International Urology and Nephrology (2019) 51:265–277
https://doi.org/10.1007/s11255-018-2047-y

NEPHROLOGY - REVIEW

The effect of chronic kidney disease on lipid metabolism

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Received: 15 September 2018 / Accepted: 27 November 2018 / Published online: 5 December 2018

Abstract

The major cause of death among chronic kidney disease patients is cardiovascular diseases. Cardiovascular and kidney disease are interrelated and increase the severity of each other. Dyslipidemia is one the major causes of cardiovascular disease among chronic kidney disease patients along with diabetes and hypertension. The relationship between dyslipidemia and chronic kidney disease is reciprocal. Dyslipidemia is known to be a risk factor for chronic kidney disease and chronic kidney disease causes major alterations on lipoprotein profile, defined as the "dyslipidemic profile" of chronic kidney disease patients. Increased triglyceride, very low density lipoprotein and oxidized low density lipoprotein as well as decreased high density lipoprotein and changes in the composition of lipoproteins contribute to the "dyslipidemic profile." Treatment strategies targeting the "dyslipidemic profile" of chronic kidney disease could contribute to prevent cardiovascular diseases. Current therapy is based on the patient kidney function and consist mainly of statins. This review focuses on the effects of chronic kidney disease on the lipoprotein profile and how this may impact novel therapeutic approaches to cardiovascular risk.

Keywords Chronic kidney disease · PCSK9 · Cholesterol · Triglycerides · HDL · LDL

Introduction

Chronic kidney disease (CKD) is defined by the chronic, irreversible loss of kidney function. It affects millions of patients worldwide and increase the risk of cardiovascular disease and death [1]. CKD interferes with the regulation of major metabolic pathways [2–4]. Although altered lipid metabolism is a key contributor to cardiovascular diseases, CKD also plays a role in the development of dyslipidemia by dysregulating the levels or function of many molecules. There is a "dyslipidemic phenotype" that occurs in CKD patients [5]. The components of this constellation are increased triglyceride (TG) and very low-density lipoprotein (VLDL) levels, decreased high-density lipoprotein (HDL-C), and variable levels of low-density lipoprotein (LDL-C) [6]. Not only the levels of these molecules but an altered composition are the determinants of their atherogenicity in the course of CKD. A better understanding of the drivers and consequences of these changes may help to identify early biomarkers of and to optimize therapeutic approaches to decrease cardiovascular and overall mortality in CKD patients.

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Effect of CKD on HDL-C

HDL-C metabolism

HDL-C is a protective lipoprotein with antithrombotic, antioxidant, and anti-inflammatory characteristics. It participates in Reverse Cholesterol Transport from the peripheric tissues to the liver to make cholesterol molecules excretable by liver. The process begins with excretion of cellular cholesterol from cell by ATP-binding cassette-1 (ABCA1) and its interaction with apolipoprotein A1 (ApoA1) [7].

Lecithin:cholesterol acyltransferase (LCAT) then esterifies cholesterol and forms mature HDL-C particles from small pre-beta HDL-C particles [8, 9]. HDL-C contains molecules that contribute to protective actions, namely plasmalogens, sphingosine-1-phosphate (S1P), and apolipoprotein M (ApoM), among others. This composition may be modified in CKD, thus changing the protective properties of HDL-C and transforming HDL-C into molecules that actually can cause vascular injury [10].

HDL-C component alterations

HDL-C protein composition changes in CKD are summarized in Fig. 1. ApoA1 is the major protein component of HDL. Low ApoA1 levels were a stronger negative prognostic factor for adverse cardiovascular outcomes than HDL-C itself, in a study following 839 Swedish elderly men since 1970 [11]. ApoA1 levels are low in hemodialysis patients [12, 13]. As ApoA1 is in fact protective against CKD [14], so decreased ApoA1 may be one of the factors contributing to further accelerate CKD progression. In 860 peritoneal dialysis patients, the proportion of apolipoprotein B (ApoB) to ApoA1 correlated with cardiovascular events and all-cause mortality [15]. However, the ApoB/ApoA1 ratio was not a better cardiovascular event predictor than the non-HDL-C/HDL-C ratio in CKD patients [16]. Since HDL-C protective properties are attenuated in CKD, the fact that the ApoA1-based ratio does not predict better than the HDL-C-based ratio may indicate that ApoA1 function may also be affected by CKD.

ApoM is another apolipoprotein bound to HDL that plays a role in pre-Beta HDL-C formation and facilitates cholesterol efflux from macrophages [17]. Plasma ApoM levels decrease with advancing CKD and are even lower in CKD patients with known coronary artery disease, suggesting a possible relationship between ApoM levels and cardiovascular events [18].

The HDL-C subfraction distribution also differs in CKD patients. In two observational studies, one in hemodialysis patients [19] and the other in non-dialysis patient with CKD stage 2, 3, 4, and 5 [20] showed that CKD patients had larger proportions of large HDL-C subpopulations. In the general population, these large subfractions have protective roles and are inversely associated with cardiovascular diseases [21, 22], but whether their role is changed in CKD patients requires further investigation.

Finally, in a cohort study of CKD patients stage 1–5, decreased estimated glomerular filtration rate (eGFR) was associated with increased Apolipoprotein C-III (ApoC-III) and retinol binding protein 4 (RBP4) contents and decreased apolipoprotein L1 (ApoL1) and vitronectin in HDL-C particles [23]. ApoC-III levels are associated with susceptibility to coronary artery disease [24] and to conversion of anti-apoptotic properties of HDL-C to proapoptotic [25]. A case–control study suggests that HDL-C-mediated cholesterol efflux capacity was inversely associated with the ApoC-III contents of HDL-C [26]. RBP4 is associated with increased triglyceride levels and small HDL-C particles [27]. RBP induces insulin resistance and that it is increased in patients with non-diabetic CKD stage 5 [28]. The impact of ApoL1 and vitronectin on HDL function is not well characterized. Hemodialysis initiation was associated with changes in 30 protein components of HDL-C, of which eight were increased: serum amyloid A1 (SAA1), serum amyloid A2 (SAA2), serum amyloid A4 (SAA4), hemoglobin-b, haptoglobin-related protein (HPR), cholesteryl ester transfer protein (CETP), phospholipid transfer protein (PLTP), and Apolipoprotein E (ApoE) [29].

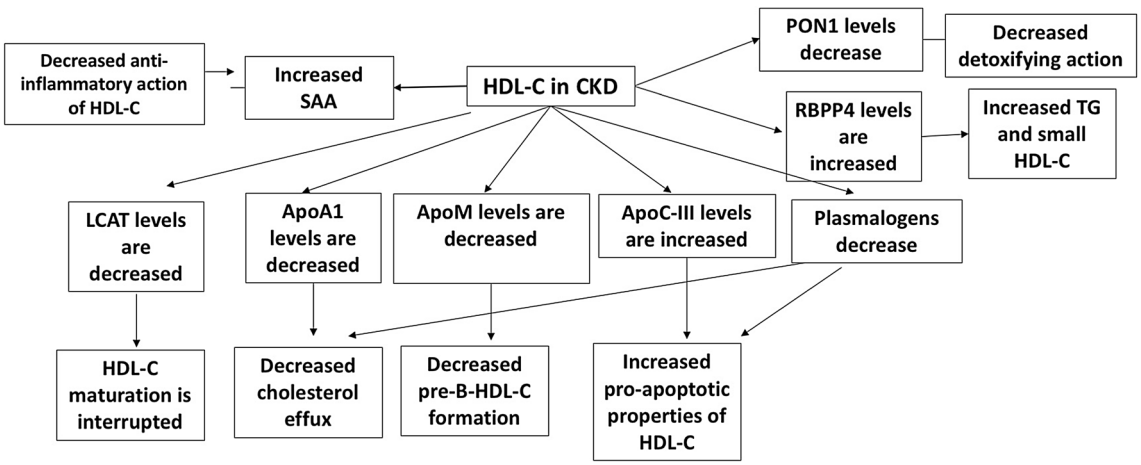

Fig. 1 HDL composition changes in CKD. *HDL-C* high-density lipoprotein, *SAA* serum amyloid A, *pre-B-HDL-C* pre-beta high-density lipoprotein, *PON1* Serum paraoxonase/arylesterase 1, *RBP4* retinol binding protein 4, *TG* triglyceride, *LCAT* lecithin-cholesterol acyltransferase, *ApoA1* apolipoprotein A1, *ApoM* Apolipoprotein M, *ApoC-III* apolipoprotein C III, *SDMA* Symmetric dimethylarginine

Other molecules

Plasmalogens are phospholipids that are associated with the cholesterol efflux capacity of HDL-C and which enhance the anti-apoptotic and anti-atherogenic properties of HDL-C [30]. A recent study reported that both HDL-C and plasmalogen levels were lower in CKD stage 5 than in stage 3/4 patients [31].

The HDL-C complex is necessary to preserve HDL-C functionality [32]. Induction of nitric oxide synthase [33, 34], prostacyclin production [35], and angiogenesis [36] are mediated by the HDL-C S1P complex (HDL-S1P). Despite lower concentrations of apoM, end stage renal disease (ESRD) patients had a higher level of S1P and HDL-C-associated S1P [37].

LCAT levels and activity tend to decline in patients with CKD. In rats with subtotal nephrectomy, liver LCAT mRNA declined after 6 weeks compared to control rats [38]. Of note, increased LCAT with subsequent increased HDL-C is not always associated with better atheroprotection and inversely, decreased LCAT levels are associated with decreased HDL-C levels but not with poorer cardiovascular outcomes, implying that HDL-C is not fully functional in CKD patients [8]. Nevertheless, LCAT levels decrease up to 60% in ESRD patients and this has been related to impaired anti-oxidant and anti-inflammatory properties of HDL-C [12]. The correlation between LCAT and HDL-C levels points out that LCAT may be a new target in the treatment of dyslipidemia in CKD patients [39].

Paraoxonase 1 (PON1) binds to HDL-C and exerts detoxifying actions [40], while paraoxonase 3 (PON3) associates with HDL-3 [41]. These proteins prevent atherosclerosis [42] and their gene polymorphisms are associated with increased cardiovascular events [41]. The PON1 contents of HDL-C are decreased in dialysis and pre-dialysis CKD patients compared to controls whereas PON3 levels were similar [40].

Modulation of HDL-C effect on anti-inflammatory activity

The anti-atherogenic effect of HDL-C has been ascribed not only to its role in Reverse Cholesterol Transport but also to its anti-inflammatory effects. As an example, HDL-C decreased palmitate-induced reactive oxygen species (ROS) generation in adipose tissue [43]. The anti-inflammatory actions of HDL-C are impaired in CKD. In a case–control study, the anti-inflammatory effects of HDL-C were lower in patients on hemodialysis than in healthy controls [44]. SAA levels in HDL-C from patients with ESRD inversely correlated with its anti-inflammatory properties [45, 46]. HDL-C in ESRD patients enhanced tumor necrosis factor alpha (TNFα) secretion [47].

In CKD, there is evidence for increased numbers of activated monocytes characterized by high CD14(++)CD16(+) monocyte counts [48]. Mild renal dysfunction is associated with lower HDL-C and the decreased HDL-C was inversely related to increased monocyte count and increased atherosclerosis [49]. Monocyte activation is a key feature of inflammation, contributes to atherogenesis, and is inhibited by HDL [13]. In CKD, both low Apo-I and low high-density lipoprotein cholesterol were associated with high CD14(++) CD16(+) monocyte counts [50]. The monocyte count:HDL-C ratio (MHR) has been used as a marker of oxidative stress and inflammation to predict cardiovascular events, including in CKD patients [51, 52]. In a prospective study following 340 subjects with stage 1–5 CKD, Kanbay et al. observed that the MHR ratio increased as the eGFR decreased. The risk for fatal and non-fatal cardiovascular events was higher in patients having MHR in the third tertile than in the first tertile [53].

HDL from CKD patients and endothelial dysfunction

HDL from CKD patients, in contrast to healthy HDL, activated toll-like receptor 2 (TLR2) to promote endothelial superoxide production and inflammation, reduced nitric oxide (NO) bioavailability, and subsequently increased arterial blood pressure. Symmetric dimethylarginine (SDMA) in HDL-C from CKD patients causes transformation to an abnormal lipoprotein inducing endothelial dysfunction [54]. Indeed, SDMA accumulation abolishes the anti-inflammatory and regenerative properties of hemodialysis [55]. The negative impact of CKD HDL-C on endothelial function was also observed in samples from children and improved post-transplantation [56].

HDL-C effects on other lipoproteins

HDL-C contributes to decrease LDL-C-VLDL complex formation and enhance LDL-mediated VLDL-triglycerides lipolysis [57]. CKD stage 3 patients had lower lipolysis efficiency than non-CKD patients and this effect was further diminished in CKD stage 4 patients. Both decreased HDL-C levels and the decreased efficacy of HDL-C to increase VLDL-triglycerides lipolysis contributed to this observation [58].

HDL-C levels as predictors of outcomes

Higher HDL-C levels are not associated with lower mortality rates in CKD patients, unlike the population with normal renal function [59]. A 3-year cohort study of 33,109 chronic hemodialysis patients suggested that HDL-C was associates with improved outcomes up to a concentration of 50 mg/dl but surprisingly, levels over 60 mg/dl were associated

with increased cardiovascular and all-cause mortality [60]. In a cohort study conducted among 1,764,896 US veterans, mortality rates in patients with HDL-C levels ≤ 25 mg/dl and ≥ 50 mg/dl were similar and were lower than for HDL-C levels in between 25 and 50 mg/dl, suggesting a U-shaped curve between HDL-C and mortality [61]. The U-shaped curve between HDL-C levels and mortality in CKD patients suggests that functionality of HDL-C is more important than its quantity or that the reason for increased mortality may not be associated with cardiovascular events in patients with high HDL-C levels [62]. Indeed in two large studies in 3310 subjects undergoing coronary angiography and in 1424 individuals, serum SDMA levels significantly predicted all-cause and cardiovascular mortality, and were significantly correlated with SDMA accumulation in HDL. Indeed, higher serum SDMA was independently associated with lower cholesterol efflux as a measure of HDL-**C** functionality. In subjects with low SDMA levels, higher HDL-C was associated with significantly lower mortality, but in subjects with high SDMA, HDL-C was associated with higher mortality [55]. Similar observations were made for serum SAA and for its interaction with HDL-C [63]. Algorithms allowing for calculation of 'biologically effective HDL-C' were developed based on measured HDL-C and SDMA or SAA which had predictive value for cardiovascular outcomes [55, 63].

Effect of CKD on LDL-C

Metabolism and role of LDL-C

LDL-C, which the remnant of VLDL and intermediate density lipoprotein (IDL), is the lipoprotein carrying majority of cholesterol [64]. LDL-C has pro-atherogenic effects and is the main target of current therapeutic interventions. Besides the levels of LDL-C, which is the only parameter assessed in routine clinical practice, the distribution of LDL-C subfractions also contributes to cardiovascular risk [65]. LDL-C levels in CKD are variable [66]. However, CKD is associated with LDL-**C** structural and composition alterations that could contribute to cardiovascular risk factors in this population (Fig. 2).

LDL-C electronegativity

LDL-C electronegativity is increased in CKD patients compared to controls. This is attributed to the increased L5 subfraction of LDL-C (L5-LDL), which is the most electronegative LDL-C. Chronic administration of electronegative LDL-induced myocardial relaxation dysfunction in mice that was mediated by lectin-like oxidized LDL receptor-1 (LOX-1) induced increased inducible NO synthase expression and endothelial NO synthase uncoupling, Sarcoplasmic/endoplasmic reticulum calcium ATPase 2a (SERCA2a) nitrosylation and increased calcium [67]. L5-LDL also contributes to ST elevation myocardial infarction (STEMI) by promoting the synthesis of interleukin 1 beta (IL1β), a key proinflammatory molecule [68].

Oxidized LDL-C

Oxidized LDL-C (oxLDL-C) is more atherogenic than native LDL-C [69]. Even mild oxidation levels increase the atherogenic effects of oxLDL-C [70]. Inflammation increases oxLDL-C by increasing oxidative stress [71]. Increased oxLDL-C has been observed in non-dialysis CKD, but most studies relate to dialysis patients [72]. Peritoneal dialysis patients were reported to have higher serum oxLDL-C levels than hemodialysis patients and both dialysis populations had significantly higher oxLDL-C levels

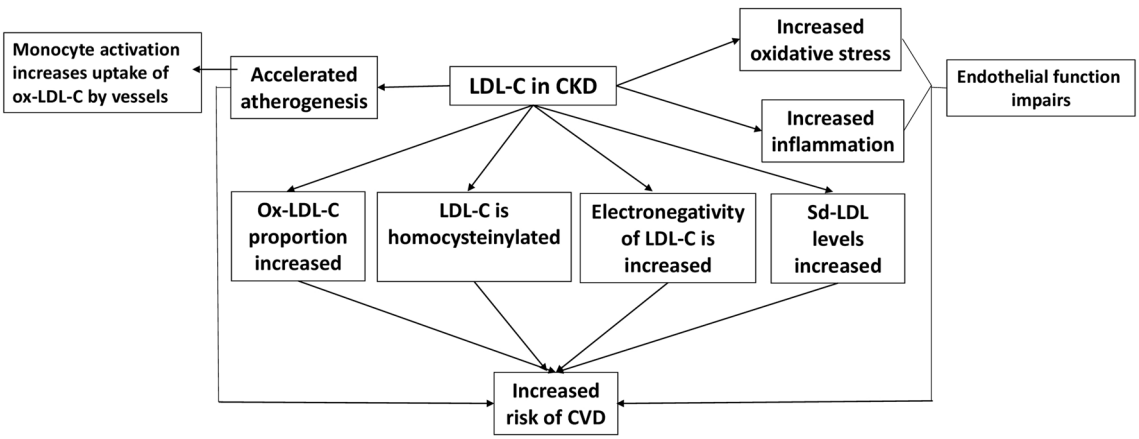

Fig. 2 LDL composition changes in CKD. *LDL-C* low-density lipoprotein, *ox-LDL-C* oxidized low-density lipoprotein, *sd-LDL* small dense low-density lipoprotein

than normal controls [73]. Despite lower LDL-C levels, hemodialysis patients had a higher oxLDL-c/LDL-C ratio than the general population [74].

Small dense LDL-C

LDL particle size is also important in CKD patients. Small dense LDL (sdLDL-C) are smaller than classical LDL lipoproteins accessing more easily access the arterial wall and are also more readily oxidized [75], fastening oxLDL-C accumulation [76]. sdLDL-C was accepted to be related with coronary heart disease in the wake of the Atherosclerosis Risk in Communities (ARIC) Study [77]. sdLDL-C is considered more atherogenic than other LDL-C subtypes [78]. sdLDL-C levels tend to increase in CKD patients and are highly correlated with cardiovascular risk in this population [79, 80]. sdLDL-C is also related to insulin resistance and hypertriglyceridemia [81].

Homocystamide LDL-C

Homocysteinylation is the modification of proteins by homocysteine [82]. LDL-C is prone to homocysteinylation and the end-product is homocystamide LDL-C (HcyLDL-C). HcyLDL-C is cytotoxic and causes oxidative damage on endothelial cells [83, 84]. HcyLDL-C levels are increased in CKD patients [85, 86]. However, the relationship of HcyLDL-C levels with outcomes has to be more extensively studied in CKD patients.

LDL-C levels as predictors of outcome

The predictor capacity of LDL-C levels for cardiovascular risk in CKD patients is debated. In some, but not all studies, cardiovascular disease risk was increased with higher LDL-C [87–89]. A confounding factor is the association of malnutrition, which is common in CKD patients, and specially in those on dialysis, with both low LDL-C and mortality. In this regard, Kidney Disease Improving Global Outcomes (KDIGO) guidelines do not recommend LDL-C levels to be used as a risk predictor, since all CKD patients above the age of 50 years were considered to be at the highest cardiovascular risk category [90]. Since the role of LDL-C assessment is controversial, oxLDL-C should be explored as a more reliable marker of cardiovascular risk stratification in CKD patients. However, for this to enter into clinical practice, it should be demonstrated that indeed its use results in the prescription of interventions that improve outcomes.

CKD impact on VLDL and IDL metabolism

VLDL and IDL are triglyceride-rich intermediary molecules in lipoprotein metabolism. VLDL-C is excreted from liver and then converted to IDL, LDL-C, and HDL-C. VLDL, IDL and triglyceride levels are increased in both dialysis and non-dialysis CKD patients [91, 92] and this increase is characteristic of the CKD dyslipidemic profile. This is due to deficiency of lipoprotein lipase (LPL), the enzyme that hydrolyzes the triglycerides to VLDL and chylomicrons, leading to delayed VLDL catabolism in CKD patients [93–95]. Elevated VLDL levels are an independent risk factor for all-cause and cardiovascular mortality in peritoneal dialysis patients [96]. In hemodialysis patients, IDL levels were closely associated with aortic stiffness in [92]. Higher ApoC-III correlated with increased VLDL and VLDL- triglycerides [97]. ApoC-III modulates plasma triglycerides levels and inflammation [98], thus making it a risk factor for cardiovascular disease [99]. ApoC-III also decreases LPL levels, thus contributing to increased VLDL-C levels [100].

Advanced oxidation products (AOPPs) are oxidative stress markers first described on uremic patients in 1996 [101]. They are also a valuable marker of oxidative stress in acute coronary syndrome patients [102]. VLDL-C is associated with the highest amount of AOPP compared to LDL-C and HDL-C but no differences were found between the AOPP fractions of VLDL-C among controls, non-dialysis CKD G2-G4, and hemodialysis patients [40].

Effect of CKD on triglycerides

The major lipid abnormality in CKD patients is hypertriglyceridemia, driven by increased lipoprotein triglyceride contents along with the delayed catabolism of triglycerides [103, 104]. Apolipoprotein C (ApoC) levels are associated with decreased catabolism of triglyceride-rich lipoproteins and increased ApoC levels contribute to increase triglycerides levels in CKD [105]. The triglycerides content of HDL-C is also increased in CKD [9].

In a recent 1-year prospective study of 150 adults with CKD stage 1–5, triglyceride levels increased with CKD progression, peaking in CKD stage 4 [2]. Increased triglycerides and low HDL-C have been associated with a high incidence of cardiovascular events in CKD patients [91, 106]. Similarly, a lipid profile rich in triglycerides-rich lipoproteins, especially in CKD stage 3 patients, was associated with coronary heart disease risk [5].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to the LDL-C receptor (LDLR), accelerating its

degradation [107]. Gain-of-function mutations in the PCSK9 gene reduces LDLR levels, causing increased LDL-C levels [108]. Interestingly, plasma PCSK9 levels positively correlated with triglycerides and Apo-B levels in patients with non-diabetic CKD, while no correlation was detected with LDL-C levels. It was postulated that PCSK9 dysregulation could be a possible factor in hypertriglyceridemia in CKD patients [109].

CKD and lipoprotein (a)

Lipoprotein (a) (Lp(a)) is a unique lipoprotein that is an independent risk factor for cardiovascular disease and whom kidney is partly responsible for clearance [110]. Lp(a) levels tend to increase in concordance with kidney disease in patients with large Apolipoprotein A (ApoA) forms, in contrast to nephrotic syndrome and continuous ambulatory peritoneal dialysis in which patients' Lp(a) levels increase irrespective of the isoform size. This attenuation is related to decreased clearance via the kidneys [111]. Lin et al. related each two-fold increment in Lp(a) levels with a decline of eGFR of 0.50 ml/min/year ($p < 0.001$) [112]. This attenuation is also validated in diabetic patients with mild eGFR impairment [113]. Furthermore, a study aiming detecting the predictive value of Lp(a) concentrations analyzed data of 904 CKD patients undergoing percutaneous coronary angiography out of 3508 CKD patients between 1997 and 2011. In conclusion of the study, Lp(a) levels are found to be a predictive factor in CKD patients undergoing percutaneous coronary angiography [114]. C study also confirms that Lp(a) can be a novel biomarker for aortic valve calcium in CKD patients [115]. This renders Lp(a) an important target in CKD patients. PCSK9 targeting is one of the few maneuvers known to decrease Lp(a), including in CKD patients [114, 116].

Treatment modalities

The fact that spontaneous dyslipidemia or caused by CKD likely increases cardiovascular mortality has led to guidelines recommending the use of lipid lowering therapy and, specifically, statins in CKD patients (Table 1). The different components of dyslipidemic profile in CKD patients (decreased HDL-C, variable LDL-C, increased VLDL, IDL and in some patients Lp(a)) should be targeted by specific (for CKD) therapeutic strategies [117].

Statins

The KDIGO committee recommends that all CKD patients aged > 50 years should be prescribed low dose statin treatment unless they are in chronic dialysis [90]. Higher doses of statin are not preferred with advanced disease even if dyslipidemia worsens since kidney plays a role in their elimination and the beneficial effects of statins on events seem to be dramatically decreased if the patient is on dialysis [118, 119]. The decision to recommend statins alone was taken based on a variety of reasons, including the higher cost of the statin-ezetimibe combination, even though the most convincing trial of the beneficial effects of statins in CKD actually tested a statin/ezetimibe combination [120]. The Study of Heart and Renal Protection (SHARP) trial compared 4650 patients receiving simvastatin 20 mg plus ezetimibe 10 mg to decrease LDL-C levels with 4620 patients receiving placebo. All patients had CKD (3023 on dialysis) and none had known myocardial infarction nor cardiovascular revascularization in their past medical history. Simvastatin plus ezetimibe reduced major cardiovascular events, but benefit was not observed in dialysis patients [120]. It has been argued that combining ezetimibe to low dose statins instead of increasing statin dose improves the adverse effects profile of statins [121]. The effect of statins on mortality in CKD is disputed. No impact on mortality was observed in the largest trial to date [120]. An analysis of 6 randomized controlled trials (RCTs) comparing high-dose statin (atorvastatin 80 mg or rosuvastatin 20/40 mg) vs. moderate/low-dose statin concluded that the stroke risk is decreased in CKD patients with high-dose statin, but the effect on overall mortality remains unclear and more studies are required to ensure safety [122]. In contrast, a study of 16,428 CKD patients with dyslipidemia observed that statin use was not associated with decreases ischemic stroke rates although they lowered all-cause mortality [123]. In US veterans with CKD G3a-G4 who initiated statin therapy recently and maintained it for over 1 year, no association between the intensity of statin regimen and all-cause mortality was found [124].

In addition to SHARP; other major trials failed to find a benefit of statins in hemodialysis patients. The 4D trial explored whether atorvastatin improved cardiovascular outcomes in 1255 diabetic patients on hemodialysis. Atorvastatin reduced the LDL-C levels and all cardiac events combined but had no impact on cerebrovascular events combined nor all-cause mortality, and, importantly on the composite primary end-point of cardiovascular death, non-fatal myocardial infarction, and stroke [125]. Later on, the 4D study was modeled in a larger observational study where 5144 statin users were matched with non-user controls. In adjusted models, statins were associated with a reduction in the composite primary outcome of cardiac death, non-fatal myocardial infarction, and stroke, but the magnitude of the benefit was much lower than in non-dialysis patients [126].

The A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival

Table 1 Therapeutic intervention on the lipid profile of CKD patients

	CKD stage 1 and 2	CKD stage 3	CKD stage 4	CKD stage 5	Unspecified
KDIGO [90]	> 50 y/o should receive low dose statin	> 50 y/o should receive low dose statin	> 50 y/o should receive low dose statin	> 50 y/o should receive low dose statin	
Yan et al. [122]					Stroke risk is decreased with high dose statin
Chung et al. [122]			Statins reduce overall mortality but do not affect stroke risk	Statins reduce overall mortality but do not affect stroke risk	
Walther et al. [124]		Intensity does not affect mortality	Intensity does not affect mortality		
Fukumoto [121]					Low dose statin should be combined with ezetimibe instead of high dose statin
Shen et al. [153]		Statins are effective with CAD	Statins are effective with CAD		
SHARP [120]					Simvastatin + ezetimibe is better than placebo in lowering LDL-C
4D [125]				Atorvastatin had no effect on all-cause mortality in diabetic HD patients	
Chan et al. [126]				Statins may have some cardiovascular benefit in diabetic HD patients	
AURORA [127]				Rosuvastatin does not decrease all-cause mortality in ESRD	
Athyros et al, Cho et al [128, 129]	Statins effective in earlier CKD stages				
Jun et al. [134]	Fibrates are successful in lowering cardiovascular risk in mild-to-moderate CKD				
Weinstein et al. [135]		Fenofibrate and rosuvastatin combination resulted in better triglycerides and HDL-C profile than rosuvastatin alone			
K/DOQI [136]					Fibrates + statins increase the risk of myositis and rhabdomyolysis
Toth et al. [147]					Alirocumab decreases LDL-C levels regardless of renal function
Hassan et al. [138]				Omega 3 decreased triglycerides levels in peritoneal dialysis patients	

Table 1 (continued)

	CKD stage 1 and 2	CKD stage 3	CKD stage 4	CKD stage 5	Unspecified
Jin Kang et al. [140]					Niacin increased HDL-C levels and decreased triglycerides levels
Kalil et al. [144]		ERN + simvastatin better in increasing HDL-C and decreasing triglycerides than simvastatin alone, but cardiovascular outcome unchanged			
Miele et al. [151]		Exercise intervention does not improve the decreased HDL-C levels			
Barcellos et al. [150]					Exercise does not improve LDL-C nor HDL-C profile

CKD chronic kidney disease, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglyceride, *ERN* extended-release niacin, *HD* hemodialysis, *CAD* coronary artery disease

and Cardiovascular Events (AURORA) study investigated the effects of rosuvastatin on cardiovascular morbidity and mortality in hemodialysis patients. Rosuvastatin decreased LDL-C, total cholesterol, triglycerides and C-reactive protein, but there was no significant difference in cardiovascular mortality [127]. It is thought that for statins to provide clear benefits, they should be started earlier in the course of CKD [128, 129]. Similar to the general population, statins displayed anti-inflammatory effects in hemodialysis patients, but despite this, no reduction in the primary endpoint was observed [130, 131].

Fibrates

Fibrates are one the most commonly prescribed lipid-lowering agents yet not as widely studied on CKD patients in contrast to statins. They decrease the production and increase the removal of triglycerides, and hence their overall effect is lowering triglycerides levels. They are preferred in CKD patients with severe hypertriglyceridemia (> 1000 mg/dl) [90]. Their immediate effect of increasing creatinine levels has raised concern about their safety in CKD patients [132, 133]. Fibrates are successful in lowering cardiovascular risk in mild-to-moderate CKD [134] but their efficacy is questionable in higher stages of CKD.

A multicenter, randomized trial compared fenofibrate plus rosuvastatin to rosuvastatin alone for 16 weeks in CKD stage 3 patients. The combination resulted in lower triglycerides and higher HDL-C than rosuvastatin alone [135]. However, the stain-fibrate combination increases the risk of myositis and rhabdomyolysis and guidelines recommend avoiding this combination [136]. The impact of the combination on cardiovascular event has not been studied in CKD patients.

Other agents

Additional agents have been tested in CKD, as recently reviewed [137]. Omega 3 for lipid lowering was studied in a small ($n = 15$) pilot peritoneal dialysis study. Omega 3 supplementation for 8 weeks along with simvastatin did not modify inflammatory markers but omega 3 succeeded to decrease triglyceride levels more than in the control group [138].

Niacins are lipid-lowering agents not cleared by the kidneys, so they may be safe to use in CKD patients [139]. They may improve both the dyslipidemic profile and hyperphosphatemia in CKD patients [140–142]. Niacin increased HDL-C levels and decreased triglycerides and lipoprotein levels but tolerance is poor [143]. In a small study, 23% of 34 CKD patients complained of side effects or discontinued the treatment [140]. Extended release niacin (ERN) in addition to simvastatin increased HDL-C by a mean of 11.3 mg/dl and decreased triglycerides by a mean of 59.0 mg/dl in 505

CKD stage 3 patients. However, the addition of ERN to simvastatin did not improve cardiovascular outcome, although the study was underpowered for this endpoint [144].

PCSK9 inhibition with neutralizing monoclonal antibodies reduces LDL-C to a greater extent than statins and also reduces Lp(a) and cardiovascular events [145, 146]. Clinical trials have included patients with mild and moderate CKD and subanalyses of CKD patients are becoming available. Among 4629 hypercholesterolemic patients both with impaired and normal renal function, pooled from eight phase 3 Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY) trials, alirocumab safely decreased LDL-C levels regardless of renal function [147]. It is important to understand the physiological and pharmacological properties of this novel therapy, the possible side effects of its usage in patients with decreased renal function and create a target population among CKD patients, that may include nephrotic syndrome [148]. The combination of statins plus fibrate was associated to increased PCSK9 levels in diabetic kidney disease patients, likely reducing the efficacy of lipid lowering therapy: patients with elevated PCSK9 as a result of this dual therapy may also benefit from PCSK9 targeted therapy [149].

Exercise

A systematic review including randomized controlled trials, evaluating the effect of exercise on adult CKD patients found no benefit on lowering LDL-C nor increasing HDL-C levels [150]. A recent study confirmed that the decreased HDL-C levels in stage 3 CKD patients were unchanged with aerobic exercise intervention [151].

In addition to traditional and non-traditional cardiovascular risk factors, the lipid alterations in CKD patients make them more prone to cardiovascular morbidity and mortality [3, 152]. However, all treatment modalities of cardiovascular disease do not apply to CKD patients since their lipid compositions alter from non-CKD patients and lipid lowering treatment modalities are not as effective as in patients without kidney disease in CKD patients. This could be a possible reason why future research may be directed specifically for this group of patients. As the findings expand, new molecular targets can be found and specifically targeted. Also, the renal clearance of some drugs such as fibrate limit their trial due to safety concerns but whether the improved cardiovascular outcomes may outweigh increased creatinine levels to some extent is also negotiable.

Conclusion

In CKD patients, the lipoprotein profile and the metabolism and function of specific lipoproteins is altered (Fig. 3). HDL-C number tends to decline and the protective anti-inflammatory effect of HDL-C is lost. ApoA1, the main component of HDL-C, possibly loses its atheroprotective properties and its levels decrease. LDL-C levels are variable and suffer changes that increase their association with cardiovascular risk in CKD patients: LDL-C electronegativity, oxidation, and homocysteinylation are all increased and associated with cardiovascular disease. VLDL levels tend to increase due to delayed catabolism and decreased levels of LPL. Hypertriglyceridemia is the major component of the dyslipidemic profile of CKD. Finally, Lp(a) levels are increased in CKD in persons people with large apo(a) isoforms, while Lp(a) is increased

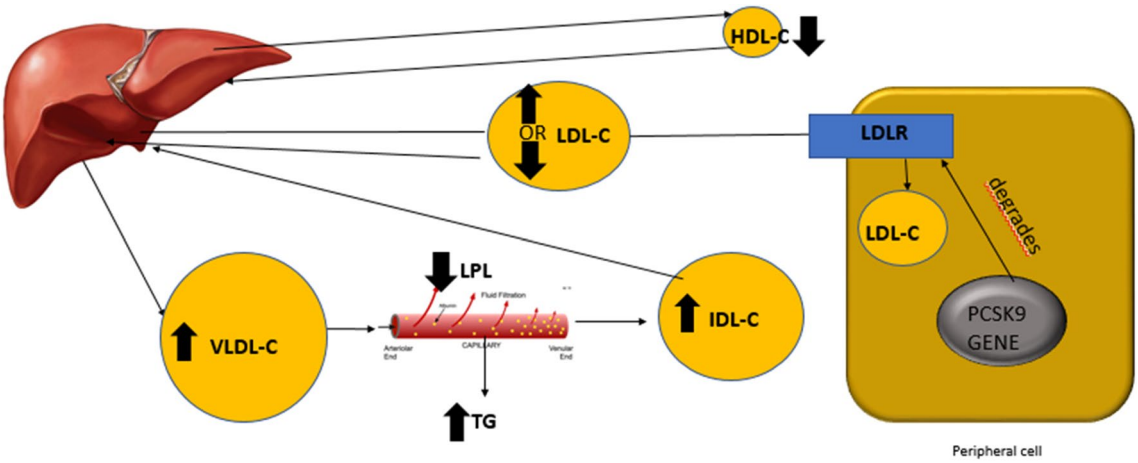

Fig. 3 Overall view of lipoprotein changes in CKD. *VLDL* very low-density lipoprotein, *LPL* lipoprotein lipase, *TG* triglyceride, *IDL* intermediate density lipoprotein, *LDL* low-density lipoprotein, *LDLR* low-density lipoprotein receptor, *PCSK9* proprotein convertase subtilisin-kexin like-9, *HDL* high-density lipoprotein. Arrows indicate changes in the number of particles in CKD

irrespective of apo(a) isoform size in peritoneal dialysis and nephrotic syndrome. Treatment strategies differ from otherwise healthy people since the kidney function must be considered. High-dose statins are not preferred because they are eliminated in kidney. Statins may be combined with ezetimibe. PCSK9 inhibitors are novel promising agents. Unlike in healthy subjects, exercise did not reverse the decreased HDL-C in CKD patients. Further research is required into the contribution of lipoprotein abnormalities to the high cardiovascular risk and above all, on how to counterbalance them to improve outcomes.

Acknowledgements MK gratefully acknowledges use of the services and facilities of the KoC University Research Center for Translational Medicine (KUTTAM), funded by the Republic of Turkey Ministry of Development. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Ministry of Development. AO was supported by FIS PI16/02057, ISCIII-RETIC REDinREN RD016/0009 FEDER funds, Sociedad Española de Nefrología, Fundacion Renal Iñigo Álvarez de Toledo (FRIAT), Comunidad de Madrid Biomedicina B2017/BMD-3686 CIFRA2-CM.

Funding This study was not funded by any Grant.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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