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DYSLIPIDEMIA AND LIPID-LOWERING THERAPY IN PATIENTS ON RENAL REPLACEMENT THERAPY: A LITERATURE REVIEW

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Dyslipidemia in patients with chronic kidney disease (CKD), particularly those on renal replacement therapy (RRT), is a major risk factor for cardiovascular complications. The pathogenesis of lipid metabolism disorders in this population is multifactorial and influenced by the underlying kidney disease, the specific characteristics of RRT, and, in transplant recipients, the effects of immunosuppressive therapy. Despite the high prevalence and clinical significance of dyslipidemia in CKD, therapeutic strategies for its correction remain insufficiently studied. This review analyzes current pharmacologic approaches to the management of dyslipidemia and evaluates the potential for their application in patients receiving RRT. Literature search was conducted using electronic databases Medline/PubMed (https://pubmed.ncbi.nlm.nih.gov) and eLIBRARY/Russian Science Citation Index (https://www.elibrary.ru).

Keywords: dyslipidemia, chronic kidney disease, renal replacement therapy, hemodialysis, peritoneal dialysis, kidney transplantation.

INTRODUCTION

Patients with chronic kidney disease (CKD) are at a significantly increased risk of developing cardiovascular complications. The onset and progression of cardiovascular disease in this population are driven by A variety of factors, including dyslipidemia, hyperhomocysteinemia, chronic inflammation, oxidative stress, disturbances in calcium–phosphate metabolism, and endothelial dysfunction [1]. Evidence indicates that CKD progression is accompanied by a progressive deterioration of the lipid profile. The pathogenesis of dyslipidemia in CKD is complex and multifactorial, involving alterations in lipoprotein metabolism, oxidative stress, inflammatory processes, and declining renal function [2].

Among patients with CKD, those receiving renal replacement therapy (RRT) represent a subgroup at particularly high cardiovascular risk – the incidence of myocardial infarction in this cohort is approximately 20 times higher than in the general population. Data from routine coronary angiography in Japan revealed that 60% of patients on maintenance hemodialysis (HD) had asymptomatic stenosis of at least one coronary artery [3]. Thus, patients receiving RRT are more likely to have pronounced atherosclerotic changes. Importantly, dyslipidemia is not the sole mechanism underlying the progression of atherosclerosis in individuals with end-stage renal disease. These patients also possess unique metabolic and physiological characteristics that complicate the management and correction of dyslipidemia [4].

Numerous studies have demonstrated a clear association between serum cholesterol (SC) levels and the risk of cardiovascular events. In particular, a multifactorial risk study showed a progressive increase in mortality from coronary heart disease (CHD) with rising SC levels, beginning at 5.2 mmol/L; at 7.8 mmol/L, the risk of CHD-related mortality increased fourfold [5]. Data from the Framingham Heart Study further confirmed a direct correlation between total SC levels and CHD risk. Specifically, individuals with total SC levels of 7.8 mmol/L had approximately twice the risk of developing CHD compared with those with levels around 5.2 mmol/L [6].

Subsequent meta-analyses of the Framingham data reinforced the direct relationship between low-density lipoprotein (LDL) cholesterol levels and the incidence of CHD [7]. According to current clinical guidelines for the management of lipid disorders in very high-risk patients, the target LDL cholesterol level should be below 1.4 mmol/L, with at least a 50% reduction from baseline values. These guidelines also emphasize the pathogenic role of elevated lipoprotein(a) [Lp(a)] levels in increasing the risk of cardiovascular events [8].

Current approaches to lipid-lowering therapy (LLT) in patients undergoing RRT include the use of statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, as well as other methods aimed at reducing serum cholesterol and lipoprotein(a) [Lp(a)] levels to lower the risk of cardiovascular complications.

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Statins remain the cornerstone of LLT and can be prescribed to patients in the early stages of CKD. However, their use in individuals on RRT, particularly those on HD, requires caution and individualized risk assessment, since high-dose statin therapy in this group is often associated with an increased incidence of adverse effects. Ezetimibe may be used in combination with statins in patients on RRT, particularly when statin monotherapy fails to achieve target lipid levels.

PCSK9 inhibitors are considered an appropriate therapeutic option for RRT patients with persistently elevated LDL cholesterol levels despite maximally tolerated statin and ezetimibe therapy. These drugs may also be considered in patients with markedly elevated LDL levels, particularly when other interventions prove ineffective [1].

FEATURES OF LIPID METABOLISM IN PATIENTS WITH CKD RECEIVING RRT

The metabolism of endogenous and exogenous lipoproteins in healthy individuals (Fig. 1, Fig. 2) differs significantly from that in patients with CKD. These differences are primarily associated with a range of pathological factors caused by CKD.

IMPAIRED CLEARANCE OF TRIGLYCERIDE-RICH LIPOPROTEINS

Patients with CKD exhibit a reduced fractional catabolic rate of triglyceride (TG)-rich lipoproteins, including very low-density lipoproteins (VLDL), their subfractions VLDL1 and VLDL2, as well as intermediate-density lipoproteins (IDL) and apolipoprotein B-100 (apoB-100). This indicates impaired clearance mechanisms, resulting in the accumulation of these particles in plasma. In contrast, the synthetic rate of VLDL, IDL, and apoB-100 in CKD patients is comparable to that of healthy individuals, indicating that the primary disturbance lies in delayed degradation rather than excessive production of lipoproteins.

Apolipoprotein C-III (apoC-III) plays a key role in lipid metabolism disorders in patients with CKD. Normally, the kidneys filter and excrete apoC-III; however,

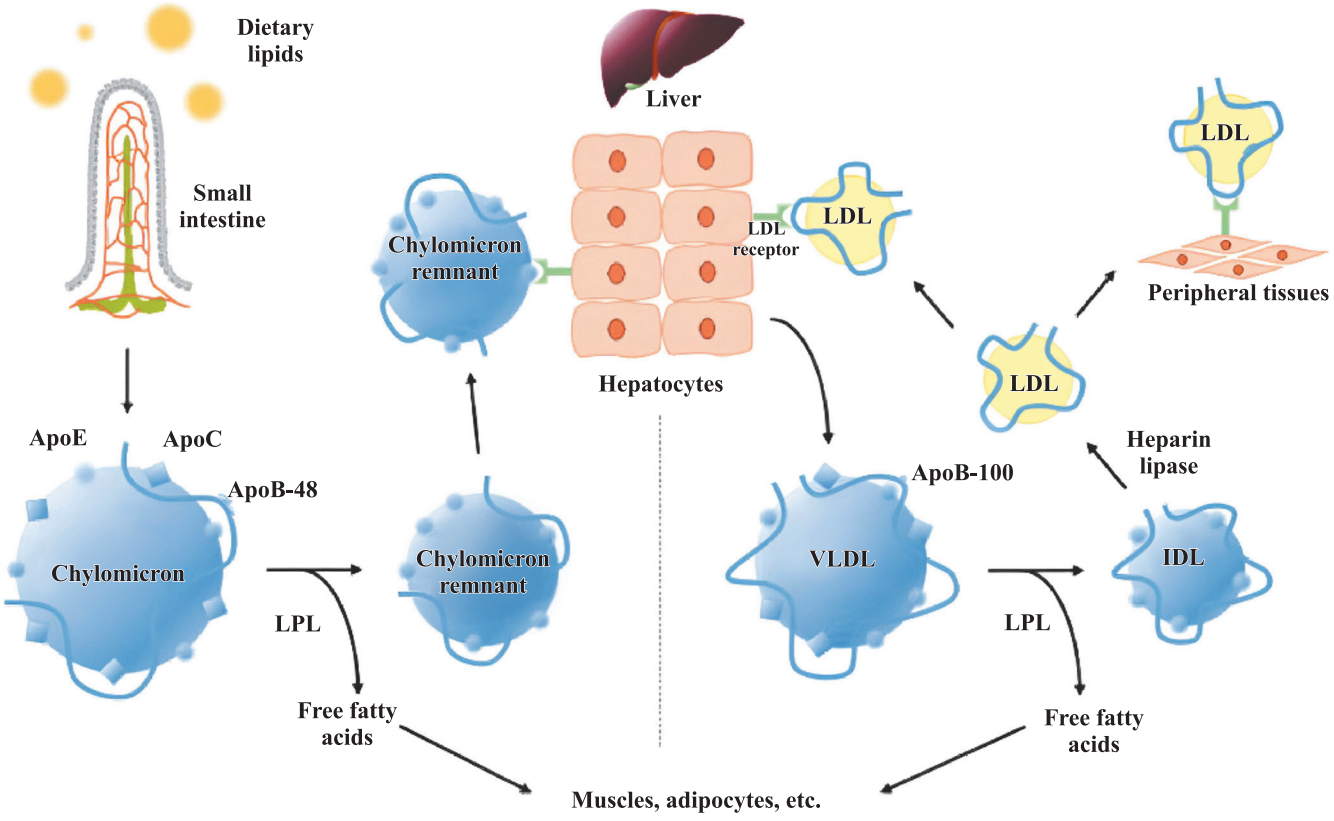

Fig. 1. Metabolic pathway of exogenous and endogenous lipoproteins. Dietary lipids are absorbed in the small intestine, where they are assembled into chylomicrons containing apolipoproteins C (apoC), E (apoE), and B-48 (apoB-48). These chylomicrons enter the bloodstream and are hydrolyzed by lipoprotein lipase (LPL) to release free fatty acids (FFAs), and shrink to chylomicron remnants. FFAs are taken up by peripheral tissues – such as skeletal muscle and adipose tissue – for energy or stored as fat. Chylomicron remnants are subsequently absorbed by the liver via low-density lipoprotein (LDL) receptors. Within hepatocytes, very low-density lipoproteins (VLDL), which also contain apolipoprotein B-100. VLDL is broken down by LPL in the blood into FFAs and intermediate-density lipoproteins (IDL). IDL is then converted by hepatic lipase into LDL, which transports cholesterol to peripheral tissues. Adapted from: Suh SH, Kim SW. Dyslipidemia in Patients with Chronic Kidney Disease: An Updated Overview

renal impairment leads to its systemic accumulation. In addition, uremic inflammation enhances hepatic synthesis of apoC-III through cytokine-mediated pathways, particularly via interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Elevated plasma apoC-III levels are strongly correlated with slowed catabolism of VLDL and its subfractions, as apoC-III inhibits the activity of lipoprotein lipase (LPL) and hepatic lipase.

LPL is a key enzyme responsible for hydrolyzing triglycerides (TG) contained in chylomicrons and VLDL into free fatty acids and glycerol, which are subsequently utilized for energy production or stored in adipose tissue (Fig. 3). ApoC-III not only suppresses LPL activity but also interferes with apoE-mediated receptor binding, thereby reducing hepatic clearance of remnant particles. CKD patients also have elevated plasma levels of apolipoprotein B-48, a marker of chylomicrons and their remnants, reflecting impaired intestinal lipoprotein metabolism [9].

Changes in LDL receptor function play a major role in impaired catabolism of LDL particles in patients with CKD. Expression of LDL receptors is significantly reduced in CKD, a phenomenon largely associated with the chronic inflammatory state characteristic of this

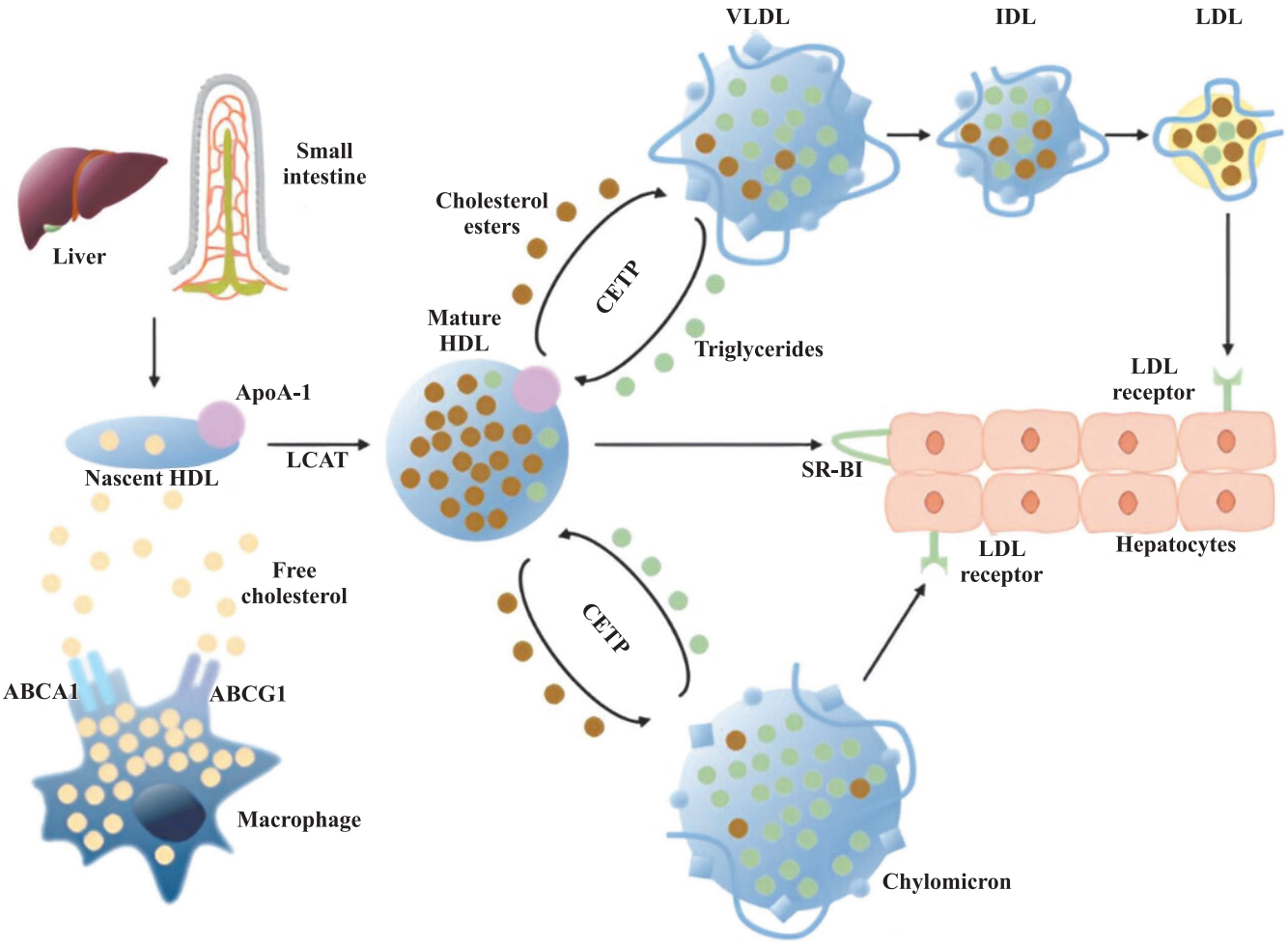

Fig. 2. High-density lipoprotein (HDL) metabolism in reverse cholesterol transport. Apolipoprotein A-I (apoA-I) is secreted by liver and intestine. It interacts with the ATP-binding cassette subfamily member 1 (ABCA1) transporter, which facilitates the transfer of free cholesterol from macrophages to apoA-I, forming nascent, disc-shaped HDL particles. These nascent HDL particles subsequently interact with other transporters, such as ABCG1, to acquire additional free cholesterol. Under the action of lecithin-cholesterol acyltransferase (LCAT), free cholesterol on the HDL surface is esterified into cholesteryl ester (CE) and incorporated into the particle's hydrophobic core, transforming immature HDL into mature, spherical HDL particles rich in CE. Cholesteryl ester transfer protein (CETP) mediates the exchange of CEs from mature HDL for triglycerides (TG) from atherogenic lipoproteins such as very low-density lipoproteins (VLDL), resulting in the formation of low-density lipoproteins (LDL). TG-enriched HDL becomes less mature and more prone to catabolism. LDL receptors on hepatocytes capture LDL particles – enriched in cholesterol after CETP-mediated exchange – providing the primary "direct" route of cholesterol delivery to the liver. In parallel, the scavenger receptor class B type I (SR-BI) receptor on hepatocytes selectively uptakes CEs directly from mature HDL without degrading the entire particle. This process constitutes the central mechanism of reverse cholesterol transport, through which cholesterol collected by HDL from peripheral tissues (notably macrophages) is returned to the liver. IDL, intermediate-density lipoprotein. Adapted from: Suh SH, Kim SW. Dyslipidemia in Patients with Chronic Kidney Disease: An Updated Overview

condition. Uremic toxins – notably indoxyl sulfate and para-cresol – have been shown to suppress LDL receptor expression through activation of the NF-κB and Smad protein signaling pathways. This molecular cascade contributes to renal fibrosis, reduced receptor-mediated uptake of LDL, and ultimately impaired cholesterol clearance [10].

In addition, oxidative stress increases in CKD, leading to oxidation of apolipoproteins (e.g., apoB-100 found in LDL). Carbamylation of apolipoproteins (e.g., ApoB-100 and ApoA-I) is another important process that can impair LDL receptor function and exacerbate dyslipidemia. Oxidation and carbamylation of ApoB-100 can lead to a decrease in LDL receptor activity, which reduces their ability to bind and utilize LDL. In addition, oxidized LDL can be absorbed by macrophages, contributing to the development of atherosclerosis [11].

Patients with CKD are more likely to have small dense LDL (sdLDL), which has a lower affinity for LDL receptors compared to large LDL. This reduces their utilization by cells and increases the duration of their circulation in the blood. In turn, impaired kidney function affects the balance of proteins and electrolytes, which can alter the concentration of apolipoproteins (especially apoB and apoE) necessary for LDL interaction with receptors. This leads to a slowdown in the removal of LDL from the blood [12].

DYSFUNCTION OF HIGH-DENSITY LIPOPROTEINS (HDL) AND LOSS OF THEIR ANTIATHEROGENIC PROPERTIES

Patients with CKD often have reduced plasma levels of HDL, resulting from both impaired synthesis and accelerated catabolism. The decrease in HDL cholesterol levels is paralleled by decreased levels of its major apolipoproteins, ApoA-I and ApoA-II. Notably, the reduction in ApoA-I and ApoA-II levels correlates with the severity of renal dysfunction. Accumulation of uremic toxins in CKD suppresses hepatic ApoA-I synthesis, leading to the formation of dysfunctional HDL particles that have

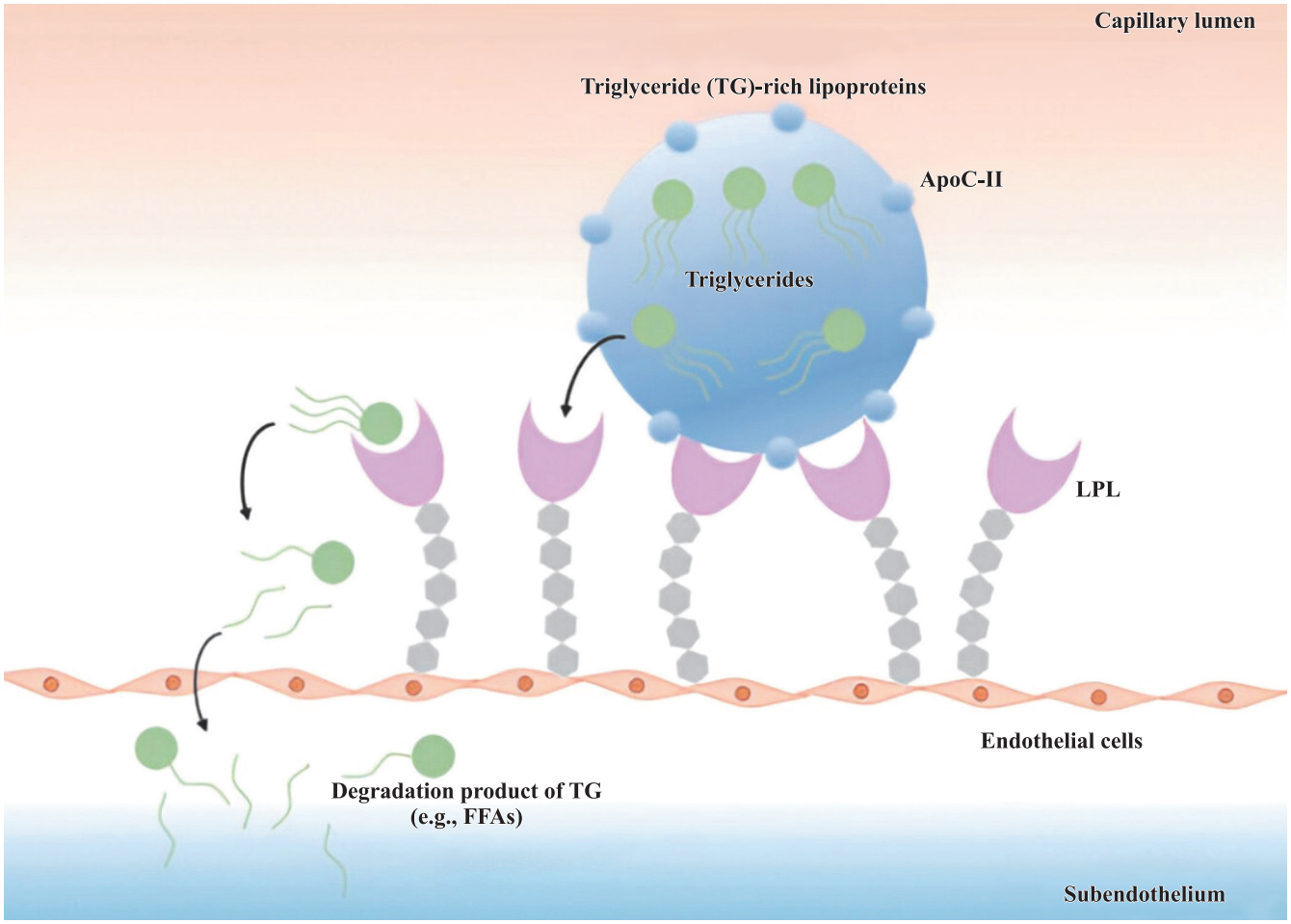

Fig. 3. Mechanism of triglyceride lipolysis. Triglyceride (TG)-rich lipoproteins (i.e., chylomicron and very low-density lipoprotein [VLDL]), enter the capillary lumen. Apolipoprotein C-II (apoC-II) on the surface of these particles activates lipoprotein lipase (LPL), an enzyme anchored on the surface of endothelial cells. LPL degrades TG to release free fatty acids (FFAs) and other degradation products. The liberated FFAs then diffuse across the endothelium into the subendothelial space, where they can be used by tissues for energy needs or stored. Adapted from: Suh SH, Kim SW. Dyslipidemia in Patients with Chronic Kidney Disease: An Updated Overview

diminished capacity for reverse cholesterol transport (RCT) [13].

Under the combined effects of oxidative stress, uremic toxins, and chronic inflammation, the activity of the ATP-binding cassette transporters ABCA1 and ABCG1 – critical mediators of cholesterol efflux from macrophages – is reduced. Impaired function of these transporters limits the removal of cholesterol and disrupts HDL maturation, resulting in an accumulation of immature, discoidal HDL particles. The decreased cholesterol efflux from macrophages promotes foam cell formation within the vascular intima, thereby accelerating atherosclerosis [12].

In addition, HDL lose their ability to remove cholesterol from peripheral tissues due to reduced expression of the scavenger receptor class B type I (SR-BI) in the liver. SR-BI mediates the selective uptake of cholesterol from HDL, and its deficiency results in cholesterol accumulation within the vascular wall, further promoting the formation of atherosclerotic plaques [14].

Oxidative stress, a hallmark of CKD, contributes to the generation of reactive oxygen species that oxidize HDL-associated lipids and proteins. This, along with elevated TG levels, a consequence of decreased LPL activity, these changes substantially impair the cholesterol-transporting capacity of HDL. Oxidized HDL not only loses its antiatherogenic and antioxidative functions, but may also acquire proinflammatory and proatherogenic properties. Moreover, CKD is associated with accelerated clearance of HDL particles from circulation due to structural and functional impairements. This reduces the circulation time of HDL in the blood and decreases its overall effectiveness in maintaining lipid metabolism and protecting blood vessels [15].

Patients with CKD also exhibit reduced plasma levels of lecithin-cholesterol acyltransferase (LCAT), an enzyme that plays a central role in lipoprotein metabolism by catalyzing the esterification of free cholesterol. This process is essential for the maturation and stabilization of HDL and for maintaining reverse cholesterol transport. The decrease in LCAT activity in CKD is associated with reduced expression of the LCAT gene in the liver, the principal site of its synthesis [16].

Deficiency or dysfunction of LCAT leads to accumulation of free cholesterol within HDL particles, impairing the formation of cholesterol esters. Consequently, abnormal lipid species, including non-esterified cholesterol and phospholipids, accumulate, disrupting the structural integrity and functional capacity of HDL [17].

Moreover, the accumulation of uremic toxins such as indoxyl sulfate and para-cresol enhances the activity of cholesteryl ester transfer protein (CETP). CETP facilitates the transfer of cholesterol esters from HDL to LDL and triglyceride-rich lipoproteins (e.g., VLDL and VLDL remnants). This process increases the concentration and atherogenic potential of LDL, while simultaneously reducing the size and functional efficiency of HDL, thereby compromising reverse cholesterol transport (Fig. 4) [18].

EFFECT OF CKD ON LIPOPROTEIN (A) [LP(A)] LEVELS

Lp(a) is a complex plasma lipoprotein structurally similar to LDL, distinguished by the presence of apolipoprotein (a) [apo(a)], which is covalently linked to apoB-100 via a disulfide bond. Apo(a) contains repeating domains similar to plasminogen, a protein involved in fibrinolysis. This structural homology allows Lp(a) to compete with plasminogen for binding sites, thereby inhibiting fibrinolysis and increasing thrombogenic potential. Lp(a) is recognized as an independent risk factor for cardiovascular disease (CVD), including atherosclerosis, myocardial infarction, and ischemic stroke [19].

The plasma concentration of Lp(a) is largely determined by the rate of its synthesis in the liver and catabolism, the latter of which appears to involve the kidneys, although this mechanism is not yet fully understood. Elevated Lp(a) levels are frequently observed with declining glomerular filtration rate (GFR), even in the early stages of renal dysfunction [20]. Studies have shown that Lp(a) levels rise with moderate decrease in GFR (60–90 mL/min/1.73 m^2), independent of albuminuria.

A large multinational cohort study demonstrated a weak positive association between reduced GFR and elevated Lp(a) levels, particularly among non-Hispanic blacks, suggesting potential ethnic variability in this relationship. The authors noted that differences in apo(a) isoform size among populations could partially account for the observed heterogeneity [21].

A detailed study involving 227 white patients without nephrotic syndrome and with varying degrees of renal dysfunction showed that Lp(a) levels were significantly higher in patients with CKD compared with controls without renal impairment. Moreover, an inverse correlation was observed between renal function and plasma Lp(a) levels – the highest concentrations were detected in patients with the most severe renal dysfunction, irrespective of the underlying kidney disease. Interestingly, this relationship was evident only in the subgroup with large apo(a) isoforms and without nephrotic syndrome, suggesting that isoform size may modulate the effect of renal impairment on Lp(a) metabolism [22].

In patients with CKD, the elevation of Lp(a) is likely related to an acquired impairment of its catabolism. This hypothesis is supported by an *in vivo* metabolic study in hemodialysis patients, which demonstrated a significant reduction in the fractional catabolic rate of both apo(a) and apoB, the major protein components of Lp(a). Consequently, prolonged circulatory residence time of Lp(a) leads to its accumulation in plasma [22].

THE ROLE OF CKD IN THE DEVELOPMENT OF INSULIN RESISTANCE AND ITS EFFECT ON LIPID PROFILE

CKD disrupts the elimination of metabolic by-products and toxins, creating a uremic environment that impairs tissue sensitivity to insulin. Uremic toxins such as indoxyl sulfate and para-cresol not only exacerbate insulin resistance, but also directly damage vascular endothelium, thereby exacerbating atherosclerosis in the context of existing dyslipidemia. Furthermore, chronic inflammation and oxidative stress, both hallmarks of CKD, inhibit insulin signaling pathways and disturb the regulation of lipid metabolism [23].

Insulin resistance, being a key link in metabolic disorders, has a significant impact on the development of dyslipidemia among CKD patients, particularly those on RRT. Impaired cellular responsiveness to insulin leads to compensatory hyperinsulinemia, increased lipolysis, and elevated plasma free fatty acid (FFA) levels. These FFAs are taken up by the liver, where they stimulate triglyceride (TG) and VLDL synthesis. In CKD, this mechanism is further aggravated by reduced LPL activity. His contributes to the accumulation of atherogenic particles and the formation of a pattern characteristic of dyslipidemia: high triglyceride levels, low HDL levels, and an increase in the number of LDL particles [24].

FEATURES OF THE MECHANISMS OF DYSLIPIDEMIA DEVELOPMENT IN PATIENTS ON HEMODIALYSIS

During maintenance HD sessions, heparin is routinely administered to prevent blood clotting in the extracorporeal circuit. Although heparin transiently activates LPL, repeated HD procedures eventually lead to LPL depletion, thereby reducing its enzymatic activity between dialysis sessions. This disrupts triglyceride catabolism, resulting in hypertriglyceridemia and elevated levels of VLDL and chylomicrons [25].

During HD procedures, low molecular weight substances are lost through the semipermeable dialysis mem-

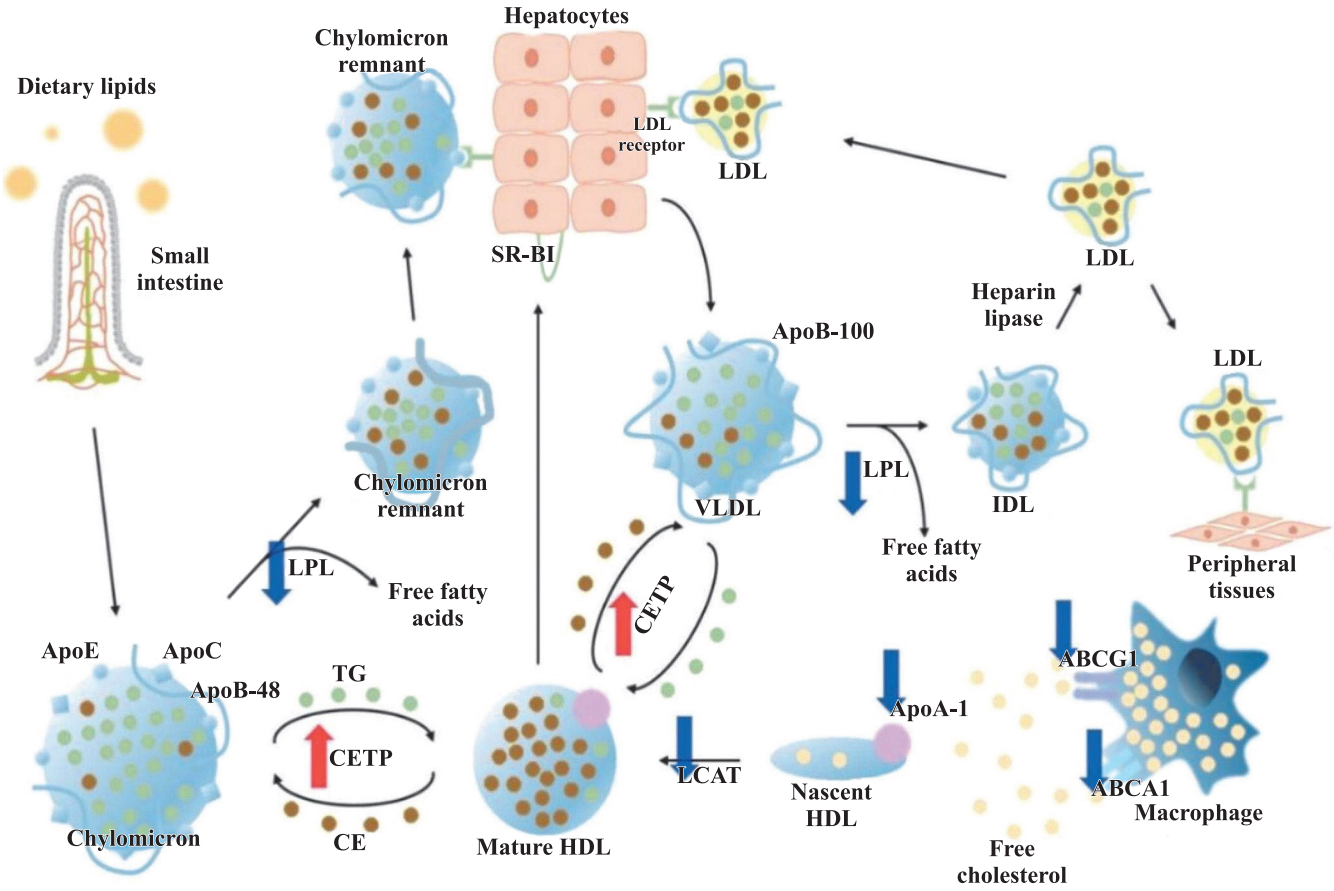

Fig. 4. Schematic representation of defective lipoprotein metabolism in chronic kidney disease (CKD). In CKD, reduced lipoprotein lipase (LPL) activity results in the accumulation of triglyceride (TG)-rich lipoproteins. Simultaneously, decreased synthesis of apolipoprotein A-I (ApoA-I) and reduced activity of lecithin-cholesterol acyltransferase (LCAT), as well as the cholesterol transporters ATP-binding cassette subfamily member 1 (ABCA1) and ATP-binding cassette subfamily G member 1 (ABCG1), lead to the formation of dysfunctional high-density lipoprotein (HDL) particles incapable of effective reverse cholesterol transport. Increased activity of cholesterol ester transfer protein (CETP) raises LDL levels and enhances their proatherogenic potential. CE, cholesteryl ester; IDL, intermediate-density lipoprotein. Adapted from: Suh SH, Kim SW. Dyslipidemia in Patients with Chronic Kidney Disease: An Updated Overview

brane. Carnitine, which is necessary for the transport of fatty acids into the mitochondria, is removed during HD. Carnitine deficiency leads to impaired beta-oxidation of fatty acids fatty acid oxidation and accumulation of triglycerides (TG) and FFAs in plasma [26].

Also, scheduled hemodialysis leads to increased oxidative stress due to a bunch of factors. One of them is blood contact with membranes, which activates leukocytes, platelets, and the complement system. Contact with the dialyser membrane increases the activity of neutrophils and monocytes, which increases the production of pro-inflammatory cytokines (IL-6, TNF-α) and releases reactive oxygen species (ROS) via NADPH oxidase and myeloperoxidase. Moreover, the use of bioincompatible membranes (e.g., cellulose-based) can stimulate the complement cascade (C3a, C5a), further amplifying inflammation and ROS production. Concurrently, there is a loss of antioxidants such as vitamins C and E and glutathione, while recurrent ischemia–reperfusion cycles inherent to HD sessions intensify ROS production [27].

Dyslipidemia is more common in patients undergoing peritoneal dialysis (PD) than in those on HD. This is largely due to the specific features of PD therapy, which relies on dialysates with high glucose content serving as an osmotic agent. Continuous exposure to glucose during PD leads to its systemic absorption, resulting in metabolic disorders. Excess glucose absorption stimulates hepatic VLDL synthesis, promoting hypertriglyceridemia. Furthermore, prolonged hyperglycemia contributes to the development of insulin resistance, which aggravates existing lipid imbalance [28].

It is also important to emphasize that patients with end-stage chronic kidney disease receiving HD almost always have a significant increase in Lp(a) levels, averaging 5–10 times higher than in patients with mild or moderate renal impairment [29]. Interestingly, among HD patients, the degree of Lp(a) elevation correlates with the size of apo(a) isoforms: a significant increase in plasma Lp(a) levels compared with healthy controls is observed only in individuals with large apo(a) isoforms. In contrast, patients on PD show high Lp(a) levels regardless of apo(a) isoform size [22].

DYSLIPIDEMIA IN KIDNEY TRANSPLANT RECIPIENTS

Dyslipidemia in kidney transplant recipients is an important clinical problem that requires special attention. It occurs in approximately 60% of patients. This metabolic disorder substantially increases the risk of cardiovascular disease, which remains the leading cause of mortality in this population. Moreover, lipid metabolism disorders can negatively affect allograft function, accelerating the progression of transplant nephropathy [30].

Following kidney transplantation, plasma Lp(a) levels typically decrease, reflecting the restored metabolic and catabolic role of the kidney in Lp(a) clearance. This supports the concept that changes in Lp(a) in CKD primarily results from loss of renal tissue function [22].

The primary etiological factor underlying post-transplant dyslipidemia in such patients is immunosuppressive therapy. Long-term use of corticosteroids (e.g., prednisolone) disrupts lipid homeostasis. Glucocorticoids enhance insulin resistance, which promotes lipolysis in adipose tissue and increases the plasma FFA levels. This stimulates the synthesis of TG and VLDL in the liver. In addition, corticosteroids suppress LPL activity, further exacerbating hypertriglyceridemia [31].

Calcineurin inhibitors (CNIs) – cyclosporine A (CsA) and tacrolimus (Tac) – play a key role in preventing transplant rejection; however, their impact on lipid metabolism remains clinically significant. Studies have shown that CsA exerts a dose-dependent effect on lipid parameters, increasing total cholesterol, triglycerides (TG), and LDL levels. Moreover, it tends to reduce HDL levels, likely due to suppression of apolipoprotein A-I synthesis. CsA also promotes LDL oxidation, converting these particles into a more atherogenic form.

Although Tac belongs to the same class of CNIs, it exerts a comparatively milder influence on the lipid profile. It is less frequently associated with hypercholesterolemia and reduces HDL to a lesser extent compared to CsA. Nonetheless, Tac may elevate TG levels in certain cases, particularly when administered concurrently with corticosteroids. Evidence regarding its effect on LDL oxidation remains inconclusive [32].

mTOR inhibitors, such as rapamycin and its derivatives (rapalogs), exert complex effects on lipid metabolism that often lead to dyslipidemia. These effects are primarily mediated through their influence on mTOR complexes (mTORC1 and mTORC2), which are central regulators of lipid metabolism. Inhibition of mTORC1 reduces lipogenesis and suppresses adipogenesis by limiting adipocyte proliferation, thereby decreasing adipose tissue accumulation. However, despite reduction in lipogenesis, mTORC1 inhibition enhances lipolysis by activating lipases such as hormone-sensitive lipase and adiponutrin triglyceride lipase, and by stimulating lipophagy (degradation of lipid droplets). Consequently, FFA release and plasma lipid levels increase.

Another important consequence of mTORC1 inhibition is the downregulation of hepatic LDL receptor expression, resulting in impaired LDL clearance and development of hypercholesterolemia [33]. Although the role of mTORC2 in lipid metabolism is less well defined, it is known to regulate lipogenesis and lipolysis through activation of protein kinase AKT1. Chronic use of rapalogs may also inhibit mTORC2, further aggravating dyslipidemia.

Despite their adverse effects on lipid profile, mTOR inhibitors exhibit notable anti-atherosclerotic properties. They reduce macrophage accumulation within atheros-

clerotic plaques, promote autophagy, and enhance cholesterol efflux from macrophages, thereby reducing foam cell formation. These mechanisms may partly offset the negative impact of dyslipidemia on progression of atherosclerosis [34].

METHODS OF PHARMACOLOGICAL MANAGEMENT FOR DYSLIPIDEMIA AND ITS POTENTIAL USE IN PATIENTS ON RENAL REPLACEMENT THERAPY

HMG-CoA reductase inhibitors (statins)

Statins play a central role in the pharmacological management of dyslipidemia owing to their proven efficacy in reducing cardiovascular risk. They are considered the first-line drugs for the treatment of lipid disorders. Their primary mechanism of action involves the competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the key rate-limiting enzyme in cholesterol synthesis in the liver. This leads to reduced intracellular cholesterol levels in hepatocytes, which in turn triggers a compensatory upregulation of LDL receptors on the surface of hepatocytes. This process enhances the clearance of atherogenic lipoproteins from circulation, particularly the small, dense LDL particles, which are the most atherogenic.

Beyond their lipid-lowering effect, statins have pleiotropic effects. These include attenuation of vascular inflammation, improvement of endothelial function, stabilization of atherosclerotic plaques, and reduction of blood thrombogenicity. Statins demonstrate dose-dependent efficacy: low doses typically reduce LDL cholesterol levels by 20–30%, whereas maximal doses can achieve reductions of up to 50–55%.

However, the use of statins requires careful monitoring due to potential adverse effects. The most clinically relevant are myopathies, which occur in approximately 0.1–0.5% of patients, and elevations in hepatic transaminases, observed in about 2–3% of cases. The risk of these complications increases when statins are co-administered with fibrates, macrolide antibiotics, or antiarrhythmic drugs metabolized via the CYP3A4 enzymatic pathway [35].

The use of statins in dialysis patients remains one of the most debated topics in modern nephrology and cardiology. It is important to recognize that dyslipidemia in this population has distinctive characteristics: normal or even reduced LDL cholesterol levels are frequently observed in conjunction with elevated triglycerides, oxidized lipoproteins, and lipoprotein (a). This atypical lipid profile complicates the use of standard therapy.

However, the key question – whether statins effectively reduce cardiovascular events in dialysis patients – remains unresolved. Large-scale randomized clinical trials, including AURORA and 4D, have shown that although statins modestly lowered LDL cholesterol levels, it did not significantly reduce overall mortality among hemodialysis patients. Nonetheless, subgroup analyses have suggested that certain patients, particularly those with diabetes mellitus or severe hypercholesterolemia (LDL-C >3.76 mmol/L), may benefit from statin therapy with agents such as rosuvastatin or atorvastatin, which were associated with a reduced incidence of myocardial infarction.

It is essential to consider dose adjustments in dialysis patients due to their increased risk of adverse effects. The Kidney Disease: Improving Global Outcomes (KDIGO) working group does not recommend initiating statin therapy in patients on dialysis, unless treatment had been started prior to the initiation of the dialysis [36].

The use of statins in kidney transplant (KT) recipients presents a complex clinical challenge that requires careful consideration of both efficacy and safety. This patient population is classified as high cardiovascular risk, and their dyslipidemia has a distinct profile, largely influenced by immunosuppressive therapy. Traditional immunosuppressants – CNIs (cyclosporine, tacrolimus) and mTOR inhibitors (everolimus, sirolimus) – interfere with statin metabolism, thereby increasing the risk of side effects [37].

According to the KDIGO guidelines, statins are recommended as first-line therapy for the management of dyslipidemia in KT recipients. However, this recommendation is rated as “weak” [36].

Cholesterol absorption inhibitor

Currently, the only drug used in this group is ezetimibe. Unlike statins, ezetimibe acts by selectively blocking the Niemann–Pick C1-like 1 (NPC1L1) transporter protein in the small intestine, thereby inhibiting intestinal cholesterol absorption. This mechanism results in approximately a 54% reduction in hepatic cholesterol influx, leading to a compensatory increase in cholesterol synthesis and a 22.3% reduction in LDL cholesterol levels [38]. When used in combination with statins, ezetimibe produces additive lipid-lowering effects, reducing LDL-C by 24%, ApoB-100 by 14%, triglycerides by 12%, and high-sensitivity C-reactive protein by 13%, while HDL levels typically remain unchanged. However, ezetimibe monotherapy offers only a moderate LDL-C reduction, which may be insufficient for patients with severe hypercholesterolemia [39].

The pharmacokinetics of ezetimibe make it suitable for dialysis patients. Unlike statins, which are primarily eliminated by the liver, ezetimibe is metabolized in the intestine and liver to form an active glucuronide. This metabolite is excreted via both the renal (approximately 10%) and biliary pathways. Importantly, clinical studies (including the SHARP trial) have shown that renal impairment, including end-stage kidney disease requiring dialysis, does not significantly affect the pharmacoki-

netics of ezetimibe, permitting the use of the standard 10 mg/day dose without the need for adjustment.

From a clinical standpoint, ezetimibe provides several key advantages in dialysis patients. It serves as an effective adjunct to statin therapy, allowing the achievement of LDL-C targets without increasing statin doses and the corresponding risk of adverse effects. However, although the SHARP study evaluated the combination of ezetimibe and simvastatin in CKD patients with, it lacked sufficient statistical power to assess cardiovascular outcomes separately in dialysis and non-dialysis subgroups [2]. Based on these findings, the KDIGO working group does not recommend initiating ezetimibe therapy in dialysis patients unless it was started prior to initiation of dialysis [36].

The use of ezetimibe in KT recipients represents an important therapeutic option for managing dyslipidemia, particularly in the context of immunosuppressive therapy. Ezetimibe has minimal pharmacokinetic interaction with immunosuppressants such as tacrolimus or cyclosporine. Unlike many statins, which are metabolized via the CYP3A4 enzyme system and are therefore prone to drug–drug interactions, ezetimibe exerts negligible effects on this metabolic pathway, thereby reducing the likelihood of adverse effects.

Clinically, ezetimibe has demonstrated significant efficacy in KT recipients. In the SHARP study, which included patients with chronic kidney disease (including transplant recipients), the combination of ezetimibe and simvastatin reduced the risk of cardiovascular events by 17% [40]. To avoid the risks associated with high-dose statin therapy, combination therapy with ezetimibe is recommended [37].

Fibrates

Fibrates play an important role in the management of dyslipidemia characterized predominantly by hypertriglyceridemia. Their mechanism of action is based on activation of peroxisome proliferator-activated receptor alpha (PPAR-α), a nuclear receptor that regulates expression of genes involved in lipid metabolism. Activation of PPAR-α enhances the synthesis of lipoprotein lipase, an enzyme responsible for the hydrolysis of triglycerides (TG) in chylomicrons and VLDL, leading to a sharp reduction in circulating TG levels. In addition, fibrates increase HDL levels by upregulating the synthesis of apolipoproteins A-I and A-II, and by stimulating reverse cholesterol transport from peripheral tissues to the liver.

However, the use of fibrates is associated with several adverse effects. The most common include gastrointestinal disorders, liver dysfunction, and liver of gallstone disease. These drugs also sometimes cause pancreatitis. The most serious complication is myopathy, particularly when fibrates are used in combination with statins [41].

The use of fenofibrate is contraindicated or restricted in patients with moderate to severe renal impairment (creatinine clearance <60 mL/min) because of high risk of adverse effects [36].

Currently, there is limited evidence supporting the use of fibrates in KT recipients. Some studies have demonstrated a favorable effect on lipid profiles in this patient cohort [42]. Nevertheless, concerns regarding potential nephrotoxicity have significantly restricted their clinical application KT recipients. Further research is required to establish the safety and efficacy of fibrates in this patient population [43].

Bile acid sequestrants

Bile acid sequestrants represent an older class of lipid-lowering drugs that are now used much less frequently in clinical practice, particularly in patients with CKD, due to several limitations. Their ability to lower LDL levels is only 10–20%, which is significantly inferior to the effectiveness of statins. Moreover, these agents may increase plasma TG levels, making them contraindicated in patients with hypertriglyceridemia. In addition, the use of bile acid sequestrants in CKD remains poorly studied: the lack of convincing data on their safety and efficacy in this group of patients, as well as the risks associated with impaired absorption of nutrients and drugs, significantly limit their use [4].

Niacin

Niacin, which is not excreted by the kidneys, can theoretically be considered safe for use in CKD. However, its clinical application remains limited due to frequent adverse effects and insufficient evidence. Short-term studies have demonstrated the drug's efficacy in lowering lipid levels in CKD patients, confirming its potential role in the correction of dyslipidemia. In recent years, growing interest has focused on niacin and its analogue, niacinamide, particularly in patients with CKD and end-stage renal disease, owing to their ability to reduce serum phosphate levels. According to a meta-analysis of randomized controlled trials, niacin therapy in dialysis patients significantly decreases serum phosphorus concentrations without affecting calcium levels, while also increasing HDL cholesterol. However, no significant effects were observed on LDL cholesterol, TG, or total cholesterol, and the impact on cardiovascular outcomes remains unexplored. Thus, despite its promising dual action in modulating both phosphorus-calcium metabolism and lipid parameters, the widespread use of niacin in CKD and dialysis patients requires further investigation, particularly regarding long-term safety and clinical outcomes [4].

Bempedoic acid

Bempedoic acid is a lipid-lowering drug approved for reducing LDL cholesterol levels in patients who fail to achieve target LDL concentrations with statin therapy or are intolerant to statins. Its mechanism of action in-

volves the inhibition of ATP citrate lyase, a key enzyme in hepatic cholesterol biosynthesis, acting at an earlier stage of the metabolic pathway than statins. In CKD patients, the use of bempedoic acid is currently approved without the need for dosage adjustment in individuals with a glomerular filtration rate (GFR) above 30 mL/min/1.73 m^2 [44].

Findings from the large-scale CLEAR Outcomes (2023) clinical trial demonstrated that bempedoic acid reduces LDL cholesterol by 15–25% as monotherapy and by up to 35–40% when combined with ezetimibe. Furthermore, it was associated with a 13% reduction in major cardiovascular events, including heart attack and stroke, in statin-intolerant patients. At the same time, bempedoic acid offers several clinical advantages: it does not induce muscle-related adverse effects, can be safely combined with other lipid-lowering agents (such as statins or PCSK9 inhibitors), and is administered once daily at a fixed dose of 180 mg, which enhances treatment adherence. However, its use is not without limitations. The drug can elevate serum uric acid levels by approximately 10–15%, increasing the risk of gout, and in rare cases, has been linked to tendinitis or tendon rupture [45]. The possibility of use in patients receiving RRT requires further study.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

The PCSK9 enzyme binds to LDL receptors on the surface of hepatocytes. By destroying the LDL receptor, PCSK9 prevents their recycling back to the cell membrane, leading to a reduction in receptor density and, consequently, an increase in circulating LDL cholesterol levels [46].

PCSK9 inhibitors, such as alirocumab and evolocumab, are monoclonal antibodies that block the interaction between PCSK9 and LDL receptors. This preservation of receptor function enhances LDL uptake and catabolism, resulting in a 50–60% reduction in plasma LDL cholesterol, even among patients with refractory hypercholesterolemia [47].

Preclinical studies have shown that PCSK9 inhibition can attenuate atherogenesis and vascular inflammation within atherosclerotic plaques. Beyond its lipid-lowering properties, PCSK9 inhibition may exert additional angioprotective effects [48]. Clinically, these drugs not only lower LDL and Lp(a) levels but also significantly reduce the incidence of major cardiovascular events in secondary prevention groups.

PCSK9 inhibitors achieve a more rapid and profound reduction in LDL cholesterol, which may be more effective than the milder reduction achieved with statins in CKD patients [49]. Furthermore, emerging evidence suggests that the extent of LDL reduction achieved with PCSK9 inhibitors may influence coronary artery calcification. In one study of 120 patients, combination therapy with a PCSK9 inhibitor and a statin was associated with a lower annual progression of coronary artery calcification compared with statin monotherapy [50].

An analysis of eight phase III ODYSSEY trials demonstrated changes in apoB, non-HDL cholesterol, Lp(a), and HDL cholesterol, irrespective of CKD severity. No specific safety concerns were identified among patients with CKD compared with the overall study population. However, the efficacy and safety of PCSK9 inhibitors in patients with an eGFR below 30 mL/min/1.73 m^2 remain unestablished [51].

In kidney transplant recipients, PCSK9 inhibitors used as adjunctive therapy to statins have shown safety and efficacy in managing hypercholesterolemia and may contribute to a reduction in post-transplant cardiovascular events. Nevertheless, long-term, large-scale studies are required to confirm their potential benefits on cardiovascular outcomes, patient survival, and graft survival [52].

Inclisiran

Inclisiran also inhibits PCSK9 but acts through a fundamentally different mechanism than alirocumab and evolocumab. It is a small interfering double-stranded modified RNA conjugated to N-acetylgalactosamine (GalNAc), a carbohydrate ligand that binds to asialoglycoprotein receptors on hepatocytes. After cellular uptake, inclisiran induces degradation of PCSK9 mRNA, leading to a sustained reduction in PCSK9 protein synthesis [53].

Evidence from the ORION-7 and ORION-1 trials, which assessed the pharmacokinetics, efficacy, and safety of inclisiran in patients with normal renal function as well as mild, moderate, and severe CKD, indicated that dose adjustment is not necessary across different CKD stages [54].

A clinical case of inclisiran use in a patient who received RRT by kidney transplantation has been reported. The graft GFR was calculated at approximately 20 mL/min. Despite receiving the maximum tolerated lipid-lowering therapy (80 mg of atorvastatin and 10 mg of ezetimibe daily), the patient did not achieve the target LDL level (total cholesterol 5.18 mmol/L, LDL 2.46 mmol/L, HDL 2.12 mmol/L, and TG 1.79 mmol/L). Inclisiran was administered according to the following schedule: first injection, then after 3 months, and then every 6 months. LDL levels decreased to 1.03, 1.14, and 1.32 mmol/L after 6, 9, and 12 months, respectively [55].

The use of inclisiran in patients receiving RRT requires further study.

CONCLUSION

Dyslipidemia in CKD patients, especially those on RRT, represents a complex clinical challenge and a major contributor to cardiovascular morbidity and mortality in this population. The pathogenesis of lipid metabolism

disorders in CKD patients on RRT is multifactorial. Current evidence indicates that pharmacological strategies for managing dyslipidemia in this group remain limited.

Therapeutic approaches should be individualized, taking into account the type of RRT, comorbid conditions, and potential drug interactions. Drug treatment of dyslipidemia in patients receiving RRT requires research to explore ways to improve the prognosis for this group of patients who are at high risk for cardiovascular events.

The authors declare no conflict of interest.

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