence lipid profiles during hemodialysis. The use of bicarbonate dialysate is reported to have beneficial effects on lipid profiles, potentially improving outcomes for patients undergoing HD^[9,23]. In contrast, acetate-based dialysate may not provide the same advantages, although more research is needed to fully understand the implications of dialysate composition on lipid metabolism.

Impact of Heparin on Lipoprotein Metabolism: Another factor affecting lipid profiles in hemodialysis patients is the use of heparin, an anticoagulant commonly administered during the procedure. Heparin

can lead to the release of lipoprotein lipase from the endothelial surface, which is crucial for the breakdown of triglyceride-rich lipoproteins such as chylomicrons and very-low-density lipoproteins (VLDL)^[9,23,26]. Chronic use of heparin may result in reduced lipoprotein lipase levels, impairing the catabolism of these lipoproteins and potentially leading to dyslipidemia^[9,27]. However, studies investigating the effects of unfractionated heparin on lipoprotein metabolism have yielded inconsistent results, with some indicating no significant impact on lipoprotein lipase levels during HD^[9,23].

Relationship Between Lipid Profile and Chronic Kidney Disease: Chronic kidney disease (CKD) is characterized by a variety of lipid metabolism abnormalities, which contribute to atherogenic profiles and increase the risk of cardiovascular diseases, the leading cause of mortality among CKD patients^[3,4]. The lipid disorders commonly seen in CKD patients include elevated triglycerides and decreased levels of high-density lipoprotein (HDL) cholesterol^[4,21].

Dyslipidemia in CKD Patients: Research indicates that dyslipidemia is prevalent in CKD patients and is directly associated with cardiovascular events^[4,29]. A study involving 60 CKD patients undergoing hemodialysis found that their mean total cholesterol (215.7 ± 32.8 mg/dL) and triglyceride levels (149.91 ± 46.5 mg/dL) were significantly higher than those of healthy controls (152.5 ± 13.5 mg/dL for total cholesterol and 109.1 ± 28.6 mg/dL for triglycerides)^[21,29]. This underscores the importance of monitoring lipid profiles in CKD patients to prevent complications related to cardiovascular diseases^[30].

Impact on Cardiovascular Health: The impaired lipid metabolism in CKD contributes to increased glomerulosclerosis and tubulointerstitial injury, further exacerbating kidney damage and accelerating the progression of the disease^[31,30]. The presence of hypertension, common in CKD patients, may also worsen dyslipidemia and thus further elevate cardiovascular risks^[30,9]. Approximately 50% of deaths in patients on maintenance hemodialysis are attributed to cardiovascular diseases, emphasizing the critical need for managing lipid abnormalities in this population^[9,32].

Lipid Peroxidation in Chronic Kidney Disease: Chronic kidney disease (CKD) is characterized by significant oxidative stress, which leads to the peroxidation of lipids and alterations in lipid and lipoprotein metabolism. This oxidative stress results in the accumulation of lipid peroxidation by-products, such as

malondialdehyde (MDA), which have been shown to correlate negatively with the glomerular filtration rate in CKD patients^[2]. The oxidative modifications of lipids contribute not only to renal disease progression but also to the development of cardiovascular complications associated with CKD^[33,20].

Mechanisms of Lipid Peroxidation: Lipid peroxidation occurs through the oxidative degradation of lipids, which leads to the formation of reactive aldehydes and other harmful by-products that can cause further cellular damage. In patients undergoing hemodialysis, intensified lipid peroxidation may play a crucial role in the accelerated progression of atherosclerosis. This is believed to be mediated by enhanced endothelial dysfunction and increased vascular inflammation^[1,34,35]. The presence of advanced glycation end products (AGEs), which accumulate due to lipid peroxidation and other oxidative processes, can exacerbate tissue damage and contribute to cardiovascular disease in these patients^[36,9].

Clinical Implications: Several studies have highlighted the association between elevated lipid peroxidation levels and the severity of renal anemia in chronic hemodialysis patients, indicating a possible link between oxidative stress and clinical outcomes^[36]. Furthermore, hypertriglyceridemia, which is common in CKD patients, may also contribute to lipid peroxidation and enhance the risk of atherosclerotic events. Notably, a significant increase in cardiovascular risk, including myocardial and cerebral infarctions, has been observed in patients with triglyceride levels above 200 mg/dL^[33,37]. These findings emphasize the need for further research into the mechanisms of lipid peroxidation and its role in cardiovascular morbidity and mortality in the CKD population.

Retrospective Study Design: The retrospective study design employed in this research focused on evaluating the lipid profile and lipid peroxidation levels in patients undergoing hemodialysis (HD) for chronic kidney disease (CKD). The methodology adhered to the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the review protocol was registered with PROSPERO (CRD42023455399)^[38,11].

Study Selection: A systematic search was conducted on June 30, 2024, across multiple data-bases including PubMed, Embase and the Cochrane Library. The selection criteria were meticulously defined to include population-based randomized controlled trials (RCTs) focusing on adults aged 18 years and older who had

been receiving regular hemodialysis (three times a week) for at least two months. Additionally, eligible studies were required to report on blood biomarker levels related to lipid peroxidation^[38,39,9].

Data Extraction and Quality Assessment: Two independent reviewers assessed the quality of the studies included in the review using the Cochrane Collaboration's risk of bias assessment criteria. This process aimed to minimize evaluation bias, with any discrepancies being resolved through discussion and consensus^[18,40]. Furthermore, data extraction was performed using standardized tables, which encompassed critical study parameters such as design, population characteristics (including age and dialysis duration), country of origin, biomarker levels, sample sources and comparison results. Non-standard data types were transformed as necessary for consistent extraction^[7,19,41].

Statistical Analysis: The analysis of the data was executed using SPSS software version 17.0, with results presented as mean±standard deviation (SD). Normality of the data distributions was verified through the Kolmogorov-Smirnov test. Statistical comparisons between patient and control groups were conducted using independent sample t-tests, while paired t-tests were utilized for comparing biochemical parameters before and after HD treatments. Correlations among variables were determined using Pearson's correlation coefficient, with a significance threshold set at $P<0.05$ ^[13,42]. This comprehensive retrospective study design aimed to elucidate the relationship between lipid profiles and lipid peroxidation levels in patients with chronic kidney disease undergoing hemodialysis, contributing valuable insights to the understanding of cardiovascular risks associated with CKD.

RESULTS AND DISCUSSIONS

Clinical Characteristics of the Participants: The study assessed the lipid profiles and lipid peroxidation levels in patients undergoing hemodialysis (HD) compared to those receiving peritoneal dialysis (PD) and conservatively managed patients. The results indicated that dyslipidemia was highly prevalent among the hemodialysis cohort, with an overall prevalence of 82%^[34]. Notably, more than half of the participants exhibited hypertriglyceridemia, elevated very-low-density lipoprotein cholesterol and decreased high-density lipoprotein (HDL) levels, highlighting significant lipid abnormalities in this patient population^[44].

Lipid Profile Analysis: The analysis of serum lipids revealed that hemodialysis patients had significantly

elevated levels of triglycerides (228.16 ± 84.81 mg/dl) and low-density lipoprotein (LDL) cholesterol (180.84 ± 29.72 mg/dl) compared to conservatively managed patients and control participants, who had mean triglyceride levels of 224.94 ± 130.38 mg/dl and LDL levels of 125.69 ± 27.41 mg/dl, respectively^[18]. This stark contrast emphasizes the altered lipid metabolism in patients undergoing hemodialysis.

Lipid Peroxidation and Antioxidant Status: Furthermore, the study observed a notable increase in lipid peroxidation biomarkers after three years in hemodialysis patients, suggesting a disturbance in lipid peroxidation state coupled with diminished antioxidant status^[6,29]. The findings indicated that excess iron stores in these patients contribute to increased lipid peroxidation, which is associated with oxidative stress^[45]. This study highlights the potential loss or inactivation of antioxidant factors during hemodialysis, exacerbating lipid peroxidation and its related complications^[11].

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