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Review article for Nature Reviews Nephrology

Lipoproteins and fatty acids in CKD: from molecular and metabolic alterations to pathophysiology and risk for kidney and heart

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Key points

1. HDL and LDL modifications in CKD contribute to increased cardiovascular risk. Targeting these modifications may reveal interesting future strategies for therapy.
2. In CKD, alterations in proteome content, metabolic waste accumulation and post-translational modifications transform HDL from an anti-inflammatory to a pro-inflammatory molecule and enhance the pro-inflammatory character of LDL.
3. HDL modifications and the altered relation of HDL levels with cardiovascular risk in CKD compared with the general population support the concept that HDL-functionality rather than HDL-cholesterol levels influences cardiovascular risk.
4. With increased kidney function decline, non-atherosclerotic CVD increasingly contributes to cardiovascular risk, further contributing to an altered correlation of lipoprotein levels with overall cardiovascular risk.
5. Deregulated fatty acid metabolism and mitochondrial dysfunction not only negatively impact on the heart, but also on kidney pathology through inflammation and fibrosis, with protective effects provided by autophagy.
6. Accumulation of saturated fatty acids triggers mitochondrial and cell damage in the kidney, whereas polyunsaturated fatty acids docosahexaenoic acid and eicosapentaenoic acid provide protective effects.

Content

Abstract

Chronic kidney disease (CKD) induces modifications in lipid and lipoprotein metabolism and homeostasis. These modifications can induce, modulate and/or accelerate CKD as well as the secondary disease cardiovascular disease (CVD). Lipid and lipoprotein abnormalities may involve triglyceride-rich lipoproteins, low-density lipoprotein (LDL) and high-density lipoprotein (HDL), with alterations not only linked to concentration but also to molecular structure including protein composition, small-molecule accumulation as well as post-translational modifications. These alter lipoprotein function and enhance pro-inflammatory processes. Furthermore, a deregulated metabolism of fatty acids as important lipid mediators in energy production has been identified to not only negatively impact on the heart, but to contribute also to progression of kidney damage. By summarizing causes, identity and pathophysiological consequences of lipid and lipoprotein modifications in CKD, this review aims to stimulate additional future efforts in unraveling the pathophysiological link between the failing kidney and genesis and/or progression of CVD.

Introductory box with figure

Lipids are hydrophobic and therefore not soluble in aqueous media, e.g. in plasma. Therefore, free **fatty acids** are mainly transported by binding to albumin, whereas **triglycerides** (being esters of three fatty acids with glycerol) and **cholesterol** are transported within **lipoprotein particles**. Here, lipids and proteins aggregate non-covalently to form micelle-like particles with a hydrophobic core of cholesterol esters and triglycerides. The lipoprotein shell consists of phospholipids, the hydroxyl-groups of unesterified cholesterol and proteins, generally known as apolipoproteins (**Figure 1A**).

The metabolism of lipids and lipoproteins can be divided into exogenous and endogenous pathways (**Figure 1B**). In the exogenous pathway, lipids are absorbed in the intestine. Fatty acids react with glycerol to form triglycerides, and cholesterol is esterified to form cholesterol esters. Triglycerides and cholesterol are assembled intracellularly as chylomicrons. **Chylomicrons** are metabolized to chylomicron remnants by lipoprotein lipase, releasing **free fatty acids** from its triglycerides for energy storage or production. To the latter, free non-esterified fatty acids are transported into mitochondria, where they undergo **β-oxidation** to feed the citric acid cycle and respiratory chain for energy production in the form of adenosine triphosphate (ATP). Chylomicron remnants are cleared from the circulation by hepatic chylomicron remnant receptors before further metabolism to bile acids and cholesterol.

Endogenously, the liver generates **very low-density lipoproteins** (**VLDL)**, whose triglycerides are subsequently hydrolysed by lipases in peripheral tissues for energy storage or production. The VLDL lipid content is reduced by the lipolysis process, whereby **intermediate-density lipoproteins (IDL)** are generated. By uptake of cholesterol esters from HDL, IDL is transformed to **low-density lipoproteins (LDL)**. LDL is either metabolized by the liver or, upon excess, deposited in peripheral tissues and taken up by macrophages, triggering atherosclerosis[1]. On the other hand, **high-density lipoproteins (HDL)** exert important cardioprotective properties through reverse cholesterol transport, taking up excess cholesterol from peripheral tissues for transport and removal in the liver[1,2].

These different lipoprotein classes can be distinguished based on density, which reflects their relative proportion of proteins and lipids (**Figure 1A)**[3]. Furthermore, they alter in the main apolipoprotein within their outer shell, with these apolipoproteins exerting important roles in lipoprotein metabolism and function[4].

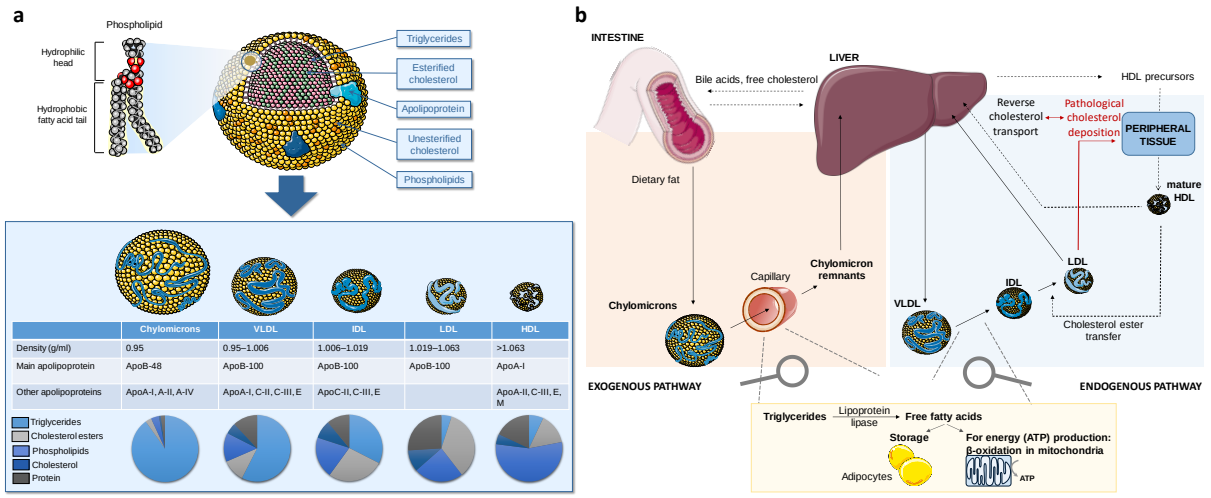

Figure 1. Lipoprotein structure, classification and metabolism. A. Within lipoprotein particles, lipids and proteins aggregate non-covalently to form micelle-like particles with a hydrophobic core of cholesterol esters and triglycerides and an outer shell of phospholipids, unesterified cholesterol and apolipoproteins. Lipoprotein particles are classified based on their density and differ in lipid and protein composition[3]. **B.** Lipid metabolism can be divided into an exogenous pathway, with dietary fat assembled into chylomicrons, and into an endogenous pathway, with VLDL particles synthesized in the liver. Both chylomicrons and VLDL mediate transfer of mainly triglycerides to cells and peripheral tissue, where triglycerides are hydrolysed into free fatty acids for energy storage in adipocytes or energy use, the latter through β-oxidation in the mitochondria. Chylomicron remnants are metabolized by the liver, whereas VLDL is transformed by triglyceride depletion over IDL into LDL. LDL mediates cholesterol removal by the liver or deposits excess cholesterol in tissue, whereas HDL mediates reverse cholesterol from peripheral tissues into the liver.

1. INTRODUCTION

Lipids play essential roles as components of cell membranes, as mediators of intracellular and intercellular signalling as well as in energy storage and production. Here, free, non-esterified **fatty acids** undergo **β-oxidation** in mitochondria, resulting in the production of ATP (**Box 1**). Fatty acids can circulate in a non-esterified form in plasma bound to albumin. Alternatively, they are esterified with a glycerol molecule to **triglycerides** and are transported together with **cholesterol** within **lipoprotein particles (Box 1)**. Chylomicrons and very-low density lipoproteins (VLDL) are formed in the intestine and liver, respectively. They contain a high proportion of triglycerides and, through triglyceride hydrolysis by lipoprotein lipases, provide fatty acids to tissues for energy production or storage. Low-density lipoproteins (LDL), formed out of VLDL due to substantial loss of triglyceride content, transport cholesterol to the liver for removal from the organism, but also trigger pathological cholesterol deposition in peripheral tissues[1]. In contrast, high-density lipoproteins (HDL) mediate cardioprotective reverse cholesterol transport from peripheral tissues for cholesterol removal by the liver[1,2] **(Box 1)**.

In the general population, increased plasma levels of LDL-cholesterol (LDL-C) highly contribute to increased risk of atherosclerosis and cardiovascular disease (CVD)[1]. Also, high triglyceride levels are associated with increased cardiovascular risk[5], whereas an inverse relation was revealed for HDL-cholesterol (HDL-C)[6,7]. Furthermore, fatty acid overload has been linked with mitochondrial oxidative stress and the accumulation of toxic fatty acid derivatives in the heart, with mitochondrial dysfunction negatively impacting on the heart[8]. Thus, lipoprotein particles and lipid metabolism highly impact on cardiovascular risk.

Patients with chronic kidney disease (CKD) are at increased cardiovascular risk, with CVD accounting for around half of deaths in patients with CKD stage 4-5[9]. In addition to an increased incidence of atherosclerosis-related cardiovascular events along all stages of CKD, patients become also more prone to non-atherosclerotic cardiovascular diseases[9,10]. Compared to the non-CKD population at high cardiovascular risk, CKD patients typically present an altered picture of dyslipidemia as well as an altered relation of lipoprotein levels with cardiovascular risk.

Furthermore, fatty acid profiles and metabolism are altered in CKD[11,12], and deregulated fatty acid metabolism has been identified to not only negatively impact on

the heart[8], but to contribute also to further kidney damage[13]. Here, we will **summarize current knowledge on dyslipidemia in CKD in terms of lipoproteins and fatty acids, including altered levels and molecular changes, underlying mechanisms, pathophysiological consequences for the kidneys and cardiovascular risk**. In this way, this review aims to stimulate future efforts unravelling the pathophysiological link between declining kidney function and genesis and/or progression of CVD.

2. ALTERED LIPID METABOLISM IN CKD

2.1 Lipoprotein particles, cholesterol and triglycerides

Serum lipid profiles from patients with moderate to advanced CKD mostly display decreased HDL-C levels[14], unaltered LDL-C levels[14] and increased levels of triglycerides[14,15] and triglyceride-rich lipoprotein particles (VLDL, IDL and chylomicron remnants)[16] (**Figure 2**).

2.1.1 High-density lipoprotein

A lower level of **HDL-C** in CKD patients compared to healthy subjects[14] can, at least in part, be explained by a reduced biosynthesis of its main apolipoprotein ApoA-I[17]. Also, CKD patients display an impaired HDL maturation due to reduced expression of lecithin-cholesterol acyltransferase (LCAT)[18,19] (**Figure 2**). This HDL-bound enzyme esterifies free cholesterol acquired by ApoA-I within nascent HDL and thereby coordinates the production of mature HDL, rich in esterified cholesterol.

2.1.2 Low-density lipoprotein

CKD patients display an increase in small dense **LDL-C**[16], with concentrations increasing with declining glomerular filtration rate (GFR) and associated with future cardiovascular events[20]. On the other hand, total serum LDL-C levels are variable in CKD patients. Hypercholesterolemia is a risk factor for CKD development and also in CKD patients with mild to moderate CKD, hypercholesterolemia and increased LDL-C levels can be observed, especially in patients with proteinuria (nephrotic syndrome), as summarized before[21,22]. However, most studies of patients with moderate to advanced CKD as well as patients with kidney failure found total LDL-C levels to be unaltered[14,22] or even decreased[16,23]. This may be explained by a reduced LDL production through reduced catabolism of triglyceride-rich lipoprotein particles, being mainly in balance with a reduced LDL clearance in CKD[24] (**Figure 2**). Reduced LDL catabolism and associated increased LDL residence time as observed in advanced CKD[24] have been linked with a higher degree of post-translational modifications, as e.g. oxidation, of LDL[25]. As discussed in more detail later on, CKD patients display increased molecular changes within lipoproteins. For LDL, this reduces binding to its receptors LDLR and LDLR related protein in the liver and may thereby contribute to reduced LDL clearance from plasma (**Figure 2**).

2.1.3 Triglycerides and very low-density lipoprotein

The concentration of **triglycerides** already increases in early stage CKD[15], with triglyceride levels above 200 mg/dl especially abundant in predialysis patients with nephrotic syndrome[21]. Increased levels of **triglyceride-rich lipoproteins** in CKD can be explained by a reduced catabolism of these particles through increased ApoC-III levels, a reduced ApoC-II/ApoC-III ratio[26,27] and an associated reduced activity of lipoprotein lipase in CKD[27]. Also, reduced activity of hepatic triglyceride lipase has been reported in CKD-5D patients[23]. Furthermore, expression of VLDLR[28] and LDLR related protein[29] were downregulated in experimental CKD, which through reduced clearance of remaining VLDL particles as well as of IDL and chylomicron remnants may contribute to increased triglyceride-rich particles in CKD (**Figure 2**). Also, direct impact of uremic toxins as well as insulin resistance[30] in conjunction with a high prevalence of diabetic comorbidity[31] have been suggested to contribute to CKD-dependent hypertriglyceridemia.

2.1.4 Lipoprotein(a)

Lipoprotein(a) (Lp(a)) is an LDL-like lipoprotein containing apolipoprotein(a) (Apo(a)) covalently bound to apolipoprotein B100 (ApoB100). Its plasma levels are strongly determined genetically[22] and it has strong pro-inflammatory properties[1]. Probably related to reduced clearance, Lp(a) levels are increased in CKD patients with large Apo(a) isoforms, especially in the more advanced stages, as well as in patients with nephrotic syndrome irrespective of the Apo(a) isoform size[22,32] (**Figure 2**).

2.2 Free fatty acids

CKD patients have increased total levels of free fatty acids in serum compared to healthy controls[11]. Among fatty acid subclasses, **saturated fatty acids**[11,12] **and monounsaturated fatty acids**[33,34] **are increased in concentration, whereas polyunsaturated fatty acid levels were mostly found to be decreased**[11,33,34]. Also, C16-C20 saturated fatty acids, as palmitic acid, are increased in patients with CKD stage 5 compared to CKD stage 2-4[12]. In addition to increased levels of free fatty acids, patients with CKD also have increased serum levels of ceramides as fatty acid derivatives, with ceramide levels increasing with declining kidney function[35].

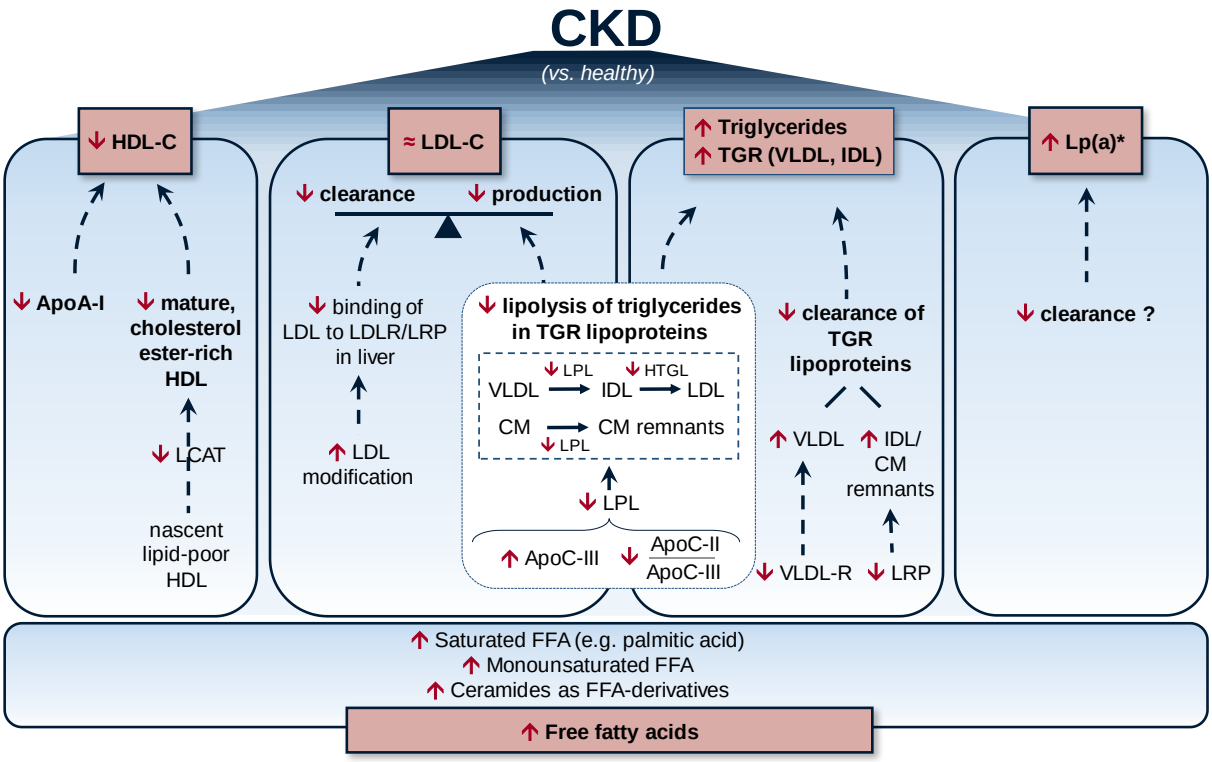

Figure 2: Dyslipidemia in CKD. Compared to healthy subjects, CKD patients display decreased serum levels of high-density lipoprotein-cholesterol (**HDL-C**) as well as impaired HDL maturation. Furthermore, whereas increased low-density lipoprotein-cholesterol (LDL-C) levels can be observed in patients with early stage CKD, **LDL-C** levels are mostly unaltered in moderate to advanced CKD stage 4-5 as well as in kidney failure, with reduced LDL production mainly balanced by reduced LDL clearance. In contrast, CKD patients typically display increased serum levels of **triglycerides, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and chylomicron (CM) remnants**. This is related to a reduced catabolism of these triglyceride-rich (TGR)-lipoproteins through a reduced activity of lipoprotein lipase (LPL) and/or hepatic triglyceride lipase (HTGL) as well as by a reduced clearance of these lipoprotein particles by reduced expression of VLDLR and LRP. ApoC-III is an inhibitor and ApoC-II an activator of LPL. Furthermore, lipoprotein(a) (**Lp(a)**) is increased in CKD patients with large Apo(a) isoforms, especially in moderate to advanced stage, most likely related to reduced clearance. Finally, also **free fatty acids (FFA)** levels are increased in CKD. The red arrows indicate the direction of up- or downregulation in CKD. *ApoA-I = Apolipoprotein A-I; ApoC = Apolipoprotein C; HTGL = hepatic triglyceride lipase; LCAT = lecithin-cholesterol acyltransferase; LDLR = LDL receptor; LRP= LDL receptor related protein; VLDLR = VLDL receptor; TGR = triglyceride-rich lipoprotein. *in patients with large Apo(a) isoform.*

3. IMPACT OF LIPID METABOLISM ON KIDNEY PATHOPHYSIOLOGY

3.1 Insights from epidemiological studies and clinical trials

3.1.1 Lipoprotein particles, cholesterol and triglycerides & CKD

Risk of **CKD development** increases with high levels of LDL-C[36], total and non-HDL cholesterol[37] and triglycerides[38], as well as with low levels of HDL-C[39].

On the other hand, risk of **CKD progression** was not associated with triglyceride levels[40]. Furthermore, the CRIC ('Chronic Renal Insufficiency Cohort') cohort reported that neither total cholesterol, VLDL-C, LDL-C nor HDL-C were independently associated with **CKD progression**[40]. Also, neither statins nor ezetimibe or PCSK-9 inhibition were found to preserve kidney function in CKD, as revealed in the SHARP ('Study of Heart and Renal Protection')[41] and FOURIER ('Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk') trial[42]. For HDL-C, some studies could not detect a correlation of HDL-C with risk of renal function decline[40], whereas others observed that both low and high HDL-C levels are associated with increased risk of renal function decline[43,44].

3.1.2 Free fatty acids & CKD

Low intake of polyunsaturated fatty acids has been associated with a higher incidence of kidney failure[45]. Also, in patients with diabetes, polyunsaturated fatty acid intake was negatively associated with CKD[46] and albuminuria progression was reported to be higher with higher saturated fatty acid to polyunsaturated fatty acid intake ratios[47]. Later studies mainly concluded that polyunsaturated fatty acids intake was associated with reduced albuminuria in diabetic nephropathy, as comprehensively discussed previously[48].

In relation to n-3 **polyunsaturated fatty acid supplementation**, a trial with diabetic patients with stable coronary artery disease but preserved kidney function revealed that combined eicosapentaenoic acid and docosahexaenoic acid supplementation could prevent the increase in urinary albumin to creatinine ratio at one year of follow-up observed in the control group[49]. On the other hand, a recent clinical trial of combined eicosapentaenoic acid and docosahexaenoic acid supplementation could

not reveal a beneficial effect in preserving kidney function in patients with type 2 diabetes mellitus over a 5 years period[50]. In conclusion, there is **currently no conclusive evidence that n-3 or n-6 polyunsaturated fatty acids supplementation is beneficial in regard to kidney function preservation**. The ´Kidney Diseases Global Outcomes´ (KDIGO) 2012 guidelines do not provide specific dietary recommendations in relation to fatty acids[51].

3.2 Insights from experimental models

Over the last years, multiple studies have investigated in experimental models the impact of altered lipid metabolism on kidney pathophysiology. This revealed a **close link of impaired fatty acid metabolism, mitochondrial overload and dysfunction with kidney damage, inflammation and fibrosis**[13,52]. Furthermore, mitochondrial dysfunction and cellular stress were not equally induced by all fatty acid subclasses, with the **saturated fatty acid palmitic acid triggering kidney cell injury in contrast to mainly protective effects of the monounsaturated fatty acid oleic acid and the n-3 polyunsaturated fatty acids docosahexaenoic acid and eicosapentaenoic acid.**

Also, high-fat diet feeding of mice as trigger of **hyperlipidemia and obesity**[53], both risk factors of CKD[21], **accelerates mitochondrial overload-induced CKD**[52] and can also trigger intracellular lipid accumulation and damage in the kidney *per se*, with a key role for inflammation. Below, each of these aspects is discussed in more detail.

3.2.1 Intracellular lipid accumulation and impaired fatty acid metabolism

Non-esterified fatty acids constitute the main energy source for the kidney and especially for the proximal tubular epithelial cells, which have a high mitochondrial density. After cellular uptake by CD36, fatty acid-binding protein or receptor-mediated endocytosis through albumin-binding, fatty acids are broken down for energy production. This occurs through β-oxidation of fatty acids in the mitochondria, which triggers ATP production by feeding the citric acid cycle via acetyl-CoA as well as the respiratory chain (oxidative phosphorylation) pathway via NADH and $FADH_2$ (**Figure 3**). However, dependent on fatty acid plasma levels and an imbalance between cellular uptake and metabolism, fatty acids may also accumulate in tissue. This has been associated with lipotoxicity and pathological consequences such as fibrosis in the heart[54]. In kidney,

intracellular lipid accumulation was observed in patients as well as mouse models presenting with tubulointerstitial fibrosis[13].

However, the hypothesis that intracellular lipids are cytotoxic *per se*, has been challenged. Whereas mice overexpressing CD36 in tubules did not develop kidney fibrosis despite increased lipid levels in tubular epithelial cells, inhibition of fatty acid β-oxidation did shift tubule epithelial cells towards a fibrotic phenotype, increased cell death and in parallel triggered intracellular lipid accumulation. In contrast, genetic or pharmacological improvement of fatty acid β-oxidation protected from kidney fibrosis[13]. In line, mitochondrial acetyl-CoA overload through genetic deficiency of the enzyme carnitine acetyltransferase in proximal tubular epithelial cells reduced mitochondrial respiration capacity and induced tubular disease with secondary glomerulosclerosis in mice, which was even more aggravated in conditions of high-fat diet[52].

Also, in tubule epithelial cells, Notch was revealed to drive fibrosis by downregulating fatty acid β-oxidation and reducing the expression of peroxisome proliferator-activated receptor alpha (PPARα) and PPARγ coactivator-1α (PPARGC1A, encoding for PGC-1α)[55], with PPARα/PGC-1α key transcriptional regulators of fatty acid uptake and oxidation and with PGC-1α also driving mitochondrial biogenesis. Impaired mitochondrial respiration and apoptosis of proximal tubule cells triggered by fatty acid overload could be counteracted by blocking mitochondrial fatty acid uptake and thus mitochondrial overload, as well as by restoring the activity of the antioxidant enzyme peroxiredoxin 2, thus linking fatty acid accumulation through mitochondrial overload to oxidative stress and cellular apoptosis[56].

Combined, these findings suggest that not intracellular lipid accumulation *per se*, but rather impaired β-oxidation of fatty acids and mitochondrial overload underlie renal damage, inflammation and fibrosis (**Figure 3a**). A multitude of recent experimental studies provide further support of this concept[57-60]. Furthermore, inflammation was identified to play a key role in mitochondrial damage-induced renal fibrosis, initiated by the innate immune pathway STING that is activated upon escape of mitochondrial DNA into the cytoplasm[61].

Also in patients with tubulointerstitial fibrosis, expression of PPARα and PGC-1α was found to be reduced[13]. Furthermore, mass spectrometric analyses of plasma from CKD patients revealed that the ratio of long-to-intermediate chain acylcarnitines as marker of the efficiency of β-oxidation, gradually decreased from early CKD stage

2 to advanced CKD stage 5, reflecting reduced β-oxidation of long-chain fatty acids with declining kidney function[12]. Comparable findings were revealed in patients with progressing diabetic kidney disease compared to non-progressors[62]. Altogether, these findings reveal **reduced β-oxidation of fatty acids and mitochondrial overload and/or dysfunction as potential therapeutic targets in fibrosis and CKD**.

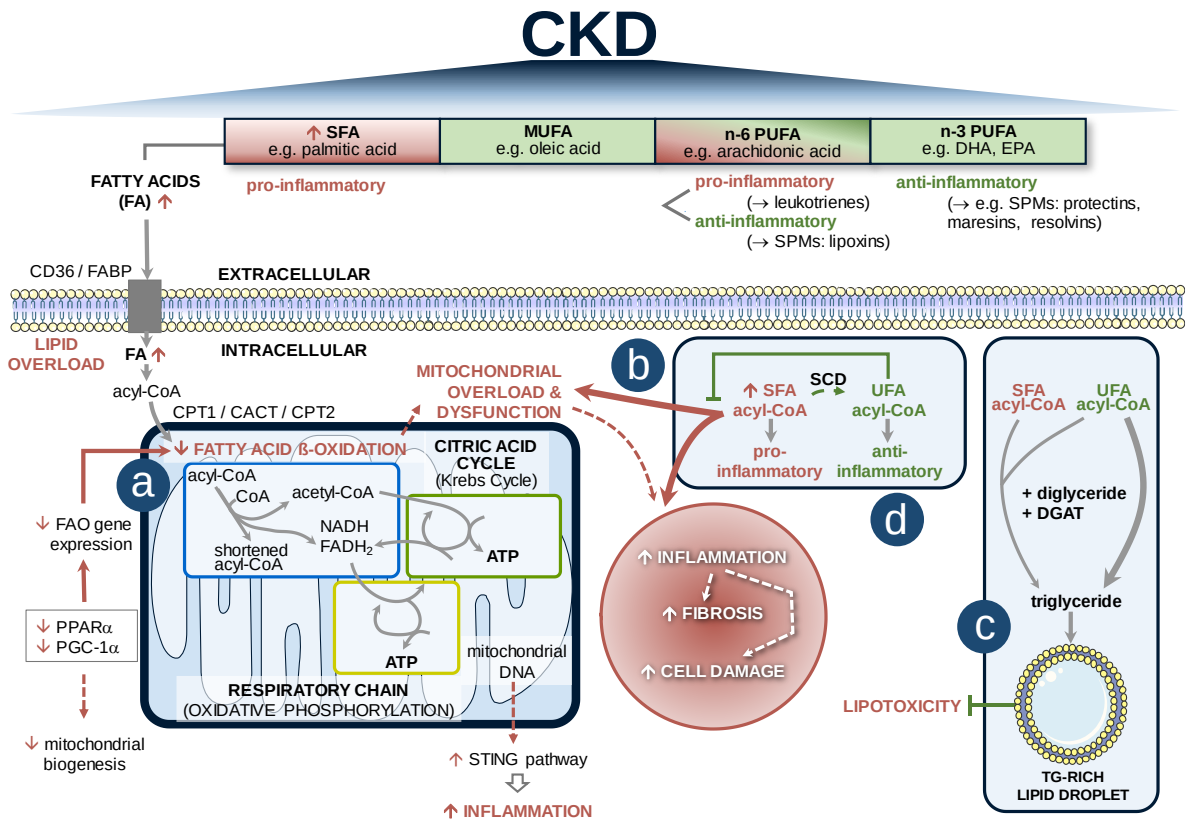

Figure 3. Impaired fatty acid metabolism and mitochondrial overload contribute to inflammation, fibrosis and cellular damage in kidney. Depending on the presence of double bonds within their chemical carbon-hydrogen structure, fatty acids are classified as saturated (SFA), monounsaturated (MUFA) or polyunsaturated (PUFA). Important subclasses among polyunsaturated fatty acids are omega-6 (n-6) polyunsaturated fatty acids (e.g. including arachidonic acid, linoleic acid) and omega-3 (n-3) polyunsaturated fatty acids (e.g. α-linolenic acid, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA)). (a) **Mitochondrial overload** by fatty acid overload **and/or impaired β-oxidation** of fatty acids triggers oxidative stress, fibrosis and kidney damage. (b) **Fatty acid subclasses differentially impact on mitochondrial dysfunction** and cellular damage: saturated fatty acid palmitate induces mitochondrial stress; monounsaturated fatty acid oleate can increase β-oxidation of fatty acids, with increased β-oxidation of fatty acids protecting from saturated fatty acid-induced injury. (c) **Integration of fatty acids in triglycerides and lipid droplets can protect against fatty acid-induced cellular toxicity**. With regard to different fatty acid classes: cellular lipotoxicity of saturated fatty acid palmitate is associated with poor incorporation into triglycerides, in contrast to monounsaturated fatty acid oleic acid. Also, oleic acid can increase palmitate incorporation into triglycerides simultaneously to reducing palmitate cytotoxicity. (d) Saturated fatty acids mainly exert

pro-inflammatory cellular effects, whereas monounsaturated fatty acids and n-3 polyunsaturated fatty acids are mainly anti-inflammatory. *ATP = adenosine triphosphate; DGAT = diglyceride acyltransferases; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FA = fatty acids; FABP = fatty acid-binding protein; FAO = fatty acid β-oxidation; MUFA = mono-unsaturated fatty acid; PUFA = poly-unsaturated fatty acid; SFA = saturated fatty acid; SCD = stearoyl-CoA desaturase; SPM = specialized pro-resolving mediators; TG = triglyceride; PPARα = peroxisome proliferator-activated receptor alpha; PGC-1α = PPARγ coactivator-1α; UFA = unsaturated fatty acid.*

3.2.2 Effect of fatty acid subclasses on mitochondrial dysfunction and kidney damage

Among the fatty acid subclasses, saturated fatty acids have been more associated with kidney cell injury compared to monounsaturated and polyunsaturated fatty acids. For example, the saturated fatty acid palmitate triggers the production of reactive oxygen species, endoplasmic reticulum stress and mitochondrial dysfunction, inflammatory responses and apoptosis in podocytes[63] and tubular cells[64,65]. In contrast, the monounsaturated fatty acids palmitoleate and oleate as well as the polyunsaturated fatty acid eicosapentaenoic acid provided protective effects against palmitate-induced cell injury[65,66], as did overexpression of stearoyl-CoA desaturase-1 (SCD1), an enzyme that converts saturated fatty acids to monounsaturated fatty acids[67].

Mechanistically, the monounsaturated fatty acid oleate increased fatty acid β-oxidation[67], and stimulating β-oxidation of fatty acids through the AMP-activated protein kinase (AMPK)/acetyl-CoA carboxylase (ACC)/carnitine palmitoyltransferase (CPT1) axis protected podocytes from saturated fatty acid-induced injury[68] (**Figure 3b**). Also, autophagy was identified to protect from saturated fatty acid palmitate-induced mitochondrial stress as well as cytotoxicity in proximal tubule cells by eliminating impaired mitochondria[64].

Furthermore, cellular lipotoxicity of palmitate was associated with a poor incorporation into triglycerides, in contrast to the monounsaturated fatty acid oleic acid[66]. In addition, oleic acid increased palmitate incorporation into triglycerides simultaneously to reducing palmitate cytotoxicity, triggering the concept that **integration of fatty acids in triglycerides can protect against fatty acid-induced cellular toxicity**[66] (**Figure 3c**). Triglyceride formation is mediated by diglyceride acyltransferases (DGAT), which integrate fatty acyl-CoA with a diglyceride to generate triglycerides. This mainly occurs in the endoplasmic reticulum, but may also occur with the help of DGAT2 in growing lipid droplets[69]. As underlying mechanism of how triglycerides within lipid droplets may

form a buffer against cellular saturated fatty acid accumulation, triglycerides were shown to mediate the release of monounsaturated fatty acid oleate from lipid droplets, thereby preventing overproduction of toxic saturated ceramides and acyl-carnitines as well as activation of the pro-inflammatory transcription factor NF-κB upon saturated fatty acid accumulation[70]. Since these findings stem from conditions of saturated fatty acid accumulation in tumor cells upon hypoxia-induced stress and associated SCD inhibition[70], it remains to be clarified whether similar mechanisms contribute to triglyceride-rich lipid droplet-mediated protection from saturated fatty acid-induced kidney cell lipotoxicity.

In addition to protective effects of monounsaturated fatty acids on kidney cells in relation to mitochondrial stress and cellular damage, the n-3 polyunsaturated fatty acid docosahexaenoic acid blocks TGFβ1-induced fibroblast activation. In line, a mouse model with endogenous production of n-3 polyunsaturated fatty acids from n-6 polyunsaturated fatty acids by transgenic overexpression of n-3 fatty acid desaturase revealed reduced kidney fibrosis and inflammation after unilateral ureter obstruction, supporting a role of n-3 polyunsaturated fatty acids in protecting from kidney fibrosis[71].

In summary, **fatty acid subclasses contribute to mitochondrial dysfunction and cellular stress in a sophisticated manner, with cellular accumulation of the saturated fatty acid palmitic acid triggering mitochondrial and kidney cell damage[63-65] in contrast to mainly protective effects of the monounsaturated fatty acid oleic acid and the n-3 polyunsaturated fatty acids docosahexaenoic acid and eicosapentaenoic acid[65-67]**. Studies in the last decade raised the concept that cellular stress from free saturated fatty acid accumulation can be **counteracted by increased saturated fatty acid breakdown through increased β-oxidation of fatty acids, by enhanced saturated fatty acid storage in cellular triglyceride pools driven by monounsaturated fatty acid supplementation as well as by monounsaturated fatty acid release from triglyceride stores, thereby interfering with saturated fatty acid-induced cytotoxic and pro-inflammatory effects** (**Figure 3**).

3.2.3 Impact of high-fat diet as trigger of obesity and hyperlipidemia on kidney pathophysiology

Obesity[72] and hyperlipidemia[37] are both well-known risk factors of CKD. In this context, renal lipid accumulation has also been observed in patients with obesity-related glo-

merulopathy[73]. In patients with diabetic nephropathy, enhanced intracellular lipid droplet accumulation coincided with a reduced expression of genes involved in β-oxidation of fatty acids and cholesterol efflux (ABCA1/G1), whereas receptors mediating uptake of LDL as well as post-translationally modified LDL (e.g. oxidized LDL, acetylated LDL) were increased[74].

Animal studies revealed that high-fat diet, as trigger of obesity and hyperlipidemia, aggravates ischemia-reperfusion kidney injury[64] as well as mitochondrial overload-induced CKD[52]. In line, in hypercholesterolemic mice subjected to unilateral ureteral obstruction, PCSK9 vaccination reduced circulating cholesterol levels as well as lipid accumulation and fibrosis in kidney, in parallel to an increased expression of genes involved in fatty acid β-oxidation[75]. Furthermore, high-fat diet *per se* induced lipid vacuole formation with accumulation of cholesteryl esters and phospholipids in kidney[64,76] and triggered renal dysfunction associated with kidney inflammation and fibrosis[64,77]. Mechanistically, high-fat diet reduced the phosphorylation of the low energy sensor AMPK and acetyl-CoA carboxylase as important events in mitochondrial fatty acid β-oxidation[76,78] and lowered the expression of genes regulating fatty acid β-oxidation[78]. Activation of AMPK could reduce renal lipid accumulation as well as renal inflammation in hyperlipidemia-induced kidney disease[77]. Also, in line with autophagy as protective mechanism against palmitate-induced damage in kidney cells *in vitro*, autophagy-deficiency through genetic knockout of *Autophagy-Related Gene 5* enabled high-fat diet to trigger mitochondrial damage and aggravated high-fat diet-induced renal inflammation as well as fibrosis[64]. In line, enlarged lysosomes with lipid accumulation and signs of impaired autophagic flux were revealed in kidneys of obese patients[64].

Combined, hyperlipidemia as risk factor of CKD genesis triggers kidney lipid accumulation, inflammation and fibrosis.

In relation to inflammation, a key role for the NLRP3 inflammasome as pro-inflammatory protein complex controlling the maturation of cytokine IL-1β, was identified in high-fat diet-induced lipid accumulation, inflammation and fibrosis in the kidney[79]. Furthermore, an **aggravating effect of chronic inflammation on high-fat diet-induced lipid deposition and kidney damage** was identified in mice, with casein-induced inflammatory stress imposed on high-fat diet triggering kidney function decline, as compared to high-fat diet alone where such effect was absent[80]. Mechanistically, inflammatory stress was shown to increase expression of CD36 and intracellular fatty

acid and triglyceride accumulation through CD36 *in vitro*, along with increased oxidative stress in kidney dependent on CD36[80]. All elements combined, **high-fat diet in mice as trigger of hyperlipidemia and obesity triggers intracellular lipid accumulation and damage in the kidney, with a key role for inflammation.**

4. LIPID METABOLISM AND CARDIOVASCULAR RISK IN CKD

4.1 Lipoprotein particles, cholesterol and triglycerides & CVD in CKD

In the general population, low HDL-C, high triglyceride and non-HDL-C levels as well as high LDL-C are associated with increased cardiovascular risk, as we recently comprehensively discussed[1]. However, **this does not uniformly hold true for CKD patients**. First, higher non-HDL-C over HDL-C[14] as well as higher cholesterol in triglyceride-rich lipoproteins[81,82] do correlate with atherosclerotic CVD in CKD patients, but are - in part - inversely associated with non-atherosclerotic CVD[82] as well as total cardiovascular risk[83]. Second, in CKD, higher HDL-C levels are not associated with improved cardiovascular survival[84], in contrast to non-CKD patients.

Not only lipoprotein levels are altered in CKD patients, CKD also affects lipoprotein composition and may in this way impact on lipoprotein function in relation to inflammation and cardiovascular risk (**Figure 4**). Lipoproteins serve as carriers of lipids, but also of **small molecules** such as vitamins, hormones, uremic retention solutes and microRNA[85]. The uremic milieu may specifically enhance this propensity for binding given the myriad of solutes that is accumulating in CKD due to the decrease in kidney filtration function[86]. Furthermore, CKD may underlay **compositional changes in the proteome of lipoprotein particles** as well as may trigger irreversible **post-translational modifications** of their proteome[87] . Combined, these **modifications of lipoproteins may highly impact on pathophysiological processes as well as cardiovascular risk in CKD** (**Figure 4**).

Furthermore, the **increased importance of non-atherosclerotic CVD in CKD patients** as well as potential “reverse causality effects” driven by CKD-associated inflammation have been suggested to contribute to the altered associations of lipoproteins with cardiovascular risk in CKD patients compared to the general population>.

Below, each of these aspects is discussed in more detail.

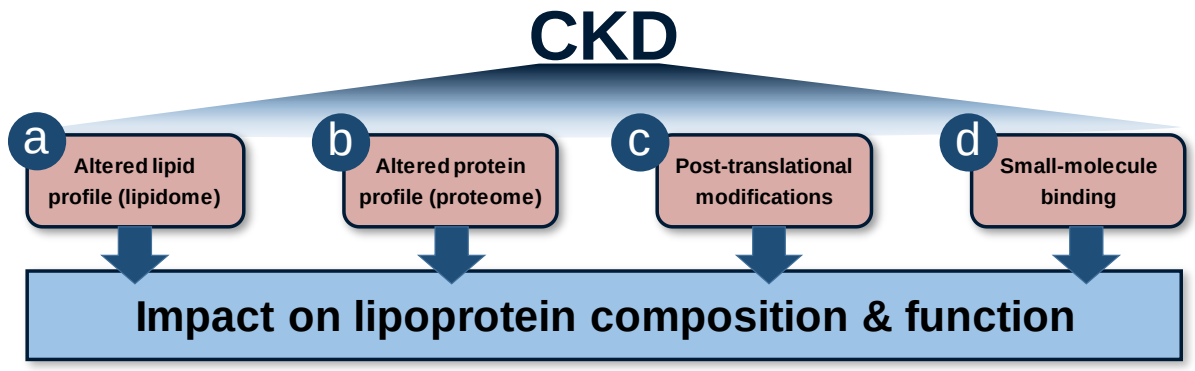

Figure 4. Impact of CKD on lipoprotein composition and function. (a) CKD impacts on lipoproteins through changes in the lipoprotein lipidome, with serum lipid profiles from patients with CKD considerably altered compared to healthy subjects. Serum levels of HDL-C are decreased and both the triglyceride concentration and the content of triglyceride-rich lipoprotein particles are increased in CKD. (b) Mass spectrometric analyses have provided new insights into the proteome of lipoproteins, suggesting an impact of lipoproteins composition on inflammatory processes. (c) A large number proteins within the lipoprotein particles are post-translationally modified in CKD, and these modifications have profound implications on lipoprotein function. (d) Also, the accumulation of small metabolic waste and uremic retention molecules, such as SDMA, permanently alters the structure and function of lipoproteins in CKD patients. Altogether, CKD may impact on lipoprotein function and promote inflammation and increased cardiovascular risk.

4.1.1 High-density lipoprotein

Relation to cardiovascular risk: HDL from healthy subjects has essential cardioprotective functions through reverse cholesterol transport, mediated by its main apolipoprotein ApoA-I in cooperation with the HDL-bound enzyme LCAT[2]. HDL also presents strong anti-oxidative properties through ApoA-I, LCAT and paraoxonase 1 (PON1)[88]. Combined, these beneficial functions may underlie the inverse relation of serum HDL-C levels with cardiovascular risk, as observed in the general population and recently reviewed in detail[1].

However, **in CKD, higher HDL-C levels are not associated with reduced cardiovascular risk**[84,89]. Also, whereas in the general population, cholesterol efflux capacity has been identified as an even better biomarker of cardiovascular health compared to HDL-C concentration[90], cholesterol efflux capacity could not predict cardiovascular risk in CKD[91,92]. This may be explained by **compositional changes in HDL of CKD patients, negatively impacting on HDL's cardioprotective function**, as

discussed in more detail below. Also, the **increased importance of non-atherosclerotic CVD in CKD compared to non-CKD patients**, especially at advanced CKD stages, may contribute to the altered relation of HDL with cardiovascular outcome. The latter suggests that in terms of cardiovascular risk analysis in relation to HDL-C levels and function (cholesterol efflux capacity), one should **discriminate between lipid-driven, atherosclerotic CVD *versus* non-atherosclerotic CVD**. In this context, when analyzing risk factors specifically for atherosclerotic cardiovascular risk (i.e. myocardial infarction and stroke), the prospective CRIC study of pre-dialysis CKD patients did recently identify an association of low HDL-C with increased risk of atherosclerotic CVD[81]. Also, the ´Dallas Heart Study´ detected an inverse association of HDL-particle numbers with atherosclerotic CVD in a CKD cohort without prevalent CVD[93]. However, paradoxically, the same study identified cholesterol efflux capacity to be positively correlated with risk of atherosclerotic CVD, suggesting that in CKD patients, cholesterol efflux capacity as measure of HDL function may not be as useful for atherosclerotic CVD risk prediction as in the general population[93]. Although serum cholesterol efflux capacity was found to be reduced in patients on hemodialysis[88], a slightly increased serum cholesterol efflux capacity was identified in earlier stages of CKD as well as in CKD stage 5 without dialysis[94], with underlying mechanisms remaining unclear. On the other hand, serum of predialysis patients displayed a reduced capacity of cholesterol delivery to hepatocytes. This **suggests that impaired cholesterol delivery to the liver rather than altered cholesterol efflux capacity may reduce reverse cholesterol transport in these patients**[94]. As one potential underlying mechanism, oxidized albumin as present in CKD patients, was shown to inhibit HDL binding to scavenger receptor class B, type 1 as major HDL receptor in hepatocytes[95]. Further studies would be welcome to evaluate in parallel HDL-C, serum cholesterol efflux capacity and serum capacity of cholesterol delivery to the liver in relation to atherosclerotic CVD vs. non-atherosclerotic CVD risk over different stages of CKD. Also, whether impaired hepatic clearance of HDL in CKD might facilitate compositional changes of HDL and thereby contribute to an altered HDL function and thus association with cardiovascular risk, remains to be further investigated.

<u>*Compositional changes of HDL in CKD*</u> *(**Figure 5**):* The altered relation of HDL with cardiovascular risk in CKD compared to non-CKD patients has been **linked to compositional changes in HDL**:

i) Small-molecule binding: **Small-molecule metabolic waste and uremic retention solutes may modulate lipoprotein structure and enhance cardiovascular toxicity of lipoproteins in CKD** patients. For example, asymmetric dimethylarginine (ADMA) and its structural isomer **symmetric dimethylarginine (SDMA)** have been correlated with cardiovascular risk factors, negative cardiovascular outcomes and renal dysfunction[86]. SDMA has also been identified to accumulate in HDL from CKD patients. This modifies the HDL particle to mimic a damage-associated molecular pattern that activates Toll-like receptor-2, linking abnormal HDL to innate immunity, endothelial injury and dysfunction, oxidative stress as well as hypertension[96]. **In contrast to a missing inverse association of HDL-C concentration with cardiovascular risk in CKD patients, levels of serum SDMA as well as SDMA incorporation into HDL could predict cardiovascular risk in CKD**[97]. A potential accumulation of other metabolic waste and uremic retention solutes within lipoprotein particles in CKD has to our knowledge not yet been investigated. Nonetheless, these solutes impact on cellular processes involved in CVD. For example, the protein-bound uremic toxin indoxyl sulfate induces leukocyte activation, impairs cholesterol efflux to HDL and is associated with increased aortic calcification, pulse wave velocity and overall cardiovascular mortality in CKD patients[98]. Hence, although technically challenging, it would be interesting to examine a potential accumulation of protein-bound uremic retention solutes in lipoprotein particles in CKD as well as the effects of this potential process on lipoprotein function in relation to inflammation and cardiovascular health.

ii) Altered proteome: In addition to small molecule binding, **compositional changes in the proteome of HDL particles have been observed to contribute to a lower protective function of HDL** in different inflammatory diseases, including CVD[1] and CKD[99-101]. In relation to HDL-binding protective proteins, patients with kidney failure display markedly reduced circulating levels of **ApoA-I, LCAT and PON** in parallel to a reduced anti-oxidant function of HDL[102].

Furthermore, quantification of HDL-associated proteins in CKD patients using proteomic approaches has provided evidence for an association between declining kidney function and an altered HDL protein profile[100,101,103,104], with proteins with anti-oxidative properties like **ApoA-I, ApoM and PON1** found to be less associated with HDL in dialysis patients compared to healthy subjects[100,101]. On the other hand, the amount of **serum amyloid A1**[99-101,105], **apolipoprotein A-IV (ApoA-IV)**[100,101] **and apolipoprotein C-III (ApoC-III)**[100,101] are increased in HDL isolated from patients with

CKD stage 5, with levels of HDL-bound serum amyloid A1[100,105] and ApoC-III[100,106] being associated with reduced HDL cholesterol efflux capacity.

Serum amyloid A1 proteins are the most prominent agents of the acute phase response. They can displace ApoA-I from the HDL particle to become themselves a major apolipoprotein of HDL and thereby influence the structural remodeling and functions of HDL[107]. For example, serum amyloid A incorporation into HDL reduces cholesterol efflux capacity[108] and transforms HDL from an anti-inflammatory to a pro-inflammatory lipoprotein particle[99]. Mechanistically, serum amyloid A-enriched HDL triggers pro-inflammatory NF-κB signaling through Toll-like receptors 2 and 4[109]. HDL-bound serum amyloid A is associated with increased cardiovascular risk in the general population as well as in patients with CVD[110], in diabetic patients on hemodialysis[111] and in patients with CKD stage 2-4[112]. In the latter group, the association of HDL-associated serum amyloid A with cardiovascular risk was lost after adjustment for C-reactive protein as pro-inflammatory marker, supporting an essential pro-inflammatory role of serum amyloid A-enriched HDL[112].

ApoC-III is not only increased in plasma of CKD patients[26], but also in their HDL particles[100,101]. ApoC-III is well-known to inhibit both lipoprotein and hepatic lipase activities, as well as uptake of triglyceride-rich lipoproteins by hepatic lipoprotein receptors[113], which underlies its association with hypertriglyceridemia[113]. Beyond this role, increasing evidence also points to a correlation between ApoC-III and HDL dysfunction[114], such as reduced cholesterol efflux capacity[106], which makes modification of ApoC-III metabolism a promising therapeutic target.

ApoA-IV as the third most abundant HDL-associated lipoprotein has a beneficial effect in numerous processes involved in vascular damage such as lipid metabolism, atherogenesis, platelet aggregation, thrombosis and glucose intolerance, as recently reviewed[115]. ApoA-IV protects lipoproteins from oxidative stress and modulates ApoC-II-mediated activation of lipoprotein lipase[116]. Also, by activating LCAT[115], ApoA-IV acts as an anti-atherogenic factor. Given the protective role against atherosclerosis and diabetes, apolipoprotein A-IV might become a new therapeutic target for the treatment of these comorbidities in CKD[115].

iii) Post-translation modifications: In pathological contexts like CVD or CKD, HDL can undergo significant **post-translational modifications** via carbamyla-

tion[117,118], oxidation[119], glycation[120], nitration[121,122], chlorination[121] and homocysteinylation[123], **resulting in a loss of protective properties**, as recently discussed in detail for HDL in the context of CVD[1]. **Post-translationally modified HDL** is no more promoting endothelial regeneration, but instead triggers dysfunctions, e.g. by inhibiting endothelial cell migration[124] and reducing anti-inflammatory mechanisms[125]. Also, it has decreased capacity to remove cholesterol from macrophages within arterial walls for transport to the liver[118]. For example, **oxidized HDL** can induce oxidative stress and inflammatory signaling through toll-like receptor 4[126], CD36[127] as well as LOX-1[128] and triggers endothelial dysfunction, macrophage apoptosis[126] and smooth muscle calcification[129]. In CKD patients stage 5D, high levels of oxidized HDL were associated with increased cardiovascular mortality and events, especially with simultaneously increased levels of the pro-inflammatory cytokine interleukin-6[130]. Furthermore, in hemodialysis patients, HDL is **carbonylated** by 4-hydroxynonenal groups derived from n-6 fatty acid peroxidation, which through CD36 receptor binding severely reduces the anti-aggregatory effect of HDL on platelets[131]. In addition, HDL and its anti-oxidant constituent PON1 are increasingly **carbamylated** in patients in CKD stage 5, in line with reduced anti-oxidant capacity of HDL in these patients[124,132]. Apo-AI as component of HDL can also be carbamylated, triggering cholesterol accumulation in macrophages through scavenger receptor-B1[118]. In CKD patients with type 2 diabetes, plasma carbamylated HDL but not carbamylated LDL was independently associated with progression of CKD[117]. Carbamylation is a non-enzymatic post-translational modification induced upon exposure of free amino groups to urea-derived cyanate[133] or reactive cyanate/isocyanate generated by the leukocyte heme peroxidase myeloperoxidase[134]. This leads to the formation of epsilon-amino-carbamoyl-lysine (homocitrulline), the most abundant carbamylation-derived product[135]. Protein carbamylation is increasingly considered as a contributing factor to CVD, also in CKD patients, and could predict cardiovascular risk[134] and mortality in CKD patients[136].

All combined, these findings suggest that modified HDL contributes to increased cardiovascular risk in CKD patients (Figure 5). As we recently summarized[1], modifications and dysfunctionality of HDL have also been revealed in patients with CVD. This may explain why neither genetic nor pharmacological interventions increasing HDL cholesterol levels could reduce cardiovascular risk in the general population[137], and **support the concept that HDL composition and functionality rather than HDL-C levels determine cardiovascular risk**[90,138]. For example, nicotinic acid

increased HDL-C by 15-20% without reducing cardiovascular events in high risk statin-treated patients with low LDL-C. No difference was observed between patients without CKD vs. CKD patients in stage 3a and beyond, the latter group comprising 14% of 25,673 patients treated with nicotinic acid or placebo in HPS2-THRIVE ('Treatment of HDL to Reduce the Incidence of Vascular Events')[139]. With both reverse cholesterol transport as well as the anti-inflammatory effect of HDL impaired in CKD, **novel therapies should target HDL function rather than HDL-C levels**. In this context, ApoA1 peptide mimetics are already being tested in clinical trials, aiming at increased reverse cholesterol transport and reduced cardiovascular risk, as discussed in more detail by Ferro et al.[22]. The 'CSL112_2001' phase 2 clinical trial recently demonstrated acceptable renal safety of ApoA-I mimetic CSL112 in patients with CKD stage 3 and prior myocardial infarction[140], supporting a follow-up trial to examine effects on cardiovascular outcome. Furthermore, with the negative impact of lipoprotein modifications on lipoprotein function increasingly being recognized, **targeting protein modifications** might be an interesting alternative strategy to explore. For example, amino acid supplementation could reduce carbamylation in hemodialysis patients[141], but the clinical benefit remains to be investigated.

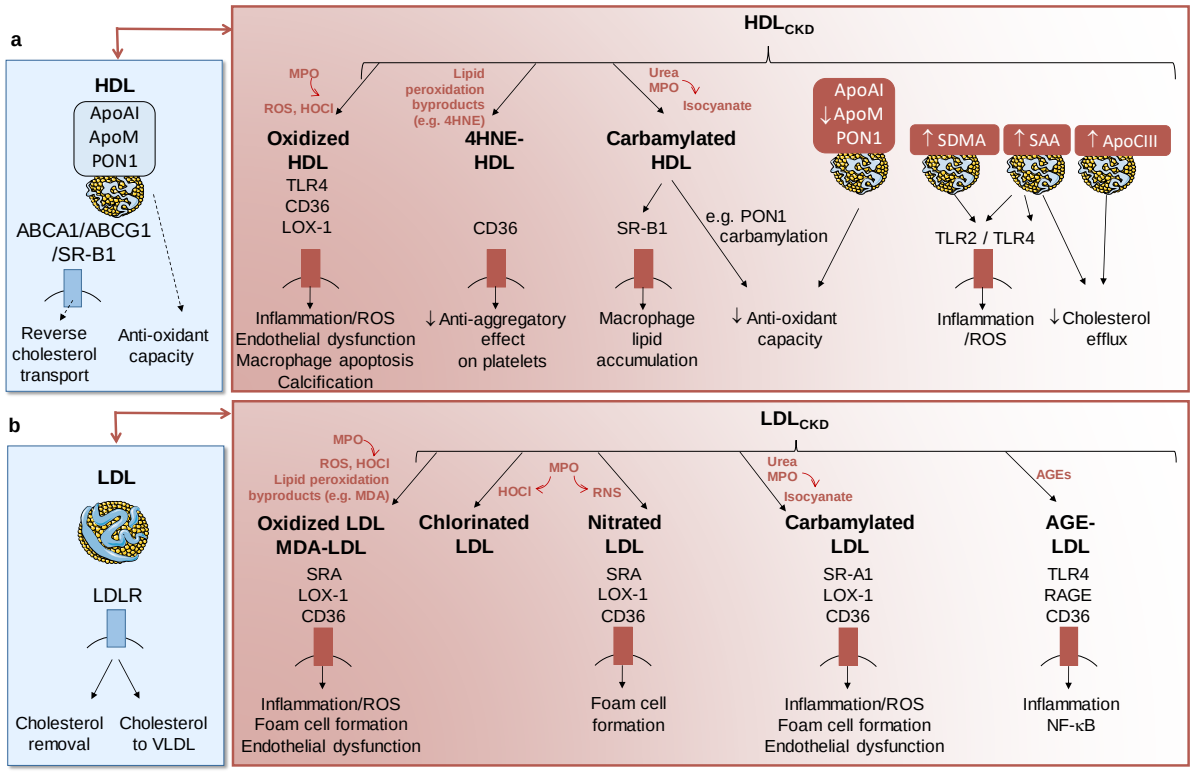

Figure 5. Impact of compositional changes of (a) HDL and (b) LDL in CKD on receptor signaling and cellular effects. Upon declining kidney function, increased oxidation stress and inflammatory conditions as well as the accumulation of uremic retention solutes (e.g. SDMA) alter the molecular composition of **high-density lipoprotein (HDL)** by post-translational modifications. Also, pro-inflammatory proteins (e.g. SAA) accumulate in HDL of CKD patients, whereas the content of protective molecules (e.g. ApoA-I, ApoM, PON1) is reduced. Combined, this reduces the anti-oxidant capacity of HDL and through altered receptor binding, transforms HDL from a cardioprotective into a pro-inflammatory lipoprotein particle. Also **low-density lipoprotein (LDL)** is post-translationally modified in CKD, further increasing its pro-inflammatory character in CKD. *ABCA1 = ATP binding cassette subfamily A member 1; ABCG1= ATP binding cassette subfamily G member 1; AGE = advanced glycosylation end product; ApoA-I = apolipoproteinA-I; ApoC-III = apolipoproteinC-III; ApoM = apolipoproteinM; HOCl = hypochlorous acid; LDLR = LDL receptor; LOX-1 = lectin-like-oxidized LDL receptor-1; MDA = malondialdehyde; MPO = myeloperoxidase; PON = paraoxonase; RAGE = receptor for advanced glycosylation end products; RNS = reactive nitrogen species; ROS = reactive oxygen species; SAA = serum amyloid A; SDMA = symmetric dimethylarginine; SRA = scavenger receptor A; SR-B1 = scavenger receptor-B1; TLR = toll-like receptor; VLDL = very-low-density lipoprotein.*

4.1.2 Low-density lipoprotein

Relation to cardiovascular risk: LDL particles and their oxidized form (oxLDL) are main drivers of lipid accumulation and inflammation in the vascular wall, thereby triggering atherosclerosis initiation and progression[1]. Small dense LDL particles have been

shown to be even more atherogenic than larger subfractions of LDL, which mechanistically can be linked to their higher circulation time as well as high capacity to infiltrate into the vessel wall. In line, in the general population, levels of small dense LDL-C as well as of LDL-C have been associated with increased risk of coronary heart disease[142].

Recently, patients with CKD stage 3-5D without prior history of myocardial infarction or coronary revascularization within the SHARP cohort revealed an association of high LDL-C with increased risk of atherosclerotic CVD[82]. Combination therapy with simvastatin and ezetimibe, which significantly lowered LDL-C, reduced the risk of major atherosclerotic events in this trial[82,143].

On the other hand, an association of LDL-C with cardiovascular risk could not be observed in the ´Cardiovascular Health Study´[144], the ´Modification of Diet in Renal Disease´ (MDRD) study[145], or the CRIC study of non-dialysis CKD patients in relation to risk of atherosclerotic CVD[81]. Nonetheless, in the latter study, discrimination between patients in CKD stage 3b-4 vs. CKD stage 3a or earlier did suggest that Apo-B levels as marker of the number of all proatherogenic lipoprotein particles (including LDL-C as well as small dense LDL-C) may increase atherosclerotic CVD risk in earlier but not in more advanced CKD stage[81]. Based on these findings, **drug-mediated LDL-C lowering may mainly be beneficial in reducing atherosclerotic CVD risk in early CKD stage 2-3**[146]. This is in line with findings of a 2016 meta-analysis of 28 randomized trials by the ´Cholesterol Treatment Trialists´ (CTT)[147] and may be the consequence of increased competing risk for non-vascular death with declining kidney function.

Also, in a recent post-hoc analysis of the SHARP study, a linear correlation of LDL-C and risk of cardiovascular events was identified only for atherosclerotic CVD, whereas no correlation or even an inverse correlation was revealed between LDL-C and non-atherosclerotic CVD, and this mainly in CKD patients with high systemic inflammation[82]. This again highlights **the importance of discriminating between atherosclerotic and non-atherosclerotic CVD in CKD patients in clinical outcome analyses as well as underlines the need to investigate in more detail CKD-specific mechanisms underlying CVD**, as discussed in more detail elsewhere[10]. Also, these findings complement a previously observed inverse association of LDL-C with total and cardiovascular mortality in CKD patients stage 2-5. Of note, this association

was lost after adjustment for the malnutrition-inflammation-cachexia syndrome[148]. An association of low LDL-C with high mortality risk has also already been reported in earlier studies of dialysis patients, and this specifically in patients with high systemic inflammation or protein-energy wasting[149].

All combined, **these findings suggest that inflammation- and/or malnutrition-driven effects on cholesterol homeostasis underlie the inverse LDL-C-mortality association in CKD, rather than LDL-C reduction representing a causal factor for mortality in CKD**. Mouse studies have revealed that inflammation can indeed drive alterations in cholesterol production as well as cholesterol uptake and redistribution among circulation and tissues, including kidney, as discussed in more detail previously[150].

Post-translational modifications of LDL in CKD (***Figure 5***)*:* Like HDL, also LDL is modified post-translationally in the context of CKD and CVD. **Oxidized LDL** is the best-known post-translationally modified LDL and recognized as an important pro-inflammatory and atherogenic factor[1]. Within the apoB100 protein of LDL, multiple oxidative modifications are induced upon incubation with reactive oxygen species, e.g. as triggered by myeloperoxidase, and these LDL-oxidations could also be identified in CKD patients on hemodialysis[151]. In contrast to the binding of unmodified LDL to the LDL receptor, cellular uptake of oxidized LDL occurs through different scavenger receptors such as scavenger receptor-A1/A2, lectin-like-oxidized LDL receptor-1 (LOX-1) and CD36[152], the latter in part dependent on dietary fatty acid binding[153]. This triggers macrophage foam cell formation, pro-inflammatory responses in vascular and blood cells[1] as well as endothelial stiffening[154]. Also, oxidized LDL in plasma and carotid plaques is associated with plaque instability and is a strong predictor for acute cardiovascular events[155]. Oxidative modifications of LDL are increased in CKD stage 5 compared to earlier CKD stage, as shown in children and young adults[156]. Furthermore, the ratio of oxidized LDL to oxidized LDL-directed auto-antibodies has been identified as biomarker of carotid atherosclerosis in dialysis patients[157].

A special type of oxidative LDL modification entails the addition of malondialdehyde (MDA) as lipid peroxidation by-product to ApoB100. **MDA-modified LDL** levels could predict aortic stiffness in patients on hemodialysis[158].

Furthermore, high levels of **carbamylated LDL** have been quantified in plasma of CKD patients compared to subjects with normal kidney function[159]. Carbamylation

of LDL highly reduces its binding affinity to LDL receptor but instead mediates its uptake by scavenger receptor-A1[134], LOX-1 and CD36[160] (**Figure 5**). This triggers pro-atherogenic mechanisms, such as macrophage foam cell formation[134]. Carbamylated LDL also induces endothelial cell injury[159] and endothelial reactive oxygen species production through LOX-1 activation, leading to endothelial nitric oxide synthase uncoupling[161]. In line, increasing urea concentrations in a CKD mouse model enhanced LDL carbamylation as well as atherosclerosis[162]. The level of LDL carbamylation could also predict cardiovascular outcome in CKD patients[161].

Furthermore, myeloperoxidase-catalyzed reactive nitrogen species trigger LDL modification by **nitration** of ApoB100, as also reported in patients with CKD[122]. LDL nitration interferes with LDL receptor binding and instead triggers pro-atherogenic macrophage foam cell formation through CD36[163], LOX-1 and scavenger receptor A[164]. Also **LDL-chlorination** on ApoB100 can be catalyzed by myeloperoxidase[151], with protein tyrosine-chlorination higher in CKD stage 5 and 5D compared to controls, as well as in CKD patients with coronary artery disease as compared to those without[165,166]. Finally, patients in CKD stage 5 display increased levels of advanced glycosylation end products (AGEs) as well as **AGE-modified LDL**[167], which triggers pro-inflammatory signaling via Toll-like receptor 4, CD36 and RAGE[168].

In summary, LDL displays multiple molecular modifications in CKD, with modified LDL showing reduced LDL receptor binding as required for lipid removal through the liver. Instead, modified LDL binds to scavenger receptors, further enhancing the pro-inflammatory character of LDL in CKD (**Figure 5**).

4.1.3 Triglycerides and very low-density lipoprotein

In the general population, epidemiological and genetic studies revealed increased plasma levels of triglycerides as well as of triglyceride-rich lipoproteins, their remnant particles and non-HDL-C, to be associated with increased risk of atherosclerotic CVD[1]. In patients with acute coronary syndrome on statin treatment, fasting triglyceride levels were shown to be predictive for residual cardiovascular risk[169], although it remains to be further clarified whether reduction of triglyceride levels in statin-treated patients can indeed reduce this residual risk[170].

In CKD patients, several studies could previously not detect an association of triglycerides with all-cause mortality[144,145] or cardiovascular mortality[148], and neither was an association of non-HDL-C with cardiovascular mortality detected in the MDRD study[145].

On the other hand, the ´Atherosclerosis Risk in Communities´ (ARIC) study did reveal increased risk of coronary heart disease in CKD patients with an increased ratio of non-HDL-C to HDL-C[14]. Furthermore, high levels of VLDL-C were associated with increased risk of atherosclerotic CVD, as revealed in the CRIC cohort of non-dialysis CKD patients[81]. Also, in the SHARP study, an increased ratio of triglyceride to HDL-C as well as increased levels of cholesterol within triglyceride-rich lipoproteins (i.e. total cholesterol minus LDL-C minus HDL-C) were associated with increased risk of atherosclerotic CVD, and this was not affected by a combination therapy of simvastatin plus ezetimibe[82]. Combined, this suggests a **potential benefit of targeting triglyceride-rich lipoproteins to reduce atherosclerotic CVD in CKD patients, as has been suggested in the general population**[169] and recently discussed by us in detail[1]. When comparing CKD stages, an association of high triglycerides with increased cardiovascular risk was detected in CKD stage 3-4, but this association declined with reducing kidney function, being absent in CDK stage 5[171]. Instead, a lower triglyceride/HDL-C ratio as well as lower non-HDL-C and non-HDL/HDL-C ratio did associate with increased cardiovascular and overall mortality in patients on hemodialysis[83]. Also, in contrast to their positive association to atherosclerotic CVD, **triglycerides, triglyceride/HDL-C ratio and triglyceride-rich lipoprotein-cholesterol were inversely associated with risk of non-atherosclerotic CVD in CKD patients**[82]. As also described for LDL-C, this inverse association between triglycerides and non-atherosclerotic CVD risk was especially observed in patients with high systemic inflammation as measured by CRP levels[82], **suggesting triglycerides and triglyceride-rich lipoproteins as non-causal biomarkers of increased non-atherosclerotic CVD in CKD**[82].

4.1.4 Lipoprotein(a)

The efficacy of cardiovascular risk reduction by Lp(a) lowering remains to be proven. While lifestyle intervention or statin therapy fail to reduce Lp(a) concentrations, other lipid lowering drugs including PCSK-9 inhibitors or nicotinic acid reduce Lp(a) concentrations by approximately 20% in addition to their cholesterol lowering potential. Post-hoc analysis of the ODESSEY Outcomes (‘Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab’) trial suggested alirocumab-dependent Lp(a) lowering to reduce cardiovascular risk in patients with high baseline Lp(a) levels independent of LDL-C[172]. This was similarly reported for evolucumab based on the FOURIER trial[173]. Still, none of both trials specifically

included patients with high baseline Lp(a) levels or had Lp(a) as primary outcome, and it remains challenging to attribute treatment effects specifically to Lp(a) reduction. In contrast, nicotinic acid failed to lower cardiovascular risk in AIM-HIGH ('Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes') and HPS2-THRIVE ('Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events') despite an Lp(a) lowering potential comparable to that of PCSK9 inhibition[139,174-176]. A new antisense oligonucleotide technology (AKCEA-APO(a)-LRx) does now allow specific targeting of LPA messenger RNA, leading to Lp(a) lowering by approximately 80% while leaving LDL-C unaffected. Cardiovascular benefit of this intervention is currently evaluated in patients with high (≥ 70 mg/dL) Lp(a) levels and existing CVD in the Lp(a)HORIZON trial ('Assessing the Impact of Lp(a) Lowering With TQJ230 on Major Cardiovascular Events in Patients With CVD')[177]. This trial will finally allow to decipher the relevance of Lp(a) lowering for cardiovascular risk reduction. However, patients with significant kidney disease will be excluded.

4.2 Free fatty acids & CVD in CKD

Multiple studies have **associated saturated fatty acids (e.g. palmitate) with pro-inflammatory effects, whereas anti-inflammatory functions were revealed for n-3 polyunsaturated fatty acids (as e.g. for the marine-derived docosahexaenoic acid and eicosapentaenoic acid) (Figure 3)**[1]. Furthermore, eicosanoids as derivatives of mainly the n-6 polyunsaturated fatty acid arachidonic acid have been intensively studied in relation to inflammation and CVD, with pro-inflammatory roles for e.g. leukotrienes and thromboxanes[178]. In contrast, the fatty acid-derived class of "specialized pro-resolving mediators" (SPMs) are strong anti-inflammatory molecules that are increasingly being recognized as potential therapeutic targets in relation to CVD. Here, the n-3 polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid have been linked to the production of the SPM subclasses of protectins, maresins and resolvins, whereas n-6 polyunsaturated fatty acids (such as arachidonic acid) give rise to the SPM subclass lipoxins[1] (**Figure 3**). In conditions of acute inflammation, leukocytes, platelets as well as the vasculature produce these specialized pro-resolving mediators to counteract inflammation and initiate inflammation resolution[179]. The role of

these lipid mediators in inflammation[180] and CVD[181] as well as in diabetes-related cardio- as well as reno-vascular complications[182] was recently discussed in detail elsewhere.

Based on the anti-inflammatory properties of n-3 polyunsaturated fatty acids, many studies have investigated potential cardiovascular health benefits of increased serum levels as well as diet supplementation with these fatty acids[1]. As revealed by **studies within the cardiovascular field, serum levels of the n-3 polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid inversely correlate with cardiovascular events**[183]. A recent meta-analysis of 86 randomized controlled trials of effects of n-3 fatty acids in relation to CVD revealed that n-3 polyunsaturated fatty acid increase had only little to no effect on all-cause and cardiovascular mortality, although it could slightly reduce events and mortality related to coronary heart disease[184]. On the other hand, the REDUCE-IT (´Reduction of Cardiovascular Events With Eicosapentaenoic Acid Intervention´) trial[185] and a meta-analysis[186] revealed high **dose eicosapentaenoic acid supplementation to provide cardiovascular protection in patients with high cardiovascular risk**. Also the American Heart Association recently concluded that long-chain n-3 polyunsaturated fatty acids offer a health benefit with regards to risk of cardiac death, coronary heart disease and ischemic stroke, in line with their “2020 Impact Goals” to integrate seafood within a healthy diet pattern[187]. Among the n-6 polyunsaturated fatty acids, **linoleic acid** was shown to be **inversely associated with cardiovascular risk**[188].

In the same line, n-3 and n-6 polyunsaturated fatty acids have been investigated for potential beneficial effects in CKD patients. In hemodialysis patients an **inverse correlation has been shown between the ratio of n-3 polyunsaturated fatty acids docosahexaenoic acid and eicosapentaenoic acid vs. n-6 polyunsaturated fatty acid arachidonic acid and cardiovascular risk**[189] as well as between n-3 polyunsaturated fatty acid levels and risk of sudden cardiac death[190]. Furthermore, meta-analyses concluded that n-3 polyunsaturated fatty acid supplementation to CKD stage 5D patients reduce CRP levels[191], cardiovascular events[192] and cardiovascular but not total mortality[193].

5. CONCLUSION

Patients with CKD suffer from advanced atherosclerotic CVD and although most patients do not display increased LDL-C levels, CKD predestines them as high-cardiovascular risk patients and justifies intensive LDL-C-lowering to decrease risk of atherosclerotic cardiovascular events[194]. Lifestyle measures such as exercise and appropriate diet are simple and cost-effective interventions with a correcting impact on dyslipidemia[195]. However, such measures proved insufficient for lipids and/or lipoproteins lowering in high-risk patients, explaining the considerable efforts in correcting dyslipidemia by pharmacological interventions, as recently reviewed extensively[1,22].

A 2013 meta-analysis including 31 trials with 48,429 CKD patients found statin treatment to provide 23% relative risk reduction for major cardiovascular events and 9% relative risk reduction for cardiovascular or all-cause mortality[196]. In line, KDIGO recommends all patients above 50 years of age in CKD stages 3-5 not on dialysis to be treated with a statin or statin/ezetimibe combination, independent of baseline LDL-C[197]. ´European Society of Cardiology´ (ESC) guidelines recommend patients with CKD stage 3 to be treated to an LDL-C target < 70 mg/dl (ApoB < 80 mg/dl; non-HDL-C < 100 mg/dl), while patients with CKD stage 4-5 are to reach LDL-C < 55 mg/dl (ApoB < 65 mg/dl; non-HDL-C < 85 mg/dl) in conjunction with a reduction of baseline LDL-C by at least 50%[3]. However, benefit of starting statin therapy in CKD was revealed to decline with deterioration of kidney function and remained absent in CKD stage 5D patients[147]. The KDIGO guidelines consequently do not recommend initiation of statin therapy in CKD stage 5D patients although they advise on continuation of statins if they have been prescribed earlier, as discussed in more detail by Ferro et al.[22].

The decreased efficiency of statin therapy as well as the altered relation of lipoproteins with cardiovascular risk for declining kidney function might be the consequence of the **competing risk for non-atherosclerotic death in CKD stage 5D as well as of an altered biological environment with increased inflammation and oxidative stress**. In the past decade, multiple lipid and lipoprotein modifications have been identified in CKD patients, with contributions to pathological mechanisms like inflammation and oxidative stress. Thereby, these modifications negatively affect the functionality of organs like heart and vessels, thus most likely playing a role in the

development of comorbid disorders. **Increased knowledge of lipoprotein modifications as well as the origin and consequences of these defects is of high relevance for the understanding of molecular mechanisms of cardiovascular diseases in CKD.**

Furthermore, recent studies have increased our insights into the effect of fatty acid accumulation as well as hyperlipidemia and obesity over mitochondrial dysfunction on kidney pathophysiology. Of note, lipid accumulation and mitochondrial dysfunction also negatively impact on the heart, as discussed recently elsewhere[8]. In line, restoration of mitochondrial function, increased autophagic flux and reduced cellular stress have been identified to contribute to the protective effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors on the heart as well as the kidney[198]. Clinical studies directly targeting mitochondrial function and oxidative stress in CKD patients are currently ongoing to examine effects on microvascular and endothelial function, inflammatory and oxidative stress markers (**Table 1**), with vascular dysfunction a hallmark for CVD also in CKD[10]. Results of these trials may support further studies on the potential benefit of mitochondrial support in relation to kidney and heart function and may thus trigger interesting novel therapeutic avenues.

Table 1. Clinical studies targeting mitochondrial function in CKD. Listed are trials registered in "clinicaltrials.gov" and identified through a search for studies in relation to CKD and mitochondrial oxidative stress.

Study ID	Title	Patients	Dietary supplementation	Outcome readouts	Phase
NCT02364648	Mitochondrial Oxidative Stress and Vascular Health in Chronic Kidney Disease	CKD stage 3-5	MitoQ vs. Placebo	Microvascular function, endothelial-dependent dilation and mitochondria-derived superoxide	Phase 4
NCT03960073	Chronic Kidney Disease and Heart Failure With Preserved Ejection Fraction: The Role of Mitochondrial Dysfunction	HFpEF with and without CKD	MitoQ vs. Placebo	Maximal aerobic capacity, large blood vessel hemodynamics, mitochondrial respiration	Phase 4
NCT03579693	Trial of Nicotinamide Riboside and Co-enzyme Q10 in Chronic Kidney Disease (CoNR)	CKD (eGFR < 50 ml/min/1.73m^3)	CoQ10 vs. Nicotinamide riboside vs. Placebo	Readouts of maximal aerobic capacity and muscle function, mitochondrial energetics, systemic inflammation and heart failure symptoms	Phase 2

MitoQ is a mitochondria-targeted lipophilic antioxidant. Coenzyme Q10 (coQ10) and nicotinamide riboside (NR) are naturally occurring supplements that may directly improve mitochondrial function. *HFpEF: Heart Failure With Preserved Ejection Fraction; CKD = chronic kidney disease.*

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CONFLICT OF INTEREST

No conflict of interest.

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