Title
High-density lipoprotein in uremic patients: metabolism, impairment, and therapy

Journal
International Urology and Nephrology, 46(1)

ISSN
0924-8455

Authors
Khoueiry, Georges
Abdallah, Mokhtar
Saiful, Faisal
et al.

Publication Date
2014

DOI
10.1007/s11255-012-0366-y

Int Urol Nephrol (2014) 46:27–39
DOI 10.1007/s11255-012-0366-y

NEPHROLOGY - REVIEW

High-density lipoprotein in uremic patients: metabolism, impairment, and therapy

Georges Khoueiry · Mokhtar Abdallah · Faisal Saiful · Nidal Abi Rafeh · Muhammad Raza · Tariq Bhat · Suzanne El-Sayegh · Kamyar Kalantar-Zadeh · James Lafferty

Received: 21 August 2012 / Accepted: 12 December 2012 / Published online: 27 February 2013

Abstract Several studies have shown that HDL has altered antioxidant and anti-inflammatory effects in chronic uremia, either by the reduction in its antioxidant enzymes or by the impairment of their activity. Systemic oxidative stress, which is highly prevalent in chronic kidney disease (CKD) patients, has been shown to decrease antioxidant and anti-inflammatory effects of HDL and even transform it into a pro-oxidant and pro-inflammatory agent. For this reason, we believe that the propensity for accelerated cardiovascular disease in CKD is facilitated by a few key features of this disease, namely, oxidative stress, inflammation, hypertension, and disorders of lipid metabolism. In a nutshell, oxidative stress and inflammation enhance atherosclerosis leading to increased cardiovascular mortality and morbidity in this population. In this detailed review, we highlight the current knowledge on HDL dysfunction and impairment in chronic kidney disease as well as the available therapy.

Keywords Atherosclerosis · High-density lipoprotein · Uremia · Chronic kidney disease · Lipid metabolism

Introduction

Chronic kidney disease (CKD) is one of the major medical concerns of the health-care system today. It is

G. Khoueiry (✉)
Department of Cardiology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756-0001, USA
e-mail: khoueiry_gm@hotmail.com

M. Abdallah · M. Raza
Department of Medicine, Staten Island University Hospital, 475 Seaview Avenue, Staten Island, NY 10305, USA

F. Saiful · T. Bhat · J. Lafferty
Department of Cardiology, Staten Island University Hospital, 475 Seaview Avenue, Staten Island, NY 10305, USA

N. Abi Rafeh
Tulane University Heart and Vascular Institute, Tulane University School of Medicine, 1430 Tulane Ave, New Orleans, LA, USA

S. El-Sayegh
Department of Nephrology, Staten Island University Hospital, 475 Seaview Avenue, Staten Island, NY 10305, USA

K. Kalantar-Zadeh
Division of Nephrology and Hypertension, University of California Irvine, School of Medicine, Orange, CA, USA

K. Kalantar-Zadeh
UCLA School of Public Health, Los Angeles, CA, USA

associated with premature mortality, decreased quality of life, and enormous health-care expenditures [1]. According to 1999–2004 National Health and Nutrition Examination Survey (NHANES) data, 16.8 % of the US population aged ≥20 years had CKD [2]. Interestingly, the major cause of mortality and morbidity in this sizable CKD and end-stage renal disease (ESRD) population is attributed to cardiovascular disease.

High levels of high-density lipoprotein (HDL) are associated with decreased risk of developing coronary artery diseases (CAD). This is mainly attributed to its antioxidant, anti-inflammatory, reverse cholesterol transport, and anti-thrombotic properties which tend to decrease atherosclerosis. The antioxidant properties of HDL are due to its constituent enzymes paraoxonase and glutathione peroxidase and lipoproproteins mainly apolipoprotein-A1. The activity of key antioxidant enzymes and lipoproteins is decreased in CKD and ESRD, thus limiting the role of HDL in preventing the oxidation of LDL particles [3]. Moreover, it has been proposed that HDL plays a role in removal of the endotoxin in the blood. Low levels of HDL in CKD are also associated with high levels of endotoxin in the blood. So, HDL deficiency predisposes CKD patients to multiple infections especially by gram-negative organisms, thus increasing mortality as infections are the second most common cause of death in ESRD patients [4].

The propensity for accelerated cardiovascular disease in CKD is thought to be mediated by a few key features of this disease, namely, oxidative stress, inflammation, hypertension, and disorders of the lipid metabolism [5, 6]. In a nutshell, oxidative stress and inflammation enhance atherosclerosis by three major pathophysiologic pathways. They promote oxidation of low-density lipoprotein (LDL) and remnant particles; they support the differentiation of monocytes into foam cells in the arterial wall; and they impair HDL-mediated reverse cholesterol transport [7–10]. The oxidized LDL particles are then engulfed by macrophages and converted to foam cells in the vessel wall leading to atherosclerosis.

Many of the other "unconventional" risk factors have been identified as well, this includes hypoalbuminemia, elevated troponin levels, anemia, hyperhomocystinemia, increased calcium phosphate product, maintenance hemodialysis (MHD), and decreased nitric oxide activity [10–12]. Also, most dialysis patients ingest atherogenic diet and do not meet the dietary guidelines for cardiovascular disease risk reduction as we have shown in a previous report [11].

In this article, we intend to provide a thorough overview on the metabolism of HDL specifically in patients with CKD. We highlight the HDL antioxidant and anti-inflammatory protective role against atherosclerosis which is markedly impaired in uremic patients. We review the current advance in lipid therapy and potential advances in the future with a focus on HDL-targeting medications.

HDL metabolism and reverse cholesterol transport

High-density lipoprotein is one of the five major lipoproteins found in the plasma beside low-density lipoprotein (LDL), very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDLs), and chylomicrons. Lipoproteins play an essential role in the transport of cholesterol, cholesterol esters, and triacylglycerols in the body. They are spherical like particles, consisting of a core where the most hydrophobic particles such as cholesterol esters and triacylglycerols are located, and a surface where free cholesterol, phospholipids, and proteins are arrayed [13].

Lipoproteins are substrates for several enzymes, including lipoprotein lipase (LPL). Attached to the surface of the endothelium, LPL plays a major role in the hydrolysis of triacylglycerols carried by VLDL and Chylomicrons. This leads to the release of fatty acids (FA), phospholipids, free cholesterol, and exchangeable apoliproteins (apo) (Fig. 1). Fatty acids are then stored by adipocytes or used by cells for membrane cell formation. Chylomicrons are transformed to chylomicrons remnants which are rich in cholesterol esters and then taken up by the liver after binding to specific receptors (Fig. 1). LPL is activated by apo-C2 and heparin that is released by mast cells [13].

HDL is synthesized mainly in the liver and to a lesser extent in the intestines. It has the individual role of being a reservoir of apo-E and apo-C2, wich are both activators of LPL. HDL regulates the exchange of lipids and apoproteins between different lipoproteins in the blood. By donating apo-C-2 and apo-E to chylomicrons and VLDLs, HDL helps in the hydrolysis of triacylglycerols, resulting in the formation of chylomicrons remnants and LDL, respectively. This is followed by the return of apo-E and apo-C2 to HDL [13].

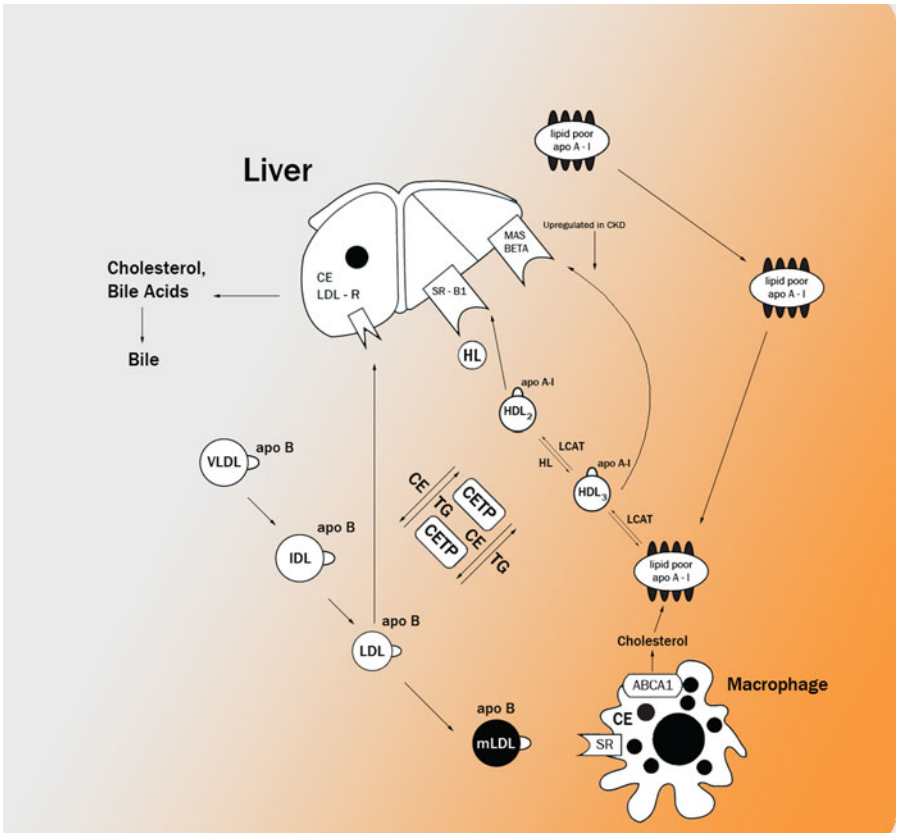

Fig. 1 An illustration showing HDL metabolism. HDL is secreted as a poor lipid apo-A1; the transport of free cholesterol by ABCA1 from non-hepatic cells membrane leads to the production of nascent HDL, ABCA1 also transfers phospholipids to the nascent HDL and leads to the production of HDL3, than LCAT transforms HDL3 into HDL2 by esterification of free cholesterol. Cholesteryl esters are then transferred to LDL and VLDL via CETP and taken up by the liver. *A-I* apo-A1, *ABCA1* ATP-binding cassette transporter ABCA1, *B* apo-B-100, *B-48* apo-B-48, *C* apo-Cs, *CE* cholesterol ester, *CETP* cholesterol ester transfer protein, *CM* chylomicron, *CMR* chylomicron remnant, *E* apo-E, *HL* hepatic lipase, *LCAT* lecithin: cholesterol acyltransferase, *LPL* lipoprotein lipase, *MAS BETA* Mitochondrial ATP synthase beta subunit, *SR-B1* Scavenger receptor class B member 1, *TG* triglycerides

HDL also plays a role in the removal of excess cholesterol from cells and its transfer to the liver, where it is eliminated as cholesterol and bile salts. This phenomenon is called reverse cholesterol transport (RCT).

HDL is secreted as apoprotein-A1 (apo-A1) without phospholipids or triacylgylcerols. The transfer of free cholesterol from other lipoproteins or plasma membrane to apo-A1 leads to the production of nascent HDL, known as pre-β HDL (Fig. 1). This transport is mediated by ATP-binding cassette transporter ABCA1. The same membrane transporter also transfers phospholipids to nascent HDL which produces HDL3 molecule (Fig. 1). This is followed by esterification of the free cholesterol by lecithin cholesterol acyl transferase (LCAT). LCAT, produced by the liver, is bound to the HDL molecule and is activated by apo-A1 in the plasma. LCAT needs phospholipids such as phosphatidylcholine to complete this reaction; for this purpose, phospholipid transfer protein (PLTP) catalyzes the transfer of phospholipids released by LPL hydrolysis of triacylglycerols, to HDL. Further addition of esterified cholesterol to HDL 3 produces HDL 2 (Fig. 1). Cholesteryl ester is then transferred to VLDL and LDL by cholesterol ester transfer protein (CETP) which is bound to HDL particles, and then taken up by the liver [13].

HDL is degraded in the liver through two major pathways. The first involves the selective uptake of cholesteryl esters by a plasma membrane protein

called scavenger receptor-B1 (SR-B1) leading to the re-release of apo-A1 to form a new HDL molecule. Of note, SR-B1 has a higher affinity to HDL-2 molecules [14]. The second uses mitochondrial ATP synthase beta subunit, a hepatic endocytic receptor, which leads to the total internalization and intracellular degradation of the whole HDL molecule. As opposed to the first pathway, beta chain of the mitochondrial ATP synthase has a higher affinity to HDL-3 than to HDL-2 and does not lead to re-release of apo-A1 (Fig. 1) [13].

Factors leading to low HDL levels and impaired metabolism in uremic patients

CKD leads to accelerated atherosclerosis and increased cardiovascular events due to a number of nonconventional risk factors that are present in this population [15]. Studies have shown that oxidative stress, inflammation, endothelial dysfunction, hypertension, dyslipidemia, insulin resistance and vascular calcification contribute to the increased mortality, and morbidity in ESRD [5, 6, 16–21]. Elevated levels of triglycerides and decreased levels of HDL are the most common features of dyslipidemia in this population. Uremia leads to dysregulation in the synthesis and activity of HDL and errors in the metabolism of triglyceride-rich apo-B containing lipoproteins [20]. The pathophysiology of this disturbed metabolism is still under investigation. Studies performed in experimental animals have shown that plasma concentration of apo-A1 and apo-A2 is decreased in patients with renal failure due to diminished gene expression in the liver. Since apo-A1 is the primary component of HDL, its deficiency contributes in part to the overall reduction in HDL (Fig. 2) [22, 23].

HDL-mediated uptake and removal of surplus of cholesterol from the peripheral tissues start by binding of cholesterol poor-HDL to ABCA-1, a process known as reverse cholesterol transport. It has been also shown that HDL is oxidized in ESRD; this oxidation impairs the binding of HDL to ABCA1, which leads to the accumulation of lipids in the arterial wall [24, 25]. In addition, ABCA-1 expression in chronic kidney disease might be altered; however, this is still under investigation. It should be noted that the potential under expression of ABCA-1 transporter can lead to the reduction in HDL levels and limits the maturation of the molecule as seen in Tangier disease [26–28].

Albumin serves as a carrier of free cholesterol from the peripheral tissues to the freely floating HDL-3, thus hypoalbuminemia in CKD due to malnutrition, external losses, or inflammation can also contribute to depressed levels of serum HDL. Of note, albumin also plays a physiologic role in the efflux of cholesterol outside the cells [29].

Studies conducted on patients with CKD showed a reduction in the level of LCAT in these patients [24, 30]. Hepatic tissue LCAT mRNA and plasma LCAT enzymatic activity were measured in male Sprague–Dawley rats 6 weeks after partial nephrectomy. These levels were found to be low in this animal model [31]. This implies that in CKD, there is a downregulation of

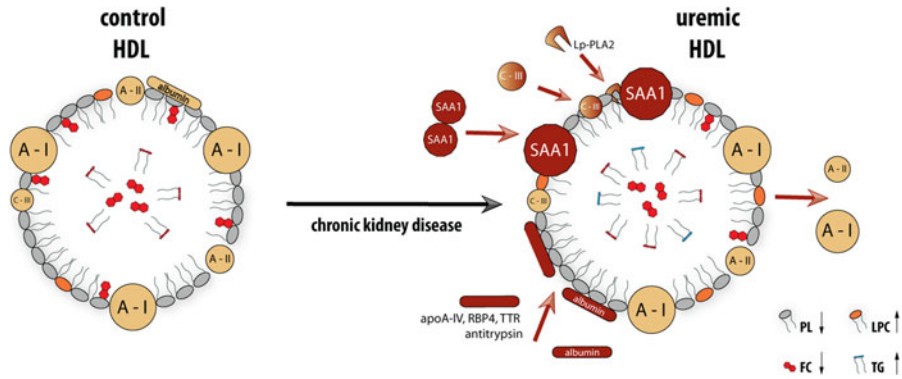

Fig. 2 Illustration showing the difference between normal HDL and uremic HDL molecule. Note that when compared to normal molecule, uremic HDL is significantly rich in SAA1, albumin, and apo-C3, TG and lyso-PC (LPC) content, as well as in the low-abundant HDL-associated proteins apo-A4, RBP4, TTR, anti-trypsin, and Lp-PLA2. While on the contrary, it is poor in apo-A1 and apo-A2, PL and FC. *apo-C3* apoprotein-C3, *apo-A4* apoprotein IV, *FC* free cholesterol, *Lp-PLA2* lipoprotein-associated phospholipase A2, *PL* phospholipids, *RBP4* retinol-binding protein 4, *SAA1* serum amyloid A protein, *TG* triglycerides, *TTR* transthyretin

LCAT gene expression [31–33]. LCAT has a major role in the maturation of HDL by esterification of free cholesterol on the surface of HDL and its sequestration in the core of the molecule. Esterification of free cholesterol plays a major role in maintaining a cholesterol gradient that facilitates cholesterol uptake and maturation of HDL (Fig. 1). Given the important role of LCAT in converting HDL3 to HDL2, LCAT deficiency favors the loss of apo-A1. This is due to the degradation of HDL3 in hepatic endocytic receptors as opposed to the selective uptake of cholesterol on HDL2 by SRB1 receptors, and the re-release of apo-A1 by the later receptors (Fig. 1). Also, HDL2 has an essential role in converting VLDL remnants also known as IDL into LDL. In this process, HDL2 exchanges with IDL part of its free cholesterol for triglycerides and is mediated by cholesterol ester transfer protein (CETP) and phospholipid transfer protein (PTLP). As opposed to IDL, LDL has a higher affinity to hepatic LDL receptors which leads to removal of LDL from the circulation and decreased atherogenicity (Fig. 1).

There is debate whether patients with ESRD have an abnormal level of CETP and PTLP. Most studies have failed to show any significant change in these levels [34–36]. However, studies on patients with nephrotic syndrome and nephrotic-range proteinuria showed elevated levels of CETP in these patients [37, 38]. This novel finding leads us to the assumption that patients on chronic peritoneal dialysis might have elevated plasma levels of CETP due to the heavy loss of plasma proteins in the peritoneal dialysis effluent. As mentioned earlier, this will lead to high levels of HDL-bound triglycerides and low levels of HDL-bound cholesterol resulting in the accumulation of dysfunctional HDL particles. This might explain in part how some of these patients can have high levels of HDL and still higher propensity to atherogenesis when compared with the normal population.

Studies conducted on rats with puromycin-induced nephrotic syndrome showed decreased levels of hepatic lipase (HL) and HL mRNA [39–41]. HL hydrolyzes triglycerides and plays an essential role in the clearance of triglyceride contents of HDL. For this reason, HL deficiency leads to triglycerides enrichment and dysfunction of HDL in patients with nephrotic-range proteinuria. Thus, patients with nephrotic syndrome have dysfunctional HDL molecules due to several potential mechanisms.

Paraxonase is an enzyme that hydrolyzes paraoxon. Although the exact role of plasma paraoxonase in lipoprotein metabolism is still to be identified, it is believed that paraoxon irreversibly inhibits LPL. In a study done by Nevin et al. [42], the LPL, HL, and arylesterase, which measure the paraoxonase mass, were independent predictors of HDL cholesterol; however, the paraoxonase genotype or activity was not. Lipoprotein-associated phospholipase-A_2 (Lp-PLA2) that has been recently associated with enhanced risk of stroke, coronary artery disease, and mortality was found to be significantly higher in the uremic HDL molecules [43].

Binding of HDL to SRB1 receptor on the surface of hepatocytes is the final step in the HDL-mediated reverse cholesterol transport as described above. These HDL receptors levels were studied in rats with puromycin-induced nephrotic-range proteinuria. This study showed reduction in SRB1 proteins despite normal mRNA levels reflecting no suppression of gene expression [44]. Studies conducted on rats with chronic kidney disease without heavy proteinuria failed to prove any significant change in SRB1 proteins levels [23]. This leads us to expect a similar reduction in SRB1 in patients on peritoneal dialysis but not on hemodialysis. The reduction in SRB1 proteins favors hepatic HDL total internalization and degradation by the mitochondrial beta chain subunit of ATP synthase on the hepatocytes plasma membrane. As explained earlier, this pathway of degradation will subsequently lead to decrease in the levels of apo-A1 and HDL (Fig. 1).

It has also been shown that apo-A1 and apo-A2 are displaced from the HDL molecule by highly abundant proteins like serum amyloid A protein (SAA1), albumin, apo-C3 and slightly abundant proteins like anti-trypsin, apo-A4, retinol-binding protein 4 (RBP4), transthyretin, and Lp-PLA2 were identified to be significantly enriched in uremic HDL (Fig. 2) [43]. This displacement leads to a decrease in HDL-mediated cholesterol efflux potential from peripheral cells, resulting in atherosclerosis.

HDL antioxidant and anti-inflammatory roles

In addition to its major role in the reverse cholesterol transport, HDL has different mechanisms in preventing atherosclerosis. HDL has antioxidant, anti-

inflammatory, and anti-thrombotic properties mediated by its constituent antioxidant enzymes like paraoxonase and glutathione peroxidase. Those enzymes help in preventing and reversing peroxidation of lipids and lipoproteins. LCAT and apo-A1 are other constituents that bind and remove oxidized phospholipids and endotoxins. In addition, HDL has anti-thrombotic effect through platelet activating factor acetylhydrolase which inhibits platelet activation, adhesion, and thrombus formation.

Several studies have shown that HDL has altered antioxidant and anti-inflammatory effects in chronic uremia, either by the reduction in its antioxidant enzymes or by impairment of their activity.

Systemic oxidative stress, which is highly prevalent in CKD patients, has been shown to decrease antioxidant and anti-inflammatory effects of HDL and even transform it into a pro-oxidant and pro-inflammatory agent, and subsequently a pro-atherogenic molecule [3, 45]. In one study, the ability of the subject's HDL to alter LDL-induced monocyte chemotactic activity (MCA) in human artery wall was significantly impaired in oxidative stress. HDL molecules are critical components of the acute phase reaction (APR). During an inflammatory reaction, they are enriched in free cholesterol, triglyceride, and free fatty acids and depleted in cholesterol ester. This will impair the protective effect of HDL against atherosclerosis, and their ability to remove cholesterol from macrophages [46–48].

Morena et al. showed that in patients with ESRD on hemodialysis, the LDL is more susceptible to oxidation and the HDL ability to prevent this oxidation is diminished [46]. These findings may explain in part the development of early atherosclerosis in ESRD patients. Plasma levels of paraoxonase, glutathione peroxidase, LCAT, PAF acetyl-hydrolase, and apo-A1 in patients with ESRD were compared to healthy controls [24]. There was 60 % reduction in LCAT, 50 % in glutathione peroxidase, 41 % in apo-A1, and 30 % in paraoxonase levels. This was accompanied by 127 % reduction in HDL antioxidant activity and its conversion into a pro-oxidant agent. These changes were supported by another study done by Kalantar-Zadeh et al. [49] who looked at the reduction in HDL anti-oxidant activity as a predictor of cardiovascular and overall mortality in 189 patients with CKD on dialysis at 30 months of follow-up. In this study, patients with low HDL anti-oxidant activity had a significant higher adjusted risk of death than those with high levels.

Oxidized phospholipids and lipoperoxides can initiate lipid peroxidation chain reaction and activate lectin-like oxidized LDL receptor and scavenger receptor class A1 leading to oxidative stress and inflammation [50–53]. HDL carries oxidized phospholipids and lipoperoxides for enzymatic processing and disposal in the liver to decrease oxidative stress and inflammation [54]. However, in systemic inflammation, there is a great increase in the amount of oxidized lipids. Conversely, in this state, the large HDL load of these agents transforms HDL into a pro-inflammatory factor [3, 55]. Also, apo-A1 oxidation diminishes its interaction with ABCA-1 and affects HDL-mediated cholesterol transport [25, 56].

Patients with uremia often have high triglycerides levels. Triglycerides enrichment makes LDL more susceptible to oxidation. Oxidized LDL is highly pro-inflammatory and abundant in patients with CKD, leading to a reduction in HDL anti-inflammatory and anti-oxidant potencies [5, 16, 18, 25].

Current advances and future perspective in treatments targeting HDL

It is well known that most patients with uremia die from cardiovascular disease before the initiation of hemodialysis [57]. While several studies have been done to guide the treatment of dyslipidemia in uremic patients, the results of some studies are still under investigation. In this section, we will discuss the results of some studies on the current lipid-lowering drugs and the new experimental drugs that might play an active role in treating dyslipidemia in the near future.

Statins

Several clinical trials assessed the efficacy of statins in reducing the risk of cardiovascular events in patients with CKD. The AURORA trial (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) was done on 2776 patients on maintenance hemodialysis. It showed a 43 % reduction in the LDL levels in patients taking 10 mg of rosuvastatin when compared with the placebo group at

3 months of follow-up. However, this reduction in LDL levels did not reflect any benefit on the primary end points of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular events (Table 1) [58]. Also, the 4D study targeting a higher risk of patients with diabetes on hemodialysis failed to show any benefit of atorvastatin in reducing cardiovascular events in this population (Table 1) [59]. It should be noted that patients with less advanced CKD may benefit from long-term treatment with statins in terms of preventing the progression of their kidneys disease, as shown by Ruan et al. [60]. In the Study of Heart and Renal Protection (SHARP), a total of 9,438 CKD patients including 3,056 on dialysis were randomized to ezetimibe 10 mg plus simvastatin 20 mg versus placebo versus simvastatin 20 mg daily. Compared with placebo, ezetimibe 10 mg plus simvastatin 20 mg daily yielded to a significant improvement in the LDL levels at median follow-up interval of 4.9 years. More importantly, there was 17 % proportional reduction in major atherosclerotic events in the simvastatin plus ezetimibe group when compared with placebo. There was no difference in the primary outcome between treatment groups for subgroups defined by baseline HDL cholesterol [61].

Niacin

Among the current drugs in the market, niacin has shown to be the most effective in raising the plasma levels of HDL [62]. The AIM-HIGH clinical trial (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes) was done on a group of patients with history of the cardiovascular disease, low HDL and high triglycerides who were all prescribed simvastatin and randomized to either high-dose niacin up to 2,000 mg per day or placebo. Surprisingly, this trial did not show any superior benefit of niacin in reducing the five-component end points of fatal or nonfatal MI, strokes, hospitalizations for acute coronary syndrome, or the need for revascularization. Of note, all these patients had a very well-controlled LDL level of <70 mg/dl. The authors concluded that in this specific group of well-controlled LDL, there is probably no room to improve outcome by improving the HDL levels. A sub-study, in the AIM-HIGH trial, is still investigating whether certain patients with very low HDL levels or LDL levels above the median would had an additional benefit from this combination [63]. It will be interesting to study patients with CKD and well-controlled LDL, looking if niacin therapy has additional benefit on decreasing cardiovascular events, as this population often have very low levels of HDL, in addition to its impaired metabolism. Due to its potent antioxidant and anti-inflammatory effects, niacin slowed the progression of renal disease in a study done on nephrectomized rats where those not treated with niacin exhibited more proteinuria, glomerulosclerosis, tubulointerstitial damage, and hypertension [64, 65].

PPARα agonists

PPARα agonists increase the plasma levels of HDL, decrease the levels of triglycerides, and to a lesser extent that of LDL [66]. A double-blind trial done on the PPARα agonist gemfibrozil in patients with mild to moderate chronic kidney disease showed a 24 percent reduction in the combined outcome of death from coronary heart disease, nonfatal myocardial infarction, and stroke ($P < 0.001$); these findings were accompanied by 6 percent increase in the HDL levels and a non-significant decrease in LDL levels (Table 1) [67]. Another study was done looking at the effect of gemfibrozil on slowing the progression of renal disease in patients with chronic kidney disease, low HDL levels, and coronary artery disease. This study did not show any relevant efficacy of this drug on slowing the renal function loss [68]. However, some patients experienced worsening in the creatinine levels which could be due to myotoxicity. Of note, the safety of these drugs in patients with severe renal disease remains unclear.

Apo-A1 and Apo-A1 mimetics

As discussed previously, apo-A1 is the cornerstone in the reverse cholesterol transport process, as well as in maintaining functional HDL. Studies on apo-A1 started with the intravenous administration of recombinant apo-A1 in humans and showed decreased rates of atherosclerosis and arterial restenosis [69]. Another study done on mice, maintained on high lipid diet for 6 weeks, showed more than 50 percent reduction in atherosclerosis in those treated with helper-dependent adenoviruses containing human apo-A1 gene when compared with mice injected with normal saline [70].

Table 1 This table summarizes the major trials on statins as well as other anti-lipids in patients with chronic kidney disease

Study	Design	Population and treatment	Outcomes
Statin trials			
AURORA; Fellstrom et al. [58]	Multicenter, randomized, double blind, placebo controlled	2,773 on MHD >3 months; 1,389 patients treated with rosuvastatin versus 1,384 with placebo; 3.8-year-median follow-up	Non-significant difference in mortality, primary (events per 100 patient years), and secondary endpoints
4D; Wanner et al. [59]	Multicenter, randomized, double blind, prospective	1,255 patients with type II DM, on MHD <2 years; 619 patients treated with atorvastatin versus 636 patients with placebo; 4-year-median follow-up	Non-significant difference in composite primary endpoint. Significantly higher risk of fatal stroke in the treatment group
SHARP; Baigent et al. [61]	Randomized, double blind	9,270 patients with CKD (3,023 on MHD); treatment regimen of simvastatin plus ezetimibe versus placebo; 4.9-year-median follow-up	17 % reduction in major atherosclerotic events (rate ratio 0.83, 95 % CI 0.74–0.94, log-rank test $P = 0.002$) in the treatment arm
Non-statin trials			
Post hoc analysis of VA-HIT; Tonelli et al. [67, 68]	Randomized, double blind, multicenter	1,046 patients had CrCl <75 and established CHD. Treatment with Gemfibrozil. 5-year-median follow-up	The incidence of coronary death or non-fatal myocardial infarction was lower in participants with CKD who received gemfibrozil compared to placebo (HR 0.73; 95 % CI 0.56–0.96, $P = 0.02$). The risk of sustained increases in serum creatinine was increased in gemfibrozil recipients compared with placebo (5.9 vs. 2.8 %, $P = 0.02$)
OPACH; Svensson et al. [94]	Randomized, double-blind placebo controlled	206 patients with CHD and on MHD. 2-year-median follow-up. Treatment with n-3 PUFA	No significant effect on the primary composite end point of cardiovascular events and death. A significant reduction was seen in the number of myocardial infarctions (four vs. 13; $P = 0.036$)

MHD maintenance hemodialysis, *DM* diabetes mellitus, *CKD* chronic kidney disease, *CrCl* creatinine clearance, *CHD* coronary heart disease, *HR* hazard ratio, *n-3 PUFA* omega-3 polyunsaturated fatty acids

A similar study assessed the effect of intravenous recombinant apo-A1 Milano/phospholipid complexes on atheroma burden in patients with acute coronary syndromes. Although it showed a decrease in atheroma area in some cases, this was not statically significant [71]. These studies were all limited by the high cost of the treatment and small sample size, which limited the widespread use of apo-A1.

Currently, researches are investigating the benefit of several synthesized short apo-A1 mimetic peptides, instead of the human apo-A1 protein which consists of 243 amino acids. Several studies were conducted on the bioavailability and the route of administration of those peptides. The apo-A1 mimetic peptide D-4F, which is orally administrated, was tested in the mice and monkey models and showed decreased atherosclerosis and improved HDL antioxidant and anti-inflammatory functions [72–76]. Also treatment with apo-A1 D-4F showed a reduction in the vessel wall thickness and improvement in the endothelial vasodilation function [77, 78].

CETP inhibitors

CETP transfers CE from HDL to TG-rich particles (TRL) resulting in CE-rich VLDLs, which are a substrate for the formation of atherogenic small dense LDL (sdLDL) [79–81]. Thus, by inhibiting CETP, HDL levels are increased; VLDLs and sdLDL levels are decreased which should hypothetically lower the risk of atherosclerosis and cardiovascular disease [82]. Torcetrapib, a new CETP inhibitor, was the subject of a large double-blind randomized study done on 15, 067 patients at high risk for coronary events. It

compared the cardiovascular outcomes in patients taking atorvastatin alone versus torcetrapib and atorvastatin [83]. This study was stopped early because of the increased risk of cardiovascular events and all-cause mortality in the torcetrapib group, despite a dramatic increase in HDL levels (72 percent). In addition, these patients had an increase in 5.4 mmHg in the arterial blood pressure compared to the atorvastatin single therapy group. Many theories where elaborated to explain these unexpected results. It is possibly that the increased size of HDL affects its recycling and attenuates its capacity to remove cholesterol from the arterial wall [84, 85]. Evacetrapib, a newer CETP inhibitor, was studied in a randomized clinical trial conducted among 398 patients with elevated LDL or low HDL. Compared with placebo evacetrapib as monotherapy increased HDLlevels up to 128 % and decreased LDL levels by 13.6 to 35.9 %. Compared with evacetrapib monotherapy, the combination of statins and evacetrapib resulted in greater reductions in LDL ($P < 0.001$) but no greater increase in HDL [86]. Anacetrapib, another new CETP inhibitor, showed a 39.8 % reduction in LDL level, and 138.1 % increase in HDL levels during the phase III DEFINE trial without the 25 % increase in cardiovascular events seen with torcetrapib [87]. Anacetrapib and evacetrapib are still being studied for cardiovascular outcomes in ongoing clinical trials. Dalcetrapib enters the list of the disappointing CETP inihibitors with torceptrapib. In dal-OUTCOMES, patients with a recent acute coronary syndrome were followed for a median of 31 months, dalcetrapib raised HDL levels by 30 %, had little effect on LDL, but did not reduce the risk of recurrent cardiovascular events [88].

ACAT inhibitors

ACAT enzymes help in the storage of cholesterol in the liver, intestines, and arterial macrophages. These enzymes have different roles in the regulation of cholesterol synthesis; they catalyze the intracellular esterification of free cholesterol to cholesterol ester to be incorporated in VLDL and chylomicrons. When the intracellular concentration of free cholesterol is decreased, the activity of SREBP (sterol regulatory element-binding proteins) which is responsible of the upregulation of free cholesterol biosynthesis is enhanced. This will provide ACAT with more substrates for esterification and facilitates foam cell formation especially in the macrophages. This process leads to an increase in atherosclerosis, dyslipidemia, and glomerulosclerosis, due to the attenuation of RCT that depends on the shift of intracellular free cholesterol to the cell membrane in its way to be incorporated into HDL.

Although the wide use of statins decreased the rate of cardiovascular events, further studies on other treatment modalities are still needed to further decrease these events. A new treatment strategy acting on the inhibition of the ACAT enzyme was the subject of the A-PLUS trial (Avasimibe and Progression of Lesions on UltraSound) [89]. This study involved patients with chronic stable angina, unstable angina, post-myocardial infarction, or post-percutaneous coronary intervention with at least one 20–50 % diameter stenosis on angiography in 1 "target" coronary artery defined as more than 2.5 mm in diameter. Serial intravascular ultrasounds (IVUS) were done at baseline to assess the mean plaque atheroma volume and at 18 months of follow-up to assess the regression of atherosclerosis in patients taking either the ACAT inhibitor avasimibe or placebo. Results of the study showed that avasimibe did not favorably alter coronary atherosclerosis, but increased the atherosclerotic burden with 6 more cases of death in the group treated with avasamibe [89]. Despite the increase in HDL levels, ACAT inhibitors will affect the stability of the cell membrane maintained by its content of free cholesterol. Thus, the unfavorable result can also be explained by the fact that ACAT inhibition lead to an increase of intracellular levels of free cholesterol facilitating cell membrane rupture and the release of macrophages intracellular metalloproteinases enzymes which will trigger plaque rupture and thrombosis.

Conclusion

Cardiovascular morbidity and mortality is enormous in patients with CKD. In point of fact, the majority of patients with CKD die of cardiovascular events prior to initiation or renal replacement therapy [90]. And in those patients who do end up requiring maintenance hemodialysis, the mortality is a staggering 10–30 times higher than the general population [91].

The culprits behind early atherosclerosis are multifactorial, and some are exclusively related to this population. Inflammation, oxidative stress, impaired cholesterol and chylomicron metabolism, and HDL dysfunction and deficiency all play an incriminating role in this destructive saga.

In this review, we have outlined the key mechanisms of HDL dysfunction in the setting of CKD and ESRD. CKD-induced reduction in the hepatic production and plasma concentration of apolipoprotein A1 and the resulting decrease in HDL; LCAT deficiency (due to CKD-mediated downregulation by the liver), which hinders the uptake and maturation of HDL; downregulation of the SR-B1 (HDL docking receptor in the liver) and upregulation of the HDL endocytic receptor (mitochondrial ATP synthase subunit β) impairing reverse cholesterol transport and decrease HDL levels, and finally, a limited HDL antioxidant properties along with significant reductions in the key anti-oxidative enzymes such as glutathione peroxidase and paraoxonase leading to an increase in LDL and lipoprotein remnants oxidative damage and subsequently increased adhesion and infiltration of monocytes into arterial walls.

Effective anti-hyperlipidemic therapy for patients with CKD and ESRD, simply put, is still not well established. More research is still needed to specifically investigate potential therapy in this specific population which has a significantly higher risk of CAD. So far, the trials investigating statin usage have not yielded a significant effect on cardiovascular or all-cause mortality [92]. However, when combined with ezetimibe statins might have a protective role in CKD patients as shown in the sharp trial. The benefit of PPARα agonists is still controversial; moreover, the long-term safety and efficacy in patients with advanced kidney disease remains a concerning point. Another potential agent, niacin, did not show an additional benefit in patients with well-controlled LDL levels; in addition, poor tolerability poses a big compliance issue. Further investigations utilizing newer agents such as the apo-A1 mimetic showed promising results in animal studies. However, clinical trials are still needed before a real solution can be offered to combat this challenging global health-care dilemma. Although CETP and ACAT inhibitors significantly improved HDL levels, the results were disappointing in the major clinical trials with an increase in cardiovascular events. Until we find the effective therapy, our efforts should be focused on addressing other risk factors such as hypertension, abnormal calcium and phosphate handling, diabetes, use of ultra-pure dialysates, biocompatible dialyzers, and arteriovenous (A-V) fistulas instead of catheters or A-V grafts [92, 93].

Acknowledgments We would like to thank Mr. Shapnil Islam for his great help in graphic design.

Conflict of interest None of the other authors, including myself, have any conflicts of interest to disclose.

References

1. Schoolwerth AC et al (2006) Chronic kidney disease: a public health problem that needs a public health action plan. Prev Chronic Dis 3(2):A57
2. Coresh J et al (2003) Prevalence of chronic kidney disease and decreased kidney function in the adult US population: third National Health and Nutrition Examination Survey. Am J Kidney Dis 41(1):1–12
3. Ansell BJ et al (2003) Inflammatory/antiinflammatory properties of high-density lipoprotein distinguish patients from control subjects better than high-density lipoprotein cholesterol levels and are favorably affected by simvastatin treatment. Circulation 108(22):2751–2756
4. Feroze U et al (2012) Examining associations of circulating endotoxin with nutritional status, inflammation, and mortality in hemodialysis patients. J Ren Nutr 22(3):317–326
5. McCullough PA (2003) Why is chronic kidney disease the "spoiler" for cardiovascular outcomes? J Am Coll Cardiol 41(5):725–728
6. Himmelfarb J et al (2002) The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. Kidney Int 62(5):1524–1538
7. Hansson GK, Robertson AK, Soderberg-Naucler C (2006) Inflammation and atherosclerosis. Annu Rev Pathol 1:297–329
8. Bobryshev YV (2006) Monocyte recruitment and foam cell formation in atherosclerosis. Micron 37(3):208–222
9. Shashkin P, Dragulev B, Ley K (2005) Macrophage differentiation to foam cells. Curr Pharm Des 11(23):3061–3072
10. Brunini TM et al (2007) Nitric oxide, malnutrition and chronic renal failure. Cardiovasc Hematol Agents Med Chem 5(2):155–161
11. Khoueiry G et al (2011) Dietary intake in hemodialysis patients does not reflect a heart healthy diet. J Ren Nutr 21(6):438–447
12. Varma R et al (2005) Chronic renal dysfunction as an independent risk factor for the development of cardiovascular disease. Cardiol Rev 13(2):98–107
13. Devlin TM Textbook of biochemistry with clinical correlations, 7th edn. Wiley, pp 722–726
14. Vaziri ND, Navab M, Fogelman AM (2010) HDL metabolism and activity in chronic kidney disease. Nat Rev Nephrol 6(5):287–296

15. Collins AJ et al (2005) Excerpts from the United States Renal Data System 2004 annual data report: atlas of end-stage renal disease in the United States. Am J Kidney Dis 45(1 Suppl 1):5–7 (S1–S280)
16. Stenvinkel P, Alvestrand A (2002) Inflammation in end-stage renal disease: sources, consequences, and therapy. Semin Dial 15(5):329–337
17. Vaziri ND (2001) Effect of chronic renal failure on nitric oxide metabolism. Am J Kidney Dis 38(4 Suppl 1):S74–S79
18. Vaziri ND (2004) Oxidative stress in uremia: nature, mechanisms, and potential consequences. Semin Nephrol 24(5):469–473
19. Vaziri ND et al (1998) Downregulation of nitric oxide synthase in chronic renal insufficiency: role of excess PTH. Am J Physiol 274(4 Pt 2):F642–F649
20. Vaziri ND (2006) Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences. Am J Physiol Renal Physiol 290(2):F262–F272
21. Vaziri ND, Moradi H (2006) Mechanisms of dyslipidemia of chronic renal failure. Hemodial Int 10(1):1–7
22. Attman PO, Samuelsson O, Alaupovic P (1993) Lipoprotein metabolism and renal failure. Am J Kidney Dis 21(6): 573–592
23. Vaziri ND, Deng G, Liang K (1999) Hepatic HDL receptor, SR-B1 and Apo A-I expression in chronic renal failure. Nephrol Dial Transpl 14(6):1462–1466
24. Moradi H et al (2009) Impaired antioxidant activity of high-density lipoprotein in chronic kidney disease. Transpl Res 153(2):77–85
25. Shao B et al (2006) Myeloperoxidase: an inflammatory enzyme for generating dysfunctional high-density lipoprotein. Curr Opin Cardiol 21(4):322–328
26. Fielding CJ, Fielding PE (2001) Cellular cholesterol efflux. Biochim Biophys Acta 1533(3):175–189
27. Lawn RM et al (1999) The Tangier disease gene product ABC1 controls the cellular apolipoprotein-mediated lipid removal pathway. J Clin Invest 104(8):R25–R31
28. Oram JF (2000) Tangier disease and ABCA1. Biochim Biophys Acta 1529(1–3):321–330
29. Zhao Y, Marcel YL (1996) Serum albumin is a significant intermediate in cholesterol transfer between cells and lipoproteins. Biochemistry 35(22):7174–7180
30. Shoji T et al (1992) Impaired metabolism of high density lipoprotein in uremic patients. Kidney Int 41(6):1653–1661
31. Vaziri ND, Liang K, Parks JS (2001) Down-regulation of hepatic lecithin:cholesterol acyltransferase gene expression in chronic renal failure. Kidney Int 59(6):2192–2196
32. Vaziri ND, Sato T, Liang K (2003) Molecular mechanisms of altered cholesterol metabolism in rats with spontaneous focal glomerulosclerosis. Kidney Int 63(5):1756–1763
33. Liang K, Kim CH, Vaziri ND (2005) HMG-CoA reductase inhibition reverses LCAT and LDL receptor deficiencies and improves HDL in rats with chronic renal failure. Am J Physiol Renal Physiol 288(3):F539–F544
34. Kimura H et al (2001) Cholesteryl ester transfer protein as a protective factor against vascular disease in hemodialysis patients. Am J Kidney Dis 38(1):70–76
35. Kimura H et al (2003) Hepatic lipase mutation may reduce vascular disease prevalence in hemodialysis patients with high CETP levels. Kidney Int 64(5):1829–1837
36. Pahl MV et al (2009) Plasma phospholipid transfer protein, cholesteryl ester transfer protein and lecithin:cholesterol acyltransferase in end-stage renal disease (ESRD). Nephrol Dial Transplant 24(8):2541–2546
37. de Sain-van der Velden MG et al (1998) Plasma alpha 2 macroglobulin is increased in nephrotic patients as a result of increased synthesis alone. Kidney Int 54(2):530–535
38. Vaziri ND (2003) Molecular mechanisms of lipid disorders in nephrotic syndrome. Kidney Int 63(5):1964–1976
39. Klin M et al (1996) Abnormalities in hepatic lipase in chronic renal failure: role of excess parathyroid hormone. J Clin Invest 97(10):2167–2173
40. Liang K, Vaziri ND (1997) Down-regulation of hepatic lipase expression in experimental nephrotic syndrome. Kidney Int 51(6):1933–1937
41. Sato T, Liang K, Vaziri ND (2003) Protein restriction and AST-120 improve lipoprotein lipase and VLDL receptor in focal glomerulosclerosis. Kidney Int 64(5):1780–1786
42. Nevin DN et al (1996) Paraoxonase genotypes, lipoprotein lipase activity, and HDL. Arterioscler Thromb Vasc Biol 16(10):1243–1249
43. Holzer M et al (2011) Uremia alters HDL composition and function. J Am Soc Nephrol 22(9):1631–1641
44. Liang K, Vaziri ND (1999) Down-regulation of hepatic high-density lipoprotein receptor, SR-B1, in nephrotic syndrome. Kidney Int 56(2):621–626
45. Van Lenten BJ et al (2006) Understanding changes in high density lipoproteins during the acute phase response. Arterioscler Thromb Vasc Biol 26(8):1687–1688
46. Cabana VG et al (1996) HDL content and composition in acute phase response in three species: triglyceride enrichment of HDL a factor in its decrease. J Lipid Res 37(12): 2662–2674
47. Van Lenten BJ et al (1995) Anti-inflammatory HDL becomes pro-inflammatory during the acute phase response. Loss of protective effect of HDL against LDL oxidation in aortic wall cell cocultures. J Clin Invest 96(6):2758–2767
48. Artl A et al (2000) Role of serum amyloid A during metabolism of acute-phase HDL by macrophages. Arterioscler Thromb Vasc Biol 20(3):763–772
49. Kalantar-Zadeh K et al (2007) HDL-inflammatory index correlates with poor outcome in hemodialysis patients. Kidney Int 72(9):1149–1156
50. Deigner HP, Hermetter A (2008) Oxidized phospholipids: emerging lipid mediators in pathophysiology. Curr Opin Lipidol 19(3):289–294
51. Mehta JL et al (2006) Lectin-like, oxidized low-density lipoprotein receptor-1 (LOX-1): a critical player in the development of atherosclerosis and related disorders. Cardiovasc Res 69(1):36–45
52. Cominacini L et al (2000) Oxidized low density lipoprotein (ox-LDL) binding to ox-LDL receptor-1 in endothelial cells induces the activation of NF-kappaB through an increased production of intracellular reactive oxygen species. J Biol Chem 275(17):12633–12638
53. Cominacini L et al (2001) The binding of oxidized low density lipoprotein (ox-LDL) to ox-LDL receptor-1 reduces the intracellular concentration of nitric oxide in endothelial cells through an increased production of superoxide. J Biol Chem 276(17):13750–13755

54. Bowry VW, Stanley KK, Stocker R (1992) High density lipoprotein is the major carrier of lipid hydroperoxides in human blood plasma from fasting donors. Proc Natl Acad Sci USA 89(21):10316–10320
55. Ansell BJ, Fonarow GC, Fogelman AM (2007) The paradox of dysfunctional high-density lipoprotein. Curr Opin Lipidol 18(4):427–434
56. Navab M et al (2006) Mechanisms of disease: proatherogenic HDL–an evolving field. Nat Clin Pract Endocrinol Metab 2(9):504–511
57. Harper CR, Jacobson TA (2008) Managing dyslipidemia in chronic kidney disease. J Am Coll Cardiol 51(25):2375–2384
58. Fellstrom BC et al (2009) Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 360(14):1395–1407
59. Wanner C et al (2005) Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 353(3):238–248
60. Ruan XZ, Varghese Z, Moorhead JF (2009) An update on the lipid nephrotoxicity hypothesis. Nat Rev Nephrol 5(12):713–721
61. Baigent C et al (2011) The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 377(9784):2181–2192
62. Carlson LA (2005) Nicotinic acid: the broad-spectrum lipid drug. A 50th anniversary review. J Intern Med 258(2): 94–114
63. Nainggolan L, Bethesda M (2011) NIH pulls plug on AIM-HIGH trial with niacin (niacin + statin) theheart.org. http://www.theheart.org/article/1231453.do
64. Cho KH et al (2009) Niacin ameliorates oxidative stress, inflammation, proteinuria, and hypertension in rats with chronic renal failure. Am J Physiol Renal Physiol 297(1): F106–F113
65. Cho KH et al (2010) Niacin improves renal lipid metabolism and slows progression in chronic kidney disease. Biochim Biophys Acta 1800(1):6–15
66. Duval C, Muller M, Kersten S (2007) PPARalpha and dyslipidemia. Biochim Biophys Acta 1771(8):961–971
67. Tonelli M et al (2004) Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. Kidney Int 66(3):1123–1130
68. Tonelli M et al (2004) Effect of gemfibrozil on change in renal function in men with moderate chronic renal insufficiency and coronary disease. Am J Kidney Dis 44(5): 832–839
69. Calabresi L et al (2006) Recombinant apolipoprotein A-IMilano for the treatment of cardiovascular diseases. Curr Atheroscler Rep 8(2):163–167
70. Belalcazar LM et al (2003) Long-term stable expression of human apolipoprotein A-I mediated by helper-dependent adenovirus gene transfer inhibits atherosclerosis progression and remodels atherosclerotic plaques in a mouse model of familial hypercholesterolemia. Circulation 107(21):2726–2732
71. Nissen SE et al (2003) Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA 290(17):2292–2300
72. Vaziri ND et al (2009) In vitro stimulation of HDL anti-inflammatory activity and inhibition of LDL pro-inflammatory activity in the plasma of patients with end-stage renal disease by an apoA-1 mimetic peptide. Kidney Int 76(4):437–444
73. Navab M et al (2010) Structure and function of HDL mimetics. Arterioscler Thromb Vasc Biol 30(2):164–168
74. Navab M et al (2005) D-4F and statins synergize to render HDL antiinflammatory in mice and monkeys and cause lesion regression in old apolipoprotein E-null mice. Arterioscler Thromb Vasc Biol 25(7):1426–1432
75. Navab M et al (2004) Oral D-4F causes formation of pre-beta high-density lipoprotein and improves high-density lipoprotein-mediated cholesterol efflux and reverse cholesterol transport from macrophages in apolipoprotein E-null mice. Circulation 109(25):3215–3220
76. Li X et al (2004) Differential effects of apolipoprotein A-I-mimetic peptide on evolving and established atherosclerosis in apolipoprotein E-null mice. Circulation 110(12):1701–1705
77. Ou J et al (2005) Effects of D-4F on vasodilation and vessel wall thickness in hypercholesterolemic LDL receptor-null and LDL receptor/apolipoprotein A-I double-knockout mice on Western diet. Circ Res 97(11):1190–1197
78. Navab M et al (2006) Apolipoprotein A-I mimetic peptides and their role in atherosclerosis prevention. Nat Clin Pract Cardiovasc Med 3(10):540–547
79. Barter PJ et al (2003) Cholesteryl ester transfer protein: a novel target for raising HDL and inhibiting atherosclerosis. Arterioscler Thromb Vasc Biol 23(2):160–167
80. Boekholdt SM, Thompson JF (2003) Natural genetic variation as a tool in understanding the role of CETP in lipid levels and disease. J Lipid Res 44(6):1080–1093
81. Le Goff W, Guerin M, Chapman MJ (2004) Pharmacological modulation of cholesteryl ester transfer protein, a new therapeutic target in atherogenic dyslipidemia. Pharmacol Ther 101(1):17–38
82. van der Steeg WA et al (2004) Role of CETP inhibitors in the treatment of dyslipidemia. Curr Opin Lipidol 15(6): 631–636
83. Barter PJ et al (2007) Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 357(21): 2109–2122
84. Ishigami M, Yamashita S, Sakai N, Arai T, Hirano K, Hiraoka H, Kameda-Takemura K, Matsuzawa Y (1994) Large and cholesteryl ester-rich high-density lipoproteins in cholesteryl ester transfer protein (CETP) deficiency cannot protect macrophages from cholesterol accumulation induced by acetylated low-density lipoproteins. J Biochem (Tokyo) 116:257–262
85. Barter PJ (2002) Hugh sinclair lecture: the regulation and remodelling of HDL by plasma factors. Atheroscler Suppl 3(4):39–47
86. Nicholls SJ et al (2011) Effects of the CETP inhibitor evacetrapib administered as monotherapy or in combination with statins on HDL and LDL cholesterol: a randomized controlled trial. JAMA 306(19):2099–2109
87. Gotto AM Jr, Moon JE (2012) Safety of inhibition of cholesteryl ester transfer protein with anacetrapib: the DEFINE study. Expert Rev Cardiovasc Ther 10(8): 955–963

88. Schwartz GG et al (2012) Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med 367(22):2089–2099
89. Tardif JC et al (2004) Effects of the acyl coenzyme A: cholesterol acyltransferase inhibitor avasimibe on human atherosclerotic lesions. Circulation 110(21):3372–3377
90. Keith DS et al (2004) Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 164(6):659–663
91. Foley RN, Parfrey PS, Sarnak MJ (1998) Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 32(5 Suppl 3):S112–S119
92. Epstein M, Vaziri ND (2012) Statins in the management of dyslipidemia associated with chronic kidney disease. Nat Rev Nephrol 8(4):214–223
93. Vaziri ND (2009) Causes of dysregulation of lipid metabolism in chronic renal failure. Semin Dial 22(6):644–651
94. Svensson M et al (2006) N-3 fatty acids as secondary prevention against cardiovascular events in patients who undergo chronic hemodialysis: a randomized, placebo-controlled intervention trial. Clin J Am Soc Nephrol 1(4):780–786