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Novel aspects of PCSK9 and lipoprotein receptors in renal disease-related dyslipidemia

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ABSTRACT

Chronic kidney disease (CKD) is a global health problem with a profound impact on quality of life. Cardiovascular disease is established as a major cause of morbidity and mortality in patients with CKD. Dyslipidemia is frequently observed in CKD patients, suggesting a causal relation between dyslipidemia and cardiovascular disease in CKD patients. Currently, lipid-lowering drugs such as statins, are the primary choice for lipid lowering therapy in high-risk populations. Despite many studies showing CVD risk reduction with statins, CVD still remains the leading cause of the death in CKD. This underscores the need for new therapeutic approaches to reduce cardiovascular risk in CKD patients. Reduced lipoprotein lipase activity, increased very low-density lipoprotein production, increased proprotein convertase subtilisin kexin type 9 (PCSK9) expression and loss of hepatic heparan sulfate proteoglycans (HSPG) syndecan-1 have been associated with CKD-related dyslipidemia. Low-density lipoprotein receptor (LDLR), low-density lipoprotein receptor-related protein 1 (LRP-1) and syndecan-1, are the most important hepatic receptors for lipoprotein clearance. However, their contributions to the pathogenesis of dyslipidemia and cardiovascular disease in CKD remain unclear. Interestingly, in CKD, increased plasma lipid levels are associated with elevated levels of PCSK9. This promotes the proteolysis of LDLR, suggesting a role for PCSK9 in CKD-associated dyslipidemia. Fully humanized monoclonal antibodies targeting PCSK9 have been approved by the US Food and Drug Administration and the European Medicines Agency as lipid lowering treatment for patients with hypercholesterolemia. In CKD sub-group analysis, ODYSSEY COMBO I and ODYSSEY COMBO II studies demonstrated strong reduction in LDL-C by alirocumab compared to placebo and ezetimibe and when added to statins. However, their efficacy in reducing plasma TG is controversial. Therefore, further research work is need for a detailed analysis on efficacy and safety of PCSK9 antibodies in CKD groups. Interestingly, novel findings on PCSK9 interaction with HSPG might shed new insight on altered lipid metabolism in CKD. In this review, we discuss various aspects of lipoprotein metabolism and hepatic lipoprotein receptor signaling pathways along with the concept of renal disease-related dyslipidemia. Furthermore, this review highlights the drawbacks of current lipid-lowering therapies and proposes novel approaches for lipid management in CKD.

1. Dyslipidemia in chronic kidney disease and cardiovascular risk

Chronic kidney disease (CKD) is a condition of decreased kidney function represented by glomerular filtration rate < 60 ml/min/1.73m^2 for at least 3 months. CKD is classified into stage I–V on the basis of glomerular filtration rate, where stage V represents end stage renal disease [1]. According to a surveillance in 2017 by the Centers for Disease control and Prevention, about 30 million people or 15% of the adults in United States (US) are estimated to have CKD [2]. Global Burden of Disease study has ranked CKD as 12th in the list of most common causes of death in 2015. This is an increase of 18.4% since 2005 [3]. Similarly, the same study reports CKD mortality as the third largest and fastest rising major causes of death. Besides higher prevalence and mortality, CKD perpetrates a huge economic burden to patients and health care system related to dialysis and transplantation as renal replacement therapies [4].

CKD is often associated with cardiovascular diseases. The cause of death in CKD patients is more likely due to cardiovascular complications than due to renal disease itself [5,6]. For instance about 40% of patients with end stage renal disease on dialysis therapy suffer from

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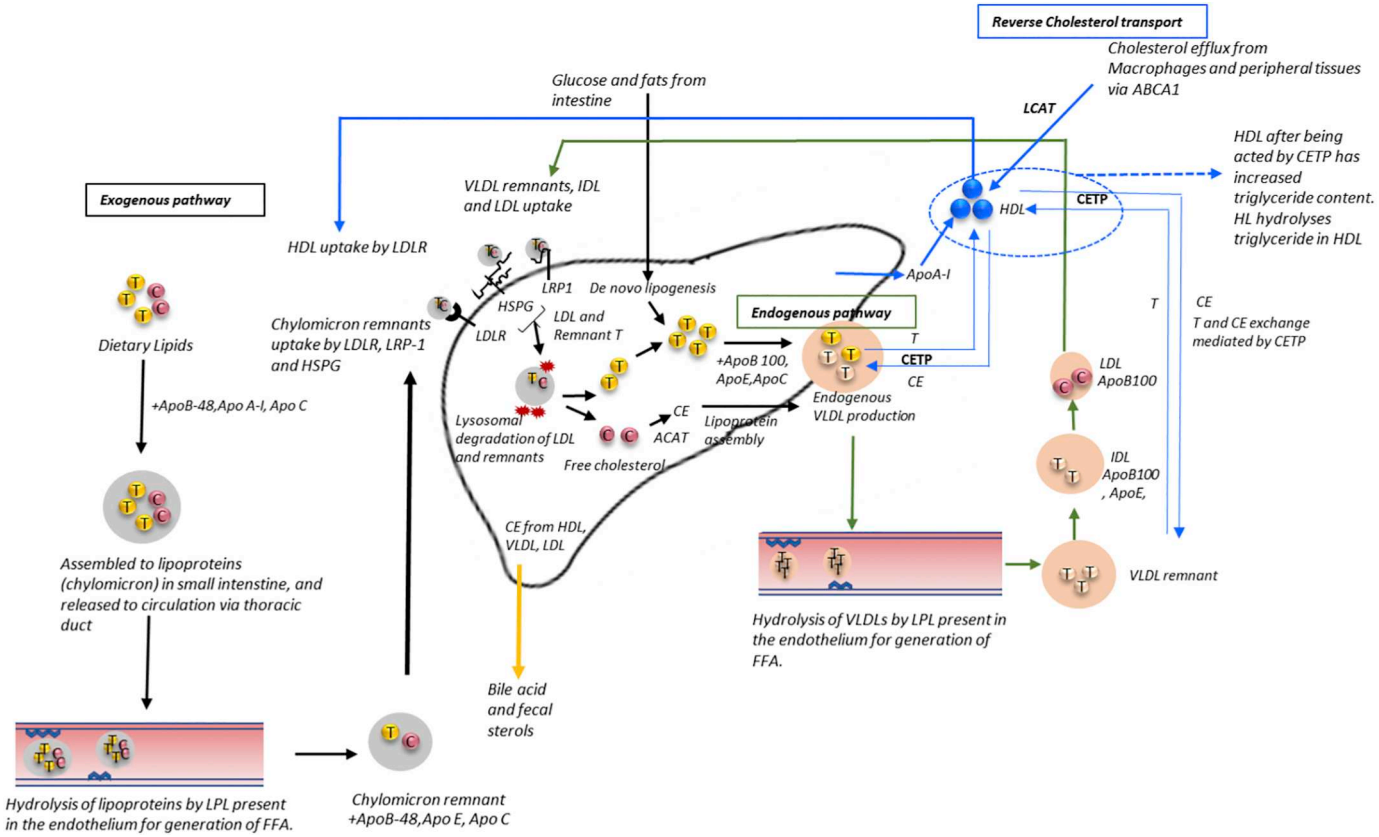

Fig. 1. Lipoprotein metabolism. Exogenous and endogenous lipoprotein metabolism pathway. T (triglycerides/TG), C (cholesterol), LPL (lipoprotein lipase), FFA (free fatty acids), LDLR (low density lipoprotein receptor); HSPG (heparan sulfate proteoglycans), LRP-1 (low density lipoprotein receptor like protein 1), VLDL (very low density lipoprotein), IDL (intermediate density lipoprotein); LDL (low density lipoprotein), Apo (apolipoproteins), CETP (cholesterylester transfer protein), LCAT (lecithin:cholesterol acyltransferase), ACAT (Acyl-CoA:cholesterol acyltransferase-2); HL (hepatic lipase); ABCA-1 (ATP-binding membrane cassette transport protein A1); CE (Cholesterol ester).

coronary heart disease. Cardiovascular-related mortality in these groups has been found to be 10–30 times higher than in the general population of the same gender, age and race [7]. This is why the American Heart Association and National Kidney Foundation has classified renal patients as having the highest risk for developing cardiovascular diseases [5]. High risk of cardiovascular events in CKD is primarily due to abnormalities in lipoprotein metabolism. Dyslipidemia, characterized by elevated plasma levels of triglycerides ($\geq$1.7 mmol/l) and total cholesterol ($\geq$5.7 mmol/l), is very common in CKD [8]. In an evaluation of 2001–2010 National Health and Nutrition Examination Survey (NHANES), the prevalence of dyslipidemia increased from 45.5% in CKD stage 1 to 67.8% in CKD stage 4 [9–12].

Several conditions like diabetes, hypertension, autoimmune diseases, primary glomerulopathies and systemic infections are regarded as the primary causative factors for developing CKD [13]. Some of these etiological factors are reported to have significant impact on lipoprotein metabolism and lipid levels. For instance, diabetic nephropathy is a major complication of diabetes leading to increased plasma triglycerides (TG) and reduced high density lipoprotein cholesterol (HDL−C) further increasing their risk for cardiovascular events. Diabetes induces insulin resistance leading to mobilization of free fatty acid from adipose tissue to liver which increases TG production [14].

Autoimmune diseases like systemic lupus erythematosus cause lupus nephritis which is associated to lipid abnormalities [15]. Studies show that the prevalence of dyslipidemia in lupus patients ranges from 36% at diagnosis to 60% or even higher after 3 years which increases the risk of myocardial infraction by 5 to 8 times compared to general population [16]. Dyslipidemia in lupus nephritis is attributable to anti-lipoprotein lipase production resulting in elevated plasma TG, LDL- C, apolipoprotein B, and decreased HDL-C [17].

Apart from dyslipidemia, proteinuria and low glomerular filtration rate (GFR) are also an important risk factors for developing atherosclerotic CVD. A study by Baigent et al. 2011 reported vascular stiffness and calcification in patients with estimated GFR < 30 ml/min/1.73m^2 with known atherosclerotic CVD [18]. However, proteinuria and low GFR are not taken into account in Framingham risk score, a scoring system to estimate an individual chances of developing CVD and could be added to risk calculators [19].

In this review, we briefly discuss about lipoproteins and their metabolism. Additionally we explain the different hepatic lipoprotein receptor signaling pathways and pathophysiology of dyslipidemia in CKD. Finally we demarcate the current and novel approaches for treatment.

2. Lipoprotein metabolism

2.1. Lipoproteins

Triglycerides (TG) and cholesterol are water insoluble molecules, which are essential for energy generation and the synthesis of cellular membranes and steroid hormones. They are either obtained from the diet (exogenous route) or by de novo synthesis (the endogenous route converting glucose into fatty acids) mainly in the liver and adipose tissue, but also in skeletal muscle cells, intestinal enterocytes and pancreatic beta cells [20–23]. These water insoluble molecules are transported in blood in association with proteins in the form of lipoproteins. Plasma lipoproteins are classified as chylomicrons, very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL),

according to their hydrated density. Apolipoproteins, present on the surface of lipoproteins along with phospholipids, serve as ligands for lipoprotein receptors and transportation and maintain structure of lipoproteins. They also serve as enzyme cofactors. For instance, Apo C-II acts a cofactor for lipoprotein lipase (LPL) [24]. Major lipoproteins with their function and structural properties have been extensively described by Feingold KR et al. and will not be discussed in depth in this review.

2.2. Exogenous lipid metabolism pathway

Exogenous lipids i.e. dietary fats, mainly in the form of TG are absorbed by the enterocytes in the intestine and are converted into chylomicrons. They are then secreted into the lymph and transported via the thoracic duct to the circulation. The delivery of postprandial intestinal lipoproteins into the thoracic duct avoids a first pass though the liver. Dietary cholesterol is also absorbed by enterocytes and reach the circulation via chylomicrons. Initially, chylomicrons have a high ratio of TG to cholesterol [25]. Chylomicrons in circulation are hydrolyzed by LPL present in adipose tissue and muscles to generate free fatty acids for energy production. This process depletes the TG content of chylomicron which decrease in size forming chylomicron remnants. These remnants are relatively rich in cholesteryl esters (much of that cholesterol was present in the original chylomicrons), contain apoE among other apo's. They also contain LPL which serves as a ligand to assist the binding of these remnants to hepatic HSPGs and accelerating their removal from the plasma as depicted in Fig. 1 [26–30].

2.3. Endogenous lipoprotein metabolism pathway

One of the important functions of the liver is the production of cholesterol (de novo synthesis) which is in the form of VLDL. Hepatic VLDL generation is sourced by free fatty acids sourced from adipocytes, chylomicron remnants, de novo lipogenesis and fatty acids stored in the liver [31,32]. Similar to chylomicrons, TG in VLDL are hydrolyzed by LPL thereby generating free fatty acids. Delipidation of circulating VLDL results in the formation of VLDL remnants, IDL and ultimately LDL. These remnants are enriched in cholesterol and are removed from the circulation by the liver. About 50% of VLDL remnants are removed from circulation via hepatic receptors, whereas another 50% first undergoes further hydrolysis to form LDL with further depleted triglyceride content. These LDL particles are subsequently removed from the circulation by the liver as shown in Fig. 1. [33].

2.4. Reverse cholesterol transport

Reverse cholesterol transport represents a pathway which aims to transport cholesterol from extrahepatic tissues and macrophages back into the liver. By reducing accumulation of cholesterol in the arterial wall, reverse cholesterol transport may protect against the development of atherosclerosis. The liver is able to synthesize apoA-I which is released into plasma where it interacts with serum phospholipids and forms HDL [33–38]. HDL mediates cholesterol efflux from macrophages and peripheral tissues via ATP-binding membrane cassette transport protein A1 (ABCA1), ABCG1, and other processes. Unesterified cholesterol is taken up by nascent HDL and subsequently esterified by lecithin cholesterol acyltransferase (LCAT). Part of HDL cholesteryl esters are transferred to apoB-containing lipoproteins such as LDL and VLDL in exchange of TG by cholesteryl ester transfer protein (CETP). These cholesteryl esters are then cleared by the liver through low-density lipoprotein receptor (LDLR); subsequently cholesterol can be converted into bile salts, and eliminated through the gastrointestinal tract, see Fig. 1 [34–38].

3. Lipoprotein receptors

Liver plays a central role in the uptake and clearance of lipoproteins. Three primary hepatic receptors that are involved in plasma lipoprotein uptake are LDLR, the low-density lipoprotein receptor related protein 1 (LRP1) and the heparan sulfate proteoglycan (HSPG), syndecan-1 (see also in Fig. 1).

3.1. Low density lipoprotein receptor

LDLR is an abundantly expressed lipoprotein receptor in the liver. This receptor is involved in the uptake of apoB containing particles like chylomicron remnants, VLDL and their remnants, and LDL. Lipoproteins bound to LDLR are internalized together with LDLR and directed to the endosomes. Endocytosis is mediated by several adaptor proteins like autosomal recessive hypercholesterolemia protein (ARH) and disabled homolog 2 (DAB2) protein (reviewed in [39]). At the endosomes, the lipoproteins are released and they undergo lysosomal degradation. Internalized LDLR are then sorted and redirected back to the cell surface via the COMMD/CCDC22/CCDC93 (CCC) and Wiskott–Aldrich syndrome protein and SCAR homolog (WASH) [40–42]. Mutations in *LDLR* affecting the synthesis of LDLR, its activity, subcellular localization or its recycling are known to cause familial hypercholesterolemia (FH), a genetic condition of severely elevated serum LDL cholesterol, associated with a strongly increased risk for atherosclerosis [43].

In addition, mutations – causing hypercholesterolemia - have been found in genes encoding for proteins involved in the coordination of intracellular LDLR trafficking. For example, mutations in the *ARH* (autosomal recessive hypercholesteremia) gene has been reported to induce defects in LDLR endocytosis resulting in high serum cholesterol levels [44]. Similar to FH patients carrying mutations in *ARH*, mice deficient for ARH show elevated LDL plasma levels. Also defects in the endosomal sorting machinery has been linked to hypercholesterolemia, as patients with X linked intellectual disability (XILD) syndrome caused by mutations in CCC component CCDC22 also present hypercholesterolemia [42]. The role of the CCC complex in the metabolism of LDL has been confirmed in mice and dogs (Bartuzi et al., Fedoseienko et al). For detailed information in LDLR mediated lipoprotein uptake we refer to recent reviews by van de Sluis et al. [45], Backlow SC et al. [46] and Wijers et al. [39].

3.1.1. Regulation of LDLR expression

LDLR levels are regulated at transcriptional and post-transcriptional levels. Transcription of *LDLR* depends on cellular cholesterol levels through the action of the sterol response element binding protein (SREBP) transcription factors [47,48]. Post-transcriptional regulation of LDLR levels are coordinated by IDOL (Inducible degrader of LDLR) and proprotein convertase subtilisin kexin type 9 (PCSK9). Both proteins promote the proteolysis of LDLR [46,48–50]. PCSK9 is a serine protease containing three structural domains, namely the prodomain, the catalytic domain and the C-terminal domain. It is synthesized as a 74 kDa soluble zymogen, which undergoes an autocatalytic process for its maturation, secretion and function [51,52]. PCSK9 was initially identified by Seidah et al. in 2003 [53]. Its role in cholesterol metabolism was discovered with the identification of two gain-of-function mutations in *PCSK9* in two French families with autosomal dominant hypercholesterolemia [54]. The gain-of-function mutation in *PCSK9* was later found to be associated with mild to severe hypercholesterolemia and an increased risk of coronary heart disease [55]. Subsequently, loss-of-function mutations (Y142X and C679X) and polymorphisms in *PCSK9* in African Americans were associated with a robust reduction in

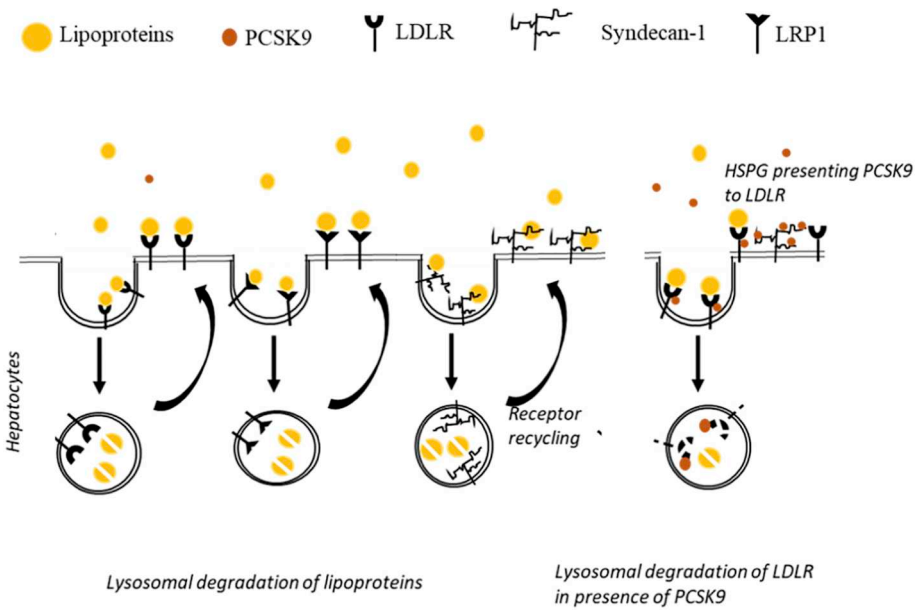

Fig. 2. Participation of Hepatic lipoprotein receptors in lipoprotein uptake and clearance and role of HSPG in LDLR degradation via PCSK9.

LDL-C coinciding with a strong reduction in the risk of coronary heart disease. These findings suggested that PCSK9 inhibition could serve as a therapeutic approach to lower plasma LDL-C and eventually cardiovascular risk [56,57].

PCSK9 targets LDLR for degradation by two pathways: an intracellular pathway and extracellular pathway (Fig. 2). In intracellular pathway, PCSK9 binds to LDLR at the trans-Golgi network after synthesis and directly targets the receptor to the lysosomes for degradation [58–60]. In extracellular pathway, PCSK9 binds to the epidermal growth factor-like A (EGFA) domain of LDLR which induces ARH-dependent internalization. In both pathways, LDLR gets escorted to the endosomes. In endosomes, normal recycling of the receptor is disrupted by preventing the acid-dependent conformational switch from open to closed. This marks the LDLR for degradation by the lysosomes where both the LDLR and PCSK9 are broken down [39,61]. Both *PCSK9* expression and *LDLR* expression, is positively regulated by sterol regulatory element binding protein 2 (SREBP2). SREBP2 is activated in the case of low levels of cellular cholesterol. Activation of SREBP2 turns on genes for cholesterol uptake such as *LDLR*. This co-regulation of PCSK9 and LDLR seems contradictory, but immediate breakdown of LDLR is prevented by the presence of LDL in the plasma. LDL binds to PCSK9 and prevents PCSK9-mediated LDLR breakdown [39,62].

Overexpression of PCSK9 in mice has been found to increase plasma LDL cholesterol. In contrast, *Pcsk9* KO mice are characterized by increased LDLR protein and reduced plasma LDL cholesterol levels [63]. In addition, CRISPR/Cas9 mediated genome editing has been found to effectively reduce hepatic PCSK9 expression with marked increase in LDLR along with reduction in plasma LDL cholesterol [64,65].

Recently, Gustafsen et al. showed that heparan sulfate proteoglycans that cover the sinusoidal surface of the hepatocytes are liver specific co-receptors that allows PCSK9 interaction with LDLR [66]. In addition, experiments performed in HepG2 cells with wild type PCSK9 and mutant PCSK9 show that PCSK9:HSPG interaction is critical in PCSK9 induced LDLR degradation. PCSK9:LDLR complex formation followed by LDLR degradation was prevented in the presence of exogenously added heparin or heparin mimetics like suramin. These exogenously added heparin and heparin mimetics bind to PCSK9 and prevent PCSK9 interaction with HSPG, thus preventing LDLR from PCSK9 mediated degradation. In vivo studies on PCSK9 activity showed that injection of heparinase I, a HS/heparin degrading enzyme, completely protected LDLR from PCSK9-mediated degradation supporting the role of HSPG in PCSK9-LDLR axis. Glycan array profiling revealed that PCSK9 binding to HSPG is selective towards trisulfated heparan sulfate/heparin disaccharide repeats. Altogether, these data show that HSPG on the hepatocyte surface plays a crucial role to capture PCSK9 and present it to LDLR for PCSK9-mediated LDLR degradation [66].

Low-density lipoprotein receptor-related protein 1 (LRP1) is a member of LDLR family and is highly expressed in the liver, neurons, brain, kidneys, endocrine tissues, lungs, pancreas and adipose tissues. LRP1 participates in apoE-mediated uptake of plasma triglyceride-rich chylomicrons remnants and VLDL by the liver [45,67–69]. However, studies have shown no overall changes in the lipoprotein profile of LRP1 deficient mice, questioning the importance of LRP1 in hepatic lipoproteins uptake [68,69]. In this context, it is noteworthy that there was a marked increase in LDLR levels in the hepatocytes of LRP1 deficient mice, suggesting that LDLR can compensate for the loss of LRP1 [45,69]. Indeed, ablation of both receptors in mouse livers exacerbates dyslipidemia compared to mice only deficient for LDLR. These data strengthen the importance of LRP1 in lipoprotein clearance but under specific physiological conditions [68]. For details on mechanism, readers are referred to the review by van de Sluis B et al. 2017 [45].

3.2. Heparan sulfate proteoglycans (HSPGs)

HSPGs are cell surface and extracellular matrix glycoconjugates containing a core protein to which one or more heparan sulfate (HS) glycosaminoglycan (GAG) chains are covalently attached [70]. HS polysaccharide chains are synthesized in the Golgi apparatus and consist of unbranched repeating disaccharide units of uronic acid linked to glucosamine. Various glycosyltransferases and modification enzymes are involved in the polymerization and modification processes of HS during their biosynthesis [71]. In detail biosynthesis of HSPG will not be discussed in this review, and can be found elsewhere [72].

Heparan sulfates (HS) and related sulfated GAGs display binding affinity to proteins involved in TG metabolism such as apoB, apoE and apoA-V. Their capacity to bind and clear lipoproteins from circulation is highly dependent on the sulfation of HSPG. For instance, sulfatase-1 (SULF-1) and sulfatase-2 (SULF-2) are important enzymes modulating the degree of sulfation of HSPG by cleaving 6-O sulfate groups thereby reducing lipoprotein uptake capacity. Hepatic overexpression of

sulfatase-2 (SULF2), has been reported to increase TG levels in obese, type 2 diabetic db/db mice [73]. Similarly, increased hepatic *SULF-2* expression found in type 2 diabetic mouse models, has been found to be significantly associated with higher plasma TG levels [74]. These data suggest 6-O sulfation of hepatic HS to be important for lipoprotein clearance. Chen K et al. [73] has reported the possibility of SULF-2 binding to syndecan-1 on hepatocytes, blocking remnant lipoprotein binding to syndecan-1 indicating alternative mechanism whereby SULF-2 could disturb remnants uptake by syndecan-1 [73].

Similarly, liver specific *N*-deacetylase/N-sulfotransferase-1 (NDST-1) knockout mice showed marked elevation in total plasma TG without changes in total plasma cholesterol. This effect was due to reduction in sulfation of hepatocyte HS induced by NDST-1 inactivation. This phenomenon hints that HSPGs plays a crucial role in the clearance of both intestinally-derived and liver-derived lipoprotein particles (chylomicrons, VLDL and their remnants) [75]. In addition, liver specific 2-O sulfotransferase (HS-2OST) knockout mice also showed increased plasma triglyceride levels [76]. Collectively, these data demonstrate the importance of properly sulfated HS for hepatic lipoprotein clearance.

3.2.1. Syndecan-1 and lipoprotein clearance

Syndecan-1, a primary transmembrane HSPG found abundantly in the liver, mediates clearance of triglyceride rich lipoproteins in vivo [75,77,78]. Syndecan-1 knockout mice show delayed clearance of injected human VLDL and intestinally derived chylomicrons. In addition, mice lacking both syndecan-1 and mutated hepatic HS did not display additionally elevated TG compared with single mutants, which strongly suggested that syndecan-1, via its HS side chains is the primary HSPG mediating hepatic triglyceride clearance. Furthermore, administration of adenovirus-encoded syndecan-1 restored binding, uptake, and degradation of VLDL in Syndecan-1 knockout mice [77]. Liver Syndecan-1/HS has higher sulfation than HSPGs in other tissues like the kidneys. This ensures selective binding of remnant lipoprotein particles to liver Syndecan-1/HS [77,78]. In addition, the localization of syndecan-1 is in hepatic space of Disse where lipoproteins are highly available, creating more opportunity for HSPGs to interact with lipoproteins and their remnants [78].

Lipoprotein bound to HS of syndecan-1 gets endocytosed together with syndecan-1 via clathrin independent internalization [79,80]. An early study by Fuki et al. showed that endocytosis of syndecan proteoglycans with lipoprotein ligands involves signals mediated by clustering of the transmembrane and cytoplasmic domains of the core protein [81]. The mechanism responsible for syndecan clustering involves binding of large, multimeric ligands that would bridge between receptors, or it may involve spontaneous polymerization mediated by the side chains [82] or by the transmembrane domain in cooperation with a conserved tetrapeptide sequence immediately outside the cell. Fuki et al. showed that this pathway requires the involvement of actin microfilaments, tyrosine kinases, cholesterol rich membrane rafts and flotillin 1 protein [79,81,83]. The process begins with ligand binding, then clustering of transmembrane and cytoplasmic domains of syndecan-1. Clustering stimulates energy-independent lateral movement into cholesterol-rich, detergent-insoluble membrane rafts, an event followed by recruitment of the actin cytoskeleton and tyrosine kinases to bring the ligands into the cell. In further work from the same laboratory, Chen et al. [84] first studied detailed characterization of the molecular events driving endocytosis of a raft-dependent receptor. They identified that a novel endocytic motif controls the interaction of syndecan-1 with cytoskeletal molecules to mediate efficient endocytosis [79,84]. In addition, Chen et al. recently reported a novel molecule, flotillin-1; in diabetic circumstances its hepatic suppression impairs the disposal of remnant lipoproteins by syndecan-1 [83]. They also observed that flotillin 1 knockout mice show impaired internalization, degradation, and hence total cellular catabolism of lipoproteins. Their data indicate that flotillin 1 facilitates normal syndecan-1–mediated endocytosis via interaction between the transmembrane/cytoplasmic region of syndecan-1 and the N-terminal hydrophobic domain of flotillin 1 [83]. An adenoviral construct to enhance hepatic expression of wild-type flotillin-1 in type 2 diabetic mice was found to normalize plasma triglycerides, whereas a mutant flotillin-1 missing its N-terminal hydrophobic domain had no effects on plasma TG [83]. These findings indicate that syndecan-1-mediated lipoprotein endocytosis is dependent on flotillin-1.

4. Pathophysiology of dyslipidemia in CKD

Dyslipidemia in CKD includes elevated total cholesterol, triglycerides and low HDL cholesterol. Hypertriglyceridemia is due to increased concentration of triglyceride-rich lipoproteins, such as VLDL. Notably, increased plasma levels of lipoprotein(a) (Lp[a]) are also observed in nephrotic syndrome [7,10,85,86]. The National Kidney Foundation has strongly recommended routine screening of CKD patients with respect to measurement of total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides [87]. The magnitude of hyperlipidemia and the associated alteration in lipoprotein metabolism in nephrotic syndrome parallels the severity of proteinuria [88]. Patients without nephrotic syndrome and even patients with mildly elevated urinary albumin excretion, designated microalbuminuria show high total cholesterol and LDL cholesterol, higher triglycerides, normal or lower HDL cholesterol although less severe than patients with nephrotic proteinuria [89–92]. In addition, serum triglycerides level has been found to be negatively associated with measured glomerular filtration rate indicating that patients with reduced kidney function are more likely to have higher serum triglyceride levels [93].

The pathophysiology related to dyslipidemia in CKD are multifactorial and will be outlined below (see also Fig. 3).

4.1. Lipoprotein lipase deficiency

As mentioned above in Section 1.2, LPL is a major enzyme involved in hydrolysis of triglycerides from chylomicrons and VLDL. The endothelium-derived glycosylphosphatidylinositol-anchored binding protein 1 (GPIHBP1) anchors LPL on the endothelium [94]. Several studies have shown marked reduction in endothelium-bound LPL in nephrotic conditions despite normal LPL mRNA expression in the adipose tissue, skeletal muscle, and myocardium in nephrotic syndrome [86]. Subsequent studies have reported downregulation of GPIHBP1 as the primary cause of the LPL deficiency in nephrotic animals [94]. In addition, decreased LPL activity has also been observed as a result of decreased apoCII (LPL activator)/apoCIII (LPL inhibitor) ratio in nephrotic syndrome [95]. Recently, upregulation of angiopoietin-like protein 4 (Angptl 4) was identified as another important cause of the decreased LPL activity in nephrotic syndrome [96]. Angptl 4 inactivates LPL activity by promoting intracellular degradation of LPL and hence impairs lipolysis of VLDL and chylomicron leading to hypertriglyceridemia. Besides LPL, Angptl 4 also inhibits hepatic lipase and limits removal of HDL and IDL triglyceride contents [97]. The inhibitory effect of Angptl 4 has been found to be lessened by GPIHBP1 [98]. However, reduced GP1HBP1 in nephrotic conditions heightens the LPL inhibitory effects of Angptl 4 leading to elevated plasma triglycerides [86]. Studies published by Clement et al. on Angptl 4 in proteinuric dyslipidemia, suggest that increases in circulating Angptl 4 in response to proteinuria may induce hypertriglyceridemia [99,100]. For more details, please refer to the review by Clement et al. [101].

4.2. Increased synthesis of fatty acids, triglycerides and cholesterol

The expression of major enzymes involved in fatty acid biosynthesis like acetyl coenzyme A (CoA) carboxylase and fatty acid synthase are found to be upregulated in nephrotic syndrome [86,102]. In addition, expression of genes that encode for phospholipid and triglyceride synthesis like glycerol-3-phosphate acyltransferase, 1-acyl-sn-glycerol-

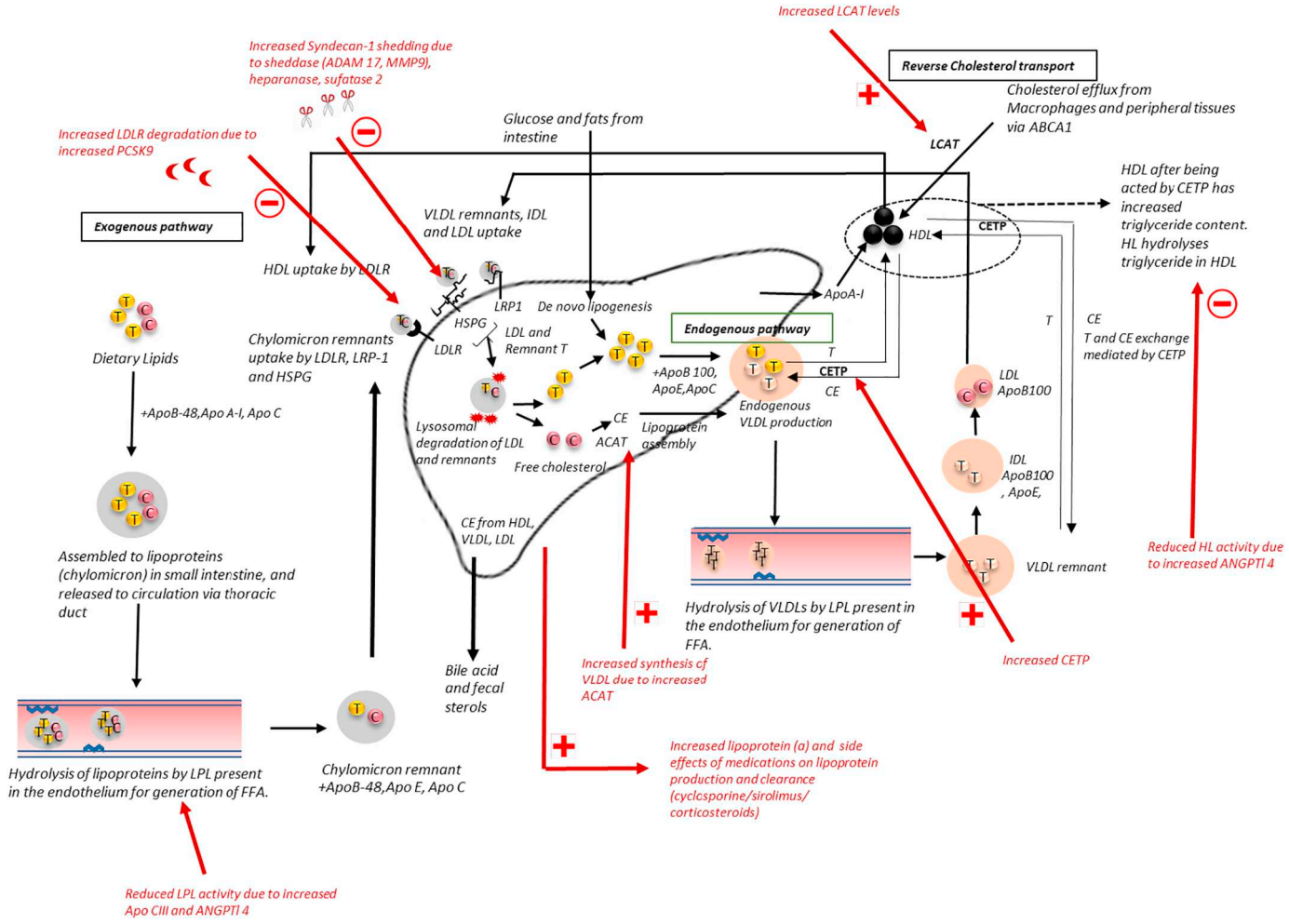

Fig. 3. Interference of CKD on normal lipoprotein metabolism. T (triglycerides/TG), C (cholesterol), LPL (lipoprotein lipase), FFA (free fatty acids), LDLR (low density lipoprotein receptor); HSPG (heparan sulfate proteoglycans), LRP-1 (low density lipoprotein receptor like protein 1), VLDL (very low density lipoprotein), IDL (intermediate density lipoprotein); LDL (low density lipoprotein), Apo (apolipoproteins), CETP (cholesteryl ester transfer protein), LCAT (lecithin:cholesterol acyltransferase), ACAT (Acyl-CoA:cholesterol acyltransferase-2); PCSK9 (proprotein convertase subtilisin kexin type 9); CE (cholesterol ester); HL (Hepatic lipase); ABCA1 (ATP binding cassette transport).

3-phosphate acyltransferase gamma and acyl-CoA diglycerolacyltransferase are also reported to be upregulated in the liver of animals with nephrotic syndrome [86,102]. These studies suggest increased production of fatty acids and triglycerides contribute to dyslipidemia in nephrotic syndrome. Moreover, the expression of 3- hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase which determines the rate-limiting step in cholesterol biosynthesis was found to be upregulated in nephrotic conditions. Thereby increasing cholesterol synthesis and aggravating dyslipidemia in CKD [86,103].

Acyl-CoA: cholesterol acyltransferase-2 (ACAT) plays an important role in transcriptional and post-translational regulation of hepatic cholesterol production. It is involved in packaging cholesterol in apoB-100 lipoproteins in the liver for release in the circulation. The expression of ACAT was highly upregulated in the livers of nephrotic animals [104]. Administration of ACAT inhibitors has been reported to improve plasma lipid levels further supporting the concept that elevated ACAT induces dyslipidemia in CKD [86,105]. In addition to increased lipid synthesis, Zaiou et al. shows that the human apoA-I gene is induced by the experimental nephrotic syndrome in apoA-I transgenic mice [106].

4.3. LDLR deficiency

The protein levels of LDLR was found to be reduced in the livers of nephrotic animals despite its normal mRNA expression and SREBP-2 expression [107,108]. This suggests that post-transcriptional modification of LDLR could explain these reduced levels. Kwakernaak AJ et al. showed a marked increase in plasma PCSK9 in CKD patient with proteinuria suggesting that upregulation of PCSK9 may contribute to the pathogenesis of dyslipidemia in CKD [109]. The other important LDL receptor degrader, IDOL, which mediates ubiquitination and degradation of the LDL receptor, was found to be upregulated in nephrotic conditions along with marked increase in serum cholesterol [110].

4.4. Syndecan-1 shedding

Recently Adepu S. et al., [111] reported the loss/shedding of hepatic syndecan-1 in renal transplantation due to increased expression of hepatic syndecan-1 sheddases like ADAM-17, MMP9, heparanase and sulfatase-2. Shedding of hepatic syndecan-1 was strongly associated

with reduced functional capacity for VLDL binding and increased plasma triglycerides. This study suggests that after renal transplantation loss of hepatic HS together with increased syndecan-1 shedding hampers lipoprotein binding and uptake by the liver. Thus contributing to dyslipidemia. This phenomenon was never reported before and was a novel mechanism for developing dyslipidemia in CKD [111].

4.5. Increased lipoprotein (a) levels

Lipoprotein(a) (Lp[a]) is an atherogenic and prothrombotic factor that promotes LDL oxidation and facilitates monocyte adhesion [86]. Lp (a) levels are found to be markedly increased in nephrotic syndrome due to its increased production by the liver [86]. Gansevoort RT et al. 1994 has reported reduction in plasma Lp(a) upon antiproteinuric therapy [112].

4.6. Abnormalities in reverse cholesterol transport

A major proportion of cholesteryl esters in plasma is generated through the esterification of free cholesterol by the action of LCAT. HDL is the preferred substrate for the LCAT reaction. Subsequently, cholesteryl esters are transferred towards apolipoprotein B-containing lipoproteins by the action of CETP [113]. Inhibition of CETP activity leads to an increase in HDL cholesterol and a decrease in LDL cholesterol [33]. An early study from our group has demonstrated elevated plasma levels of total cholesterol and TG as well as LCAT and CETP in patients with non-diabetic glomerulopathy and nephrotic-range proteinuria coinciding with cholesteryl ester depletion in HDL. This indicates that an abnormal lipoprotein profile is related to elevated activities of LCAT and CETP [113]. VLDL and LDL cholesterol levels and CETP activity were positively correlated with urinary protein excretion and inversely correlated with serum albumin concentration. Moreover, VLDL and LDL cholesterol levels were positively related to LCAT as well as to CETP activity. The activity of LCAT was found to decrease concomitantly with reduction in proteinuria during ACE inhibition therapy. Additionally, plasma CETP level decreases after treatment with losartan combined with hydrochlorothiazide and low sodium diet coinciding with LDL cholesterol reductions [114]. These findings suggest that increased activities of LCAT and CETP may play an important role in the lipoprotein abnormalities in proteinuria.

4.7. Medication induced dyslipidemia

In renal transplant recipients, the use of immunosuppressive agents like cyclosporine, corticosteroids, sirolimus is inevitable in order to prevent/reduce the risk for organ rejection. These medications have been reported to induce dyslipidemia in renal transplant patients. For instance, cyclosporine interferes with the binding of LDL cholesterol to LDLR. As a result, there is a decline in LDL clearance, leading to a rise in LDL cholesterol levels. Corticosteroids are reported to increase the activity of HMG-CoA, reduce LPL activity and down regulate the expression of LDLR leading to increased synthesis and reduced clearance of plasma lipoproteins [115]. In addition, glucocorticoids induces new-onset hyperglycemia in patients without a history of diabetes mellitus or severely uncontrolled hyperglycemia in patients with known diabetes mellitus [116].

5. Current approaches for management of dyslipidemia in CKD

Current approaches to treat dyslipidemia in CKD are aimed at correcting lipid uptake in the intestine and endogenous cholesterol synthesis in the liver. They are shown in Table 1. Treatment approaches targeting improved clearance of lipoproteins by improving the functioning of hepatic lipoprotein receptors are yet to be explored and are discussed in the next section.

6. Novel strategies

Statins are the first line and the most effective drugs in reducing total cholesterol and LDL-C. They have been reported to reduce LDL-C by 30–60%. Despite a great number of studies reporting ASCVD risk reduction with statins in general, some studies fail to show the similar CVD risk reduction in CKD. For instance, the high-efficacy statins, atorvastatin and rosuvastatin effectively, lowered LDL-C but had no statistically significant effect on cardiovascular death, non-fatal myocardial infarction, and stroke in patients with end-stage renal disease (ESRD) [127,128]. A recent review published by Verdoodt A. et al. concluded that statins are of undisputed efficacy for treatment of hypercholesterolemia and have a prominent role in primary and secondary prevention of cardiovascular disease. However, its effect in stroke risk and progression of CKD is less evident. Statin-related rhabdomyolysis remain a concern. In addition, high-efficacy agents may harm the kidney in patients with vascular compromise and CKD. Also, statins are relatively contra-indicated in patients with ESRD [129].Taken together, CVD still remains the leading cause of the death in CKD. 30% of patients do not achieve adequate cholesterol control despite maximal tolerable statin doses. Moreover, approximately 5–10% of patients develop statin intolerance. Benefits of statin use in patients receiving hemodialysis and kidney transplant recipients is highly debatable [18,130,131]. Also, it should be mentioned that statins do not have an effect on hypertriglyceridemia, elevated Lp (a) and decreased HDL levels which are often presented in CKD patients [7,85,89]. Fibrates are infrequently used in CKD due to high levels of toxicity, whereas niacin is no longer available in the regular market in several countries including The Netherlands. Therefore, given the limited efficacy of current approaches in CKD both in terms of lipid lowering and reducing CVD events, it is essential to develop new drugs and novel targets to treat dyslipidemia in CKD (Fig. 3) [10,11].

6.1. Treatment with humanized anti-PCSK9 antibodies

Various methods are being developed to inhibit PCSK9. For instance knocking down its expression by using antisense nucleotides and RNA interference (RNAi), or blocking the interaction of PCSK9 in plasma with LDLR by means of monoclonal antibodies [132–134]. These humanized anti-PCSK9 antibodies target PCSK9 and prevent PCSK9-mediated LDLR degradation. The US Food and Drug Administration (FDA) has already approved two fully humanized anti-PCSK9 antibodies: alirocumab and evolucumab for the use in patients with heterozygous familial hypercholesterolemia or for those at high cardiovascular risk who cannot sufficiently reduce their LDL cholesterol with statins [135].

A recent editorial summarized humanized PCSK9 antibody trials and their outcomes [136]. Two open-label, randomized extension studies Open Label Study of Long Term Evaluation Against LDL-C Trial (OSLER)–1 and OSLER-2, reported the effects of evolocumab (140 mg administered subcutaneously every 2 weeks or 420 mg administered monthly) on top of standard lipid-lowering therapy and showed a sustained 61% reduction in LDL cholesterol levels compared to the change in LDL cholesterol levels with standard therapy alone for a median period of 11 months [137,138]. The magnitude of this response was found to be unrelated to the baseline PCSK9 level [139]. Another study evaluating the long-term safety and tolerability of alirocumab (150 mg administered subcutaneously every 2 weeks) in high cardiovascular risk patients with hypercholesterolemia, which was not adequately controlled with conventional lipid modifying therapy (ODYSSEY long term) trial, also reported reduction in LDL-C by 61% over the period of 78 weeks. In these studies (ODYSSEY COMBO I and ODYSSEY COMBO II), Alirocumab was found to be superior in reducing LDL-C levels, in comparison to placebo and ezetimibe, respectively, in CKD sub-group analysis. When added to statins, alirocumab has been found to be effective in reducing LDL-C levels in nephrotic syndrome as

Table 1
Current treatment modalities to treat dyslipidemia in renal patients [18,117–126].

Drugs	Mechanism of action	Efficacy	Drawbacks
Statins	Inhibition of HMGCoA and increased LDLR expression	Effective in reducing total and LDL-C cholesterol	✓ Only modest reduction in triglycerides and minor increment in HDL-C ✓ Reduction in lipoprotein (a) is controversial ✓ Statin intolerance: rhabdomyolysis, pre-onset of type 2 diabetes, liver damage and neurological effects reported ✓ Contraindicated in patients with acute or chronic liver disease ✓ Multiple drug interactions
Fibrates	Activates Peroxisome proliferator activated receptor-α (PPAR-α)	Effective in lowering total cholesterol, triglycerides, ApoC-III and increasing the levels of HDL-C	✓ High muscular toxicity ✓ Increased serum creatinine reported although changes in creatinine has been shown to be reversible after fibrate withdrawal ✓ Tubular toxicity ✓ Indicated only in patients with severe hypertriglyceridemia (Triglycerides > 500 mg/dl) ✓ No effects on lipoprotein (a) ✓ Non reversible renal failure and hepatotoxicity reported
Niacin	Inhibits the activity of diacylglycerol acyltransferase–2 (DGAT2), a key enzyme involved in triglycerides synthesis	Highly effective in increasing HDL-C levels and reduction in total cholesterol levels, triglyceride levels and LDL-C levels	✓ Severe drug reactions: Prostaglandin-mediated hot flushing, liver function test disruption, exacerbation of peptic ulcer disease, nausea, vomiting, pruritus, hives, constipation, increased uric acid levels, and thrombocytopenia ✓ No longer recommended
Ezetimibe	Reduces cholesterol absorption in small intestine by blocking Niemann–Pick C1-like 1 protein (NPC1L1) in enterocytes Reported to increase LDLR expression	Effective in LDL-C reduction. In combination with simvastatin, the SHARP trial show reduction in LDL-C and major atherosclerotic events in CKD patients	✓ Incidences of hepatotoxicity has been reported ✓ More trials and data needed to evaluate its efficacy
Omega 3 polyunsaturated fatty acids	Inhibits the activity of diacylglycerol acyltransferase–2 (DGAT2), a key enzyme involved in triglycerides	Reduces triglycerides	✓ More trials and data needed to evaluate its efficacy
CETP Inhibitors	Inhibits the transfer of cholesteryl esters from HDL to very low-density lipoprotein and LDL and thus raises HDL-C level and reduces LDL-C level	Torcetrapib showed a dose-dependent increase of HDL-C up to 106% and a reduction in LDL-C up to 42% and dalcetrapib showed a dose-dependent increase of HDL-C up to 36%.	✓ Torcetrapib receiving group had 25% increase in cardiovascular events and a 58% increase in mortality due to which (ILLUMINATE) trial with torcetrapib was terminated prematurely. ✓ ILLUSTRATE trial showed no difference on atherosclerosis plaque burden using combination therapy of torcetrapib plus atorvastatin versus atorvastatin alone ✓ Dalcetrapib showed no effects on LDL-C levels with major cardiovascular events. ✓ dal-OUTCOMES trial was halted after a second interim analysis due to poor outcomes ✓ In general, Mendelian randomization studies by Voight BF et al. have repeatedly shown no clinical benefits on atherosclerotic cardiovascular disease ASCVD from genetically higher plasma HDL concentrations

well [130]. Notably, a detailed analysis of the use of PCSK9 antibodies in CKD group needs to be carried out.

However, effects of PCSK9 antibodies on lowering TG levels is relatively small, amounting to about 16% after monthly 420 mg evolocumab treatment [137,140–145]. A study by G. Reyes-Soffer et al. 2017 and Chan D.C. et al. 2018, show that administration of PCSK9 inhibitors (alirocumab and evolocumab respectively) did not affect postprandial apoB-48 concentrations [144,145]. Humanized PCSK9 antibodies reduce plasma Lp(a) levels up to approximately 30% in a dose-dependent fashion, which is an added benefit compared to statins [146]. Importantly, the incidence of major adverse cardiovascular events were found to be reduced with the use of evolocumab. Similar outcome was observed with the use of alirocumab [136,137,147,148].

A recent publication by Thakore et al. showed that the use of CRISPR-Cas9 gene editing technology can repress the hepatic expression of *Pcsk9* in adult mice, leading to reduced plasma PCSK9 levels and subsequently lower total plasma cholesterol for six months after a single treatment. This discovery is an advancement towards utilizing CRISPR as a therapeutic treatment [64].

However, Kosicki M et al. 2018 reported genomic damage in various cells like mouse embryonic stem cells, mouse hematopoietic progenitors and a human differentiated cell line caused by CRISPR-Cas9. In clinical context, such genetic consequences may trigger a first carcinogenic 'hit' in stem cells and progenitors, which have a long replicative lifespan and may become neoplastic with time. Altogether, results suggest a need to carefully examine the genome when editing is done ex vivo and complete genomic analysis is warranted to identify cells with normal genomes before administering to the patients [149].

6.2. Heparin mimetics

As discussed above, hepatic HSPGs may serve as docking platform for PCSK9 and function as indispensable co-receptors in the PCSK9-mediated degradation of LDLR. These findings are of high interest, especially in the present context of dyslipidemia where expensive PCSK9 inhibitors are being used for the treatment. Heparin and dextran sulfate treatment in humans have been observed to reduce plasma lipoprotein levels [119,150–154]. Heparin and related compounds lower plasma lipoprotein concentrations also by releasing LPL into plasma, which enhances the enzyme's ability to hydrolyze the TG in circulating lipoproteins [155]. Therefore, heparin mimetics seem to be a novel class of drugs, which could prevent PCSK9-mediated LDLR degradation

and treat dyslipidemia. However, it is generally recognized that heparinoids are pleiotropic molecules binding with many different proteins involved in anti-coagulation (like anti-thrombin), leukocyte migration (like chemokines and selectins), complement system (like properdin and factor H) and growth factor responses (like FGFs, VEGFs). This indicates that heparin-related glycomimetics should be chemically modified in such a way that PCSK9 interaction with HSPG is disrupted, without biologically relevant interactions with many other mediators. Besides this issue on specificity, long term use of heparinoids does exhibit other serious side effects like risk of fractures due to reduction in bone mineral density and hyperkalemia [156,157]. Therefore, although heparin and heparin mimetics seem to be another potential drug therapy to control dyslipidemia, further research is essential.

6.3. Apolipoprotein C III inhibitors

Another class of drugs which could potentially be used as lipid lowering therapy in future is Apo C-III (Apo CIII) inhibitors. Apo CIII suppresses the activity of LPL resulting in suppression of LPL mediated lipoprotein hydrolysis [158]. Two recent publications has shown a strong association of loss-of-function mutations in Apo CIII with low levels of triglycerides and decreased CVD [159,160]. Apo CIII antisense therapy has already entered phase 2 studies in a broad range of patient groups, with moderately to severely elevated triglyceride levels [161] where volanesorsen was found to be effective to reduce Apo B 100 and Apo A-I containing lipoproteins and Lp(a) in a dose dependent fashion. No serious treatment-associated adverse effects were identified. The apparent clinical benefits of volanesorsen was also observed in patients with familial chylomicronemia syndrome (FCS) [162,163]. Phase III trial about volanesorsen is ongoing and it includes the APPROACH study: A Study of ISIS-APOCIIIRx in Patients with Familial Chylomicronemia Syndrome, (NCT02211209), the COMPASS (the COMPASS study: A Study of Volanesorsen in Patients with Hypertriglyceridemia, NCT02300233), and the BROADEN (the BROADEN study: A Study of Volanesorsen in Patients with Partial Lipodystrophy, NCT02527343) [163,164].

6.4. Angiopoietin like protein 4 (Angptl4) inhibitors

Angiopoietin like protein 4 has been known to elevate serum lipid levels by suppressing the activity of LPL [165]. An article published by Desai U et al. 2007 reported lipid lowering activity in Angptl 4 knockout mice [166]. Similarly, transgenic mice expressing human Angptl 4 that were treated with an Angptl 4-neutralizing, fully human monoclonal antibody demonstrate a sustained reduction in plasma TG levels. In line with these findings in mice, cynomolgus monkeys and hyperlipidemic rhesus monkeys treated with an Angptl 4-neutralizing, fully human monoclonal antibody had decreased levels of plasma TGs [167]. Further, one obese rhesus monkey with a pretreatment TG level of over 1500 mg/dl treated with this antibody experienced a > 95% reduction in TG levels [168]. These data suggest that Angptl4 inhibitors are another class of novel medication which has the potential to reduce serum TGs. These molecules might be of high importance in case of CKD where TGs levels are found to be constantly elevated. Additional research remains to elucidate the full range of mechanisms through which Angptl 4 affects triglyceride and cholesterol homeostasis.

6.5. SULF-2 inhibitors

A study published by Hassing H.C. et al. 2012 show that inhibition of hepatic SULF-2 normalizes the VLDL-binding capacity of hepatocytes and cures postprandial hypertriglyceridemia. These findings provide a key proof-of-concept in vivo to support *Sulf2* inhibition as an attractive strategy to improve metabolic dyslipidemia [169].

6.6. Metalloproteinase inhibitors

Dyslipidemia associated with increased shedding of hepatic syndecan-1 due to increased expression of sheddases and metalloproteinases (like ADAM-17, MMP-9) and heparanase has been recently reported by Adepu S et al. [111] in renal transplant patients [111]. These data suggest that molecules that can inhibit sheddases and metalloproteinase might be potential novel agents to treat dyslipidemia in CKD group [170]. These molecules might prevent loss of HSPG and improve lipoprotein clearance. On the other hand, HSPG are found to present PCSK9 to LDLR and induce LDLR degradation. Thus, PCSK9 inhibitors, in combination of sheddase and metalloproteinase inhibitors might be beneficial to control dyslipidemia in CKD.

7. Conclusion

In this review, we have summarized normal process of lipoprotein metabolism, the role of lipoprotein receptors in establishing and balancing the process, the deleterious effects of CKD in normal lipoprotein metabolism, CVD risks and the present and the future aspects of treatment and preventive measures, providing overall update on dyslipidemia in CKD. In summary, hepatic lipoprotein receptors (LDLR, LRP-1 and Syndecan-1) play a crucial role in lipoprotein uptake and clearance. Changes in the expression of various molecules and prevalence of mutations and disease conditions like CKD affects the structure and function of lipoproteins receptors, which bring about disturbances in normal lipoprotein clearance leading to dyslipidemia. A large number of CKD patients with insufficiently treated dyslipidemia due to drug intolerance, (hepato) toxicity and multiple drug interactions are in need for better treatment. Moreover, dyslipidemia associated with CKD is complex and heterogeneous in nature due to complex abnormalities in lipoprotein metabolism. Further studies are required to investigate the novel approaches to treat dyslipidemia. Although novel therapies like anti-PCSK9 monoclonal antibodies are promising, their limited effects on plasma TG levels suggests a need for additional medical treatment. Development of heparin mimetics, Apo CIII inhibitors and Angptl 4 inhibitors as anti-hyperlipidemic drugs look promising and needs further investigation.

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