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UNRESOLVED ISSUES IN THE CARE OF DIALYSIS PATIENTS

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ESRD-induced dyslipidemia—Should management of lipid disorders differ in dialysis patients?

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Abstract

Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide. Although numerous modifiable risk factors in the pathogenesis of CVD and its associated mortality have been identified, dyslipidemia remains to be a key focus for therapy. In this regard, significant progress has been made in reducing cardiovascular mortality via the use of lipid-lowering agents such as HMG CoA reductase inhibitors (statins). Yet, despite the disproportionate risk of CVD and mortality in patients with advanced chronic and end stage renal disease (ESRD), treatment of dyslipidemia in this patient population has not been associated with a notable improvement in outcomes. Furthermore, observational studies have not consistently found an association between dyslipidemia and poor outcomes in patients with ESRD. However, it is imperative that examination of dyslipidemia and its association with outcomes take place in the context of the many factors that are unique to kidney disease and may contribute to the abnormalities in lipid metabolism in patients with ESRD. Understanding these intricacies and distinct features will be vital not only to the interpretation of the available clinical data in regards to outcomes, but also to the individualization of lipid therapy in ESRD. In this review, we will examine the nature and underlying mechanisms responsible for dyslipidemia, the association of serum lipids and lipoprotein concentrations with outcomes and the results of major trials targeting cholesterol (mainly statins) in patients with ESRD.

1 | INTRODUCTION

The pandemics of obesity, type 2 diabetes, and hypertension during the past two decades have led to a dramatic rise in the prevalence of chronic kidney disease (CKD) and end stage renal disease (ESRD) throughout the world. The mortality rate in ESRD patients undergoing maintenance dialysis, at 15%-20% per year in the United States, is exceptionally high.[1] A major cause of mortality as well as morbidity in both CKD and ESRD patients is cardiovascular disease (CVD).[2] In fact, mortality from CVD is 1.4-3.7 times higher in the CKD population[3] and 10-30 folds higher in the ESRD patients[4] than in the general population. The most common cardiovascular complications in ESRD include cardiomyopathy, ventricular hypertrophy/dilatation, congestive heart failure, cardiac arrhythmia, coronary atherosclerosis, and arteriosclerosis. Many factors contribute to CVD in the ESRD population including hypertension, systemic inflammation, oxidative stress, protein energy wasting, insulin resistance, hypervolemia, anemia, electrolyte disorders (e.g. hyperkalemia), abnormal mineral metabolism (e.g. hyperphosphatemia), and dyslipidemia.[5]

One of the main factors in the pathogenesis of atherosclerosis and CVD in this population is abnormalities of lipid metabolism and serum lipid profile.[6] In addition, due to the role of lipids in production and storage of energy, impairment of lipid metabolism contributes to the CKD/ESRD-associated weight loss, cachexia, and impaired physical capacity.[7] The nature of lipid abnormalities in the ESRD population is influenced by several factors including underlying systemic disorders such as diabetes, dietary regimens, use of pharmacological agents, and renal replacement modalities i.e.

hemodialysis and peritoneal dialysis (PD).[8] Moreover, when present, inherited genetic lipid disorders compound CKD-associated dyslipidemia.

Ischemic CVD in the general population as well as in patients with mild to moderate CKD and/or proteinuria, is commonly associated with hypercholesterolemia and responds favorably to cholesterol lowering by HMG-CoA reductase inhibitors (statins).[9-11] Numerous clinical trials have evaluated the effect of statin therapy on outcomes in CKD and ESRD patients. Several studies have shown partial reduction in cardiovascular complications with long-term administration of statins in patients with moderate CKD not requiring dialysis.[10,12,13] The Study of Heart and Renal Protection (SHARP) trial, the largest clinical trial to date to evaluate the effect of statin therapy in the CKD population, showed a 17% reduction in risk of CVD events in the simvastatin plus ezetimibe-treated group, compared to placebo. Nonetheless, 11.3% of the treated group still experienced major CV events during the 4.9-year study period. A recent meta-analysis of 13 randomized controlled trials evaluating statin use in patients with CKD demonstrated that despite statin therapy, major cardiovascular events occurred in 13% of the stage 3, 10% of the stage 4, and 22% of the stage 5 CKD groups, indicating that residual risk of cardiovascular events grows with the advanced stages of CKD.[14]

While statins are partially effective in patients with mild to moderate CKD, they fail to reduce the cardiovascular morbidity and mortality in the ESRD population.[15,16] It should be noted that the nature and mechanisms of dyslipidemia and the features of CVD in CKD and ESRD patients are different from those in the general population.[17] These differences should be considered in the development of individualized preventive and therapeutic strategies for the management of CVD in this population. To this end, the nature and mechanisms of dyslipidemia and its contribution to the associated adverse consequences of advanced CKD are briefly described below.

2 | DYSLIPIDEMIA IN ESRD: FEATURES AND MECHANISMS

The dyslipidemia of ESRD is characterized by hypertriglyceridemia and elevated serum concentrations of triglyceride (TG) rich lipoproteins such as very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), chylomicron remnants and atherogenic oxidized lipids and lipoproteins.[18] Furthermore, ESRD is not only associated with apolipoprotein A-I (apoAI) and high-density lipoprotein (HDL) deficiency, but also with abnormal HDL composition and function including reduced HDL mediated reverse cholesterol transport, and reduced HDL antioxidant and anti-inflammatory properties.[19] Meanwhile, serum total and LDL cholesterol (LDL-c) levels are typically within or below normal limits in the majority of patients with either nonproteinuric advanced CKD or ESRD maintained on chronic hemodialysis.

It should also be noted that there are several other elements, which can have a major impact on lipid metabolism and serum lipid profile in ESRD. These include renal replacement modality-dependent changes in lipids as seen in PD and renal transplantation, preexisting genetic disorders unrelated to kidney disease, inflammation, malnutrition, and therapy with lipid modifying medications (steroids). For example, patients with ESRD being treated with PD can develop hypercholesterolemia and elevated serum LDL-c levels. This is due to mechanisms similar to that encountered in patients with heavy proteinuria and nephrotic syndrome, given that PD therapy can be associated with significant daily losses of protein in the dialysate.[8,20] Understanding the factors and mechanisms through which ESRD-related lipid/lipoprotein metabolism can be altered is of vital importance to the interpretation of clinical evidence and formulation of effective therapies.

3 | EFFECT OF ESRD ON TG AND TG-RICH LIPOPROTEIN METABOLISM

End stage renal disease is associated with lipoprotein lipase (LPL) deficiency and dysfunction. Under normal conditions, LPL mediates the hydrolysis of the TG cargo of VLDL and chylomicrons thereby allowing for the release and uptake of fatty acids (rich source of energy) by myocytes and adipocytes. Advanced CKD results in reduced expression of LPL in adipose tissue, skeletal muscle, and myocardium.[6,21] Furthermore, depletion of glycosylphosphatidylinositol-anchored binding protein 1 (GPIHBP1), which is essential for anchoring LPL to the endothelium, and an increase in serum concentrations of parathyroid hormone (secondary hyperparathyroidism) in CKD also contribute to LPL deficiency.[22]

In addition, advanced CKD and ESRD are associated with reduced LPL activity due to increased apolipoprotein CIII (LPL inhibitor)/apo-CII (LPL activator) ratio and heparin-mediated release and degradation of endothelium-bound LPL.[22] There is also evidence indicating increased concentrations of angiopoietin-like proteins (ANGPTL) 3 and 4 in ESRD, both of which are potent inhibitors of LPL activity.[8] Meanwhile, there is down-regulation of LDL receptor-related protein (LRP) and VLDL receptor, proteins which play key roles in clearance of VLDL, chylomicrons and IDL particles.[23,24] Together, the mentioned abnormalities not only result in elevated serum content of TG and TG-rich lipoproteins, but also impaired energy delivery and utilization. Furthermore, these mechanisms also partly explain reduced clearance of various atherogenic remnant lipoproteins in ESRD.[24]

4 | EFFECT OF ESRD ON LDL METABOLISM

While ESRD may not be associated with elevated serum concentrations of LDL-c, there is abnormal LDL metabolism such that serum levels of TG-rich and cholesterol-poor small dense LDL are increased. This subgroup of LDL particles is highly prone to modification and can increase the risk of atherogenesis despite normal

LDL-c levels. The generation of LDL with these features in ESRD is mostly due to LPL deficiency and decreased activity. Under normal conditions, LDL production is dependent on the serial actions of the LPL enzyme, which by cleaving the TG content of VLDL and IDL, mediates transition of these lipoproteins to LDL. Decreased LPL activity in ESRD leads to reduced mobilization of TGs from lipoproteins and this results in increased serum concentrations of TG-rich LDL. Furthermore, under normal conditions the cholesterol content of LDL is enriched through the action of the cholesterol ester transfer protein (CETP) which mediates the exchange in LDL TG content with cholesterol from cholesterol-rich HDL. Although the serum activity of CETP can be normal or increased in ESRD, deficiency of cholesterol rich HDL in these patients leads to a lack of cholesterol substrate for CETP and increased levels of small dense cholesterol poor LDL.[25,26]

It should also be noted that while serum concentrations of lipoprotein (a) [LP(a)] are not necessarily related to serum LDL-c, current standard laboratory methods do not typically distinguish cholesterol derived from LDL from Lp(a). Given that LP(a) is a highly proinflammatory and atherogenic lipoprotein, the fraction of this lipid being reported as LDL-c can make a significant impact in the association of serum LDL-c measurements and cardiovascular outcomes. For instance, it has been shown that serum concentrations of free and LDL-bound LP(a) are increased in patients with ESRD[8,27] and serum Lp(a) contributes to the high risk of atherosclerosis and CVD in this patient population.[28]

5 | EFFECT OF ESRD ON HDL METABOLISM

End stage renal disease is associated with a significant reduction in serum concentrations of apoAI and HDL particle.[29,30] This is accompanied by reduced HDL cholesterol content and altered lipid and protein composition including enrichment with TGs and proinflammatory proteins including serum amyloid A.[19,31,32] In addition, in patients with ESRD compared to normal controls, there is a significant decrease in HDL antioxidant, anti-inflammatory, and antithrombotic properties.[33-36] Furthermore, HDL-associated vasoprotective effects including nitric oxide mediated vasodilatation are diminished in CKD and there is a significant disruption in HDL-mediated reverse cholesterol transport (RCT).[37,38]

There are many factors which contribute to these abnormalities including: (1) decreased production and increased breakdown of apoAI;[39] (2) decreased level and activity of the key enzyme involved in esterification and loading of the cholesterol cargo of HDL, lecithin cholesterol acyltransferase;[40] (3) up-regulation of acyl-Co-A cholesteryl acyltransferase-I which limits the ability of HDL to mobilize free cholesterol from the cell;[41] and (4) various types of modification of apoAI which limits the interaction of HDL with the key proteins involved in cholesterol efflux from peripheral tissues, ATP binding cassette-AI and -GI. The latter modifications can occur due to several ESRD-associated factors, including elevated urea levels (carbamylation), reactive oxygen species (oxidation), and systemic inflammation.[42-44] The mentioned processes describe some of the main mechanisms responsible for HDL deficiency, altered composition and reduced RCT. Furthermore, these modifications along with reduced HDL-associated enzymes such as paraoxonase 1 and glutathione peroxidase, can significantly reduce HDL antioxidant and anti-inflammatory properties.[35]

However, it is important to note that the mechanisms described here can also adversely impact the ability of HDL to unload its cholesterol cargo in the liver, a step vital to completion of the RCT process. For instance, oxidative modification of HDL can impair its binding to its hepatic docking receptor, scavenger receptor BI (SR-BI), which is one of the proteins that plays a key role in unloading of HDL cholesterol in the liver.[45] Hence, ESRD may be associated with compromised HDL-mediated removal of cholesterol from peripheral tissues and impaired unloading of HDL cholesterol cargo in the liver, resulting in severe abnormalities of the RCT process. Finally, in the setting of systemic inflammation and oxidative stress, HDL from subset of ESRD patients may become proinflammatory in nature thereby potentially playing a deleterious role in pathogenesis of poor cardiovascular outcomes.[46,47]

6 | ASSOCIATION OF SERUM LIPIDS AND LIPOPROTEINS LEVELS WITH OUTCOMES IN ESRD

As noted thus far, the nature and underlying mechanisms responsible for the pathophysiology of dyslipidemia in advanced CKD and ESRD are distinct from that observed in other patient populations. However, it is important to note that the association of serum lipids and lipoprotein concentrations with outcomes is also unique in this patient population. For instance, while in most patients with or at risk for CVD, elevated serum levels of LDL-c are associated with worse outcomes, in patients with ESRD, and especially in those treated with hemodialysis, these observations are not consistently found.[48,49] In fact, there are studies which have found better outcomes in subgroups of hemodialysis patients with elevated serum cholesterol levels.[50] Furthermore, higher serum concentrations of HDL-c have not been found to be associated with improved survival in hemodialysis patients and in certain subsets they are associated with worse outcomes.[47,51] Finally, unlike the general population, increasing serum levels of TG and TG-rich lipoproteins are not associated with increased mortality with some studies reporting improved survival.[52,53]

While these observations may seem paradoxical on the surface, it is imperative that they are evaluated in the context of the mechanisms responsible for dyslipidemia in ESRD (i.e. oxidative stress, inflammation, malnutrition, protein energy wasting, energy dysmetabolism), modality of renal replacement therapy and patient specific factors such as genetic background. For instance, the association of cholesterol and TG containing lipoproteins with outcomes in ESRD may be an index of various intersecting factors such as degree

of inflammation, nutritional status, uremic toxin burden, and overall health of an individual patient (Figure 2). Furthermore, while cholesterol and TG containing lipoproteins have been implicated in pathogenesis of CV disease, it has to be recognized that lipids and TGs play an important role in numerous physiologic processes which are important for normal health. For example, their role as major sources of energy and fuel delivery for a variety of organ systems including skeletal muscle and cardiomyocytes cannot be overlooked. Therefore, in a catabolic state, marked by inflammation, inefficient energy expenditure and protein energy wasting, as seen in hemodialysis patients, elevated serum levels of these lipoproteins may be part of a process to counteract the risk of cachexia and wasting. Based on the mechanisms described and the association of serum levels of LDL-c, TG and total cholesterol with outcomes, it can be postulated that treatments aimed at lowering levels of these factors may not produce the same outcomes as that observed in other patient populations.[7]

As for the association of elevated serum HDL-c levels with worse outcomes in ESRD, this can be explained by several mechanisms. First, as stated earlier, the HDL particle from subsets of CKD and ESRD patients can in fact be proinflammatory in nature, thereby playing a deleterious role in pathogenesis of poor outcomes.[19,54,55] Second, impaired unloading of HDL cholesterol cargo which can occur due to ESRD-related (oxidative modification of apoAI) and ESRD-unrelated (underlying genetic abnormalities in the HDL docking receptor, SR-BI) factors, may result in increased serum levels of HDL-c. However, this pathologic increase in HDL cholesterol content is reflective of the impaired ability of HDL to complete the RCT process and therefore, can be associated with adverse clinical outcomes.

Although treatment of HDL deficiency may hold promise in patients with ESRD, the disappointing results of studies which increased serum HDL-c using Niacin (AIM-HIGH) and various CETP inhibitors have highlighted the need for evaluation of HDL composition and function in trials evaluating the impact of HDL-c on outcomes.[56,57] Several laboratory markers of HDL function in ESRD have been studied thus far, however, none have proven to have clinical utility. For instance, higher HDL cholesterol efflux activity has not been found to be associated with improved outcomes in hemodialysis and renal transplant patients.[58-60] Future studies will need to examine HDL composition, antioxidant, anti-inflammatory and HDL cholesterol influx/unloading capacity as clinical tools in evaluating risk in patients with ESRD.[37]

7 | EFFECT OF LDL-TARGETED THERAPY ON OUTCOMES IN CKD AND ESRD

To date, there have been three prospective randomized clinical trials which evaluated the safety and efficacy of LDL-targeted therapy (HMG-CoA Reductase inhibition or statin therapy) in improving cardiovascular outcomes and survival in patients with CKD, and ESRD being treated with hemodialysis. In the 4D (Die Deutsche Diabetes Dialyse) study, 1255 hemodialysis patients with type 2 diabetes were randomized to atorvastatin (20 mg/d) or placebo and followed up for 4 years.[15] At the end of the study, there was no significant reduction in the risk of death from cardiac causes or nonfatal MI.

The 4D study was followed by another prospective double-blind randomized clinical trial in a larger group of mostly statin-naive hemodialysis patients, called AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events).[16] In this study, the effect of rosuvastatin (10 mg/d) on cardiovascular morbidity and mortality was compared to placebo in 2776 hemodialysis patients with a mean baseline LDL cholesterol concentration of about 100 mg/dL. The mean duration of exposure to the study medication was approximately 2.4 years in duration, while the mean length of follow-up time was 3.2 years. Despite a 43% reduction in serum LDL-c and a significant reduction in serum levels of C-reactive protein, rosuvastatin therapy failed to reduce the incidence of major cardiovascular events including fatal and nonfatal myocardial infarction and overall mortality.

The third large randomized statin trial, SHARP, was conducted in patients with various stages of kidney disease including those with nondialysis dependent CKD and ESRD treated with hemodialysis.[10] There were 3023 dialysis patients and 6247 CKD patients not on dialysis with an average estimated glomerular filtration rate of 27 mL/min/1.73 m^2 in this trial.[2] Patients were randomized to receive simvastatin 20 mg/d with or without ezetimibe 10 mg/d or placebo and then followed up for 4.9 years. It found that treatment with statin plus ezetimibe resulted in a 17% reduction in major atherosclerotic events, 25% reduction in nonhemorrhagic stroke, 21% reduction in coronary revascularization and a trend toward reduction in nonfatal myocardial infarction when compared with placebo. However, these findings were mainly driven by the results in patients with nondialysis dependent CKD, as therapy with simvastatin/ezetimibe failed to reduce mortality rates or cardiovascular events in the dialysis patient stratum alone.

There are many reasons why statin therapy in patients with ESRD may not result in the same outcomes as that observed in other patient populations. As described earlier, serum levels of cholesterol and cholesterol-rich lipoproteins are typically normal or subnormal in the vast majority of patients being treated with hemodialysis. Furthermore, the major underlying contributors to CVD (i.e. oxidative stress, inflammation, uremic toxins, protein energy wasting), types of cardiovascular events (i.e. sudden cardiac death, left ventricular hypertrophy, arrhythmia), and nature of dyslipidemia (accumulation of TG-rich lipoproteins, the presence of small TG-rich dense LDL and Lp(a) and HDL deficiency and dysfunction) are not necessarily remediated by inhibition of cholesterol synthesis via statins.[8] For instance, since statins do not impact Lp(a) level, the lack of efficacy of statin trials in ESRD can be partially explained if the patients studied had markedly increased serum Lp(a) levels comprising most of their measured LDL cholesterol concentrations.[27,28]

However, it is also important to note that there are most likely subgroups of patients with ESRD on hemodialysis who may benefit

from lipid lowering therapy.[61] Hence, the major challenge in treating dyslipidemia in ESRD may lie in identifying patients who can benefit from available therapies and separating them from those who stand to only suffer from the side effects. For instance, in a post-hoc subgroup analysis of the 4D Study, it was noted that treatment with atorvastatin significantly reduced the rates of adverse outcomes in patients with the highest quartile of LDL-c (>145 mg/dL).[62] However, no benefit was seen in patients with lower LDL-c levels.

The fact that there were patients with significantly elevated LDL-c levels also points to the fact that there may be subgroups of hemodialysis patients with genetic causes of hyperlipidemia. The role of genetic background will need to be examined in this context as these may be patients that can benefit from lipid lowering therapy. In another analysis of samples and data from the 4D study, it was noted that patients with the lowest HDL cholesterol efflux activity significantly benefitted from atorvastatin therapy raising the

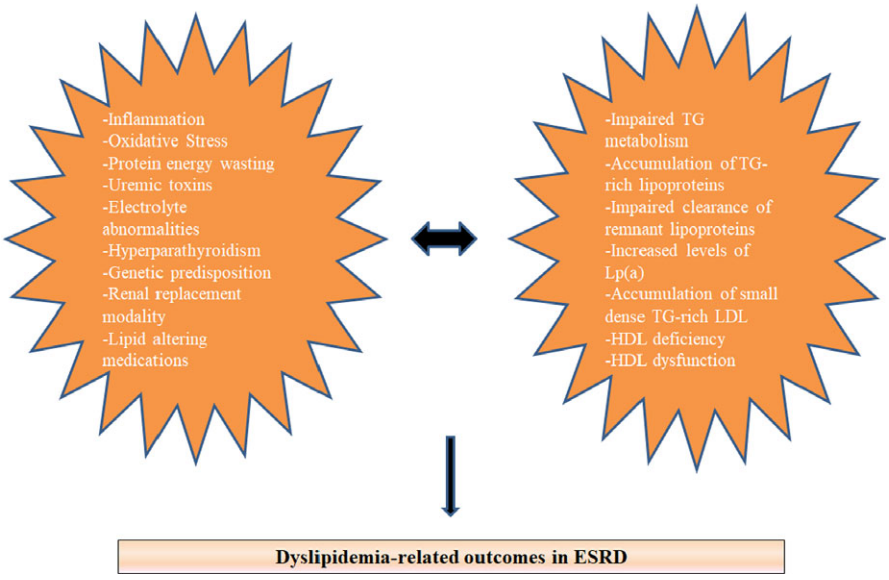

FIGURE 1 The interplay between dyslipidemia and other related factors which determines cardiovascular outcomes in ESRD [Color figure can be viewed at wileyonlinelibrary.com]

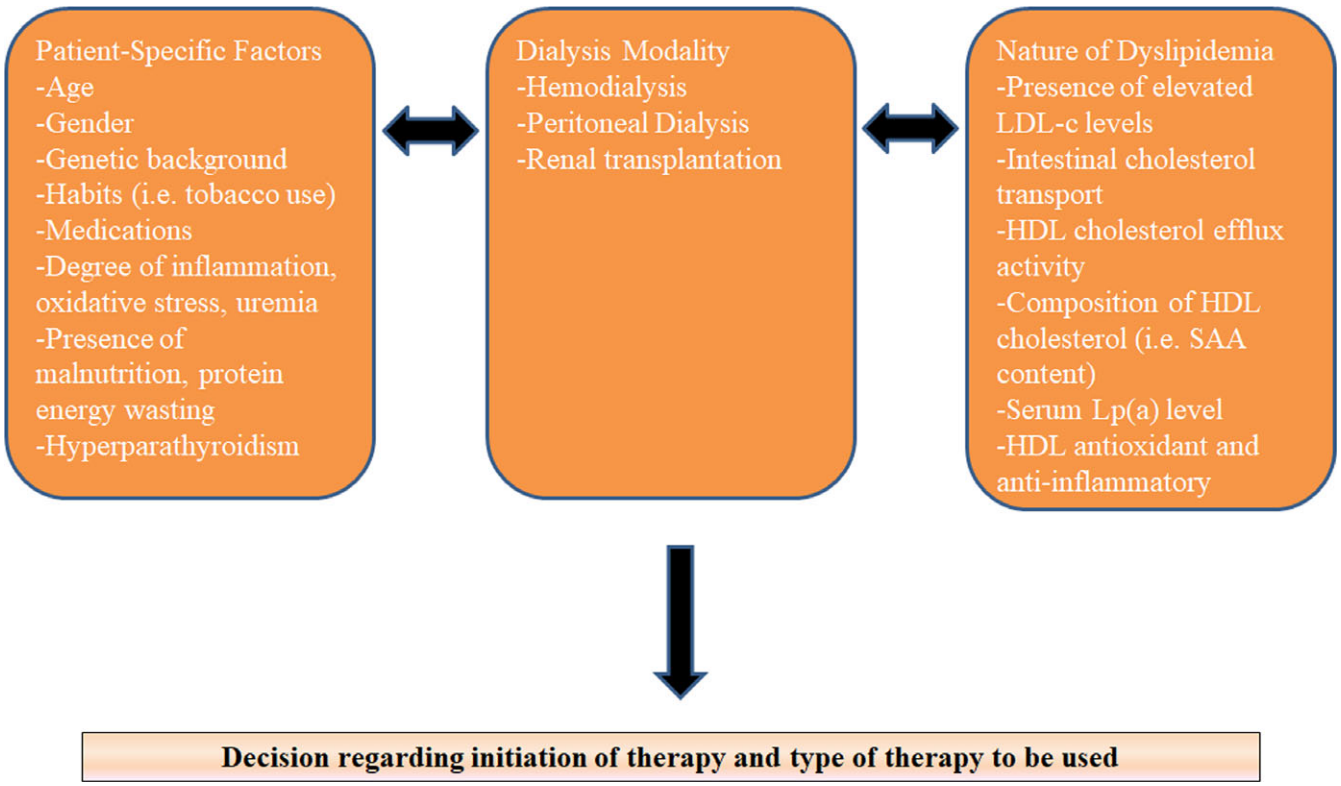

FIGURE 2 Future research should identify the factors that need to be considered when deciding if and how to treat dyslipdemia in ESRD [Color figure can be viewed at wileyonlinelibrary.com]

possibility that using this index may assist in identifying patients who are most likely to benefit from statins.[60] Furthermore, it has been reported that atorvastatin treatment reduced the risk of reaching the study primary endpoints in the 4D study in patients with the lowest intestinal cholesterol absorption (lowest tertile).[63] While these post hoc analyses should not influence current treatment decisions, future studies in patients with ESRD treated with hemodialysis will need to take into account these important patient-specific factors.

The only study which addresses the role of statin therapy in ESRD treated with transplantation is The Assessment of LEscol in Renal Transplantation (ALERT). This was a double-blind, placebo-controlled trial in 2102 patients with ESRD treated with renal transplantation who were randomized to treatment with fluvastatin or placebo.[64] While there were fewer cardiac deaths or nonfatal MI in the fluvastatin group, there was no significant difference between the two groups in the primary and secondary endpoints. Furthermore, a meta-analysis of all studies evaluating statin therapy in recipients of kidney transplantation has failed to show a convincing benefit from this therapy.[65] However, it is important to note that dyslipidemia of patients with renal allografts is significantly affected by the type and dose of immunosuppression being used independent of ESRD. Therefore, future clinical trials will need to consider the underlying mechanisms responsible for dyslipidemia (i.e. type of immunosuppression) and role of therapy in subgroups of patients who are most likely to benefit based on subgroup analysis (i.e. younger patients who are smokers).

In contrast with patients being treated with hemodialysis, there is accumulating evidence that statin therapy in patients with nondialysis dependent CKD and those with ESRD treated with PD may result in improved outcomes. The SHARP study as well as various meta-analyses have found that statin therapy in patients with mild to moderate CKD can be associated with reduced major cardiovascular events, cardiovascular death, and all-cause mortality.[13,66] Based on these findings, major dialysis guidelines have recommended lipid lowering therapy with statins in patients with predialysis CKD.[67] In addition, as described earlier, patients with ESRD being treated with PD have been noted to have increased levels of serum cholesterol and cholesterol-rich lipoproteins (LDL-c) in a pattern of dyslipidemia similar to that observed in patients with nephrotic syndrome.[68] There are observational studies which have found that the use of lipid-modifying medications including statins is associated with improved mortality in PD patients.[69,70]

Another potential therapy of interest for dyslipidemia in PD patients is inhibitors of Proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein which binds to and inhibits the LDL receptor. It has been shown that PD patients have elevated serum levels of PCSK9, and this can partly explain their elevated total and LDL cholesterol levels.[71] There is preliminary evidence that PCSK9 inhibition can improve CV outcomes in patients with CVD.[72] Hence, it would be interesting to see whether use of PCSK9 inhibitors can be a more effective mode of lipid lowering therapy in patients on PD given that it addresses a major underlying cause of dyslipidemia in this patient population.

8 | SUMMARY

The nature and mechanisms responsible for dyslipidemia in patients with ESRD are distinct from that observed in other patient populations at risk of CVD and mortality. Furthermore, these underlying mechanisms are heavily impacted by a variety of patient-specific factors including presence and burden of inflammation, oxidative stress, protein energy wasting, renal replacement modality, and genetic predisposition. The interplay between these factors can play a key role in understanding the association of serum lipid and lipoprotein levels with outcomes in ESRD patients, which on the surface may seem paradoxical (Figure 1). Furthermore, these factors most likely play a major role in the outcomes observed in trials of lipid lowering therapy (i.e. statin therapy) in this patient population. Therefore, treatment of dyslipidemia in ESRD will need to be individualized based on the underlying components that can be unique to each patient and likely substantially contribute to the pathogenesis of CVD and poor outcomes. Furthermore, there needs to be greater focus on the development of markers (i.e HDL function, intestinal LDL absorption, PCSK9 levels, LDL and HDL composition) that can be used to identify patients who may benefit from the various lipid-altering therapies that are now available. Therefore, in regards to treatment of dyslipidemia ESRD, it is becoming abundantly clear that a one-size-fits-all approach is unlikely to be successful in improving outcomes. Hence, the decision to treat and the type of therapy used will need to be tailored for each patient individually (Figure 2).

POTENTIAL CONFLICT OF INTEREST

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