High-Density Lipoprotein: Structural and Functional Changes Under Uremic Conditions and the Therapeutic Consequences

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Abstract

High-density lipoprotein (HDL) has attracted interest as a therapeutic target in cardiovascular diseases in recent years. Although many functional mechanisms of the vascular protective effects of HDL have been identified, increasing the HDL plasma level has not been successful in all patient cohorts with increased cardiovascular risk. The composition of the HDL particle is very complex and
includes diverse lipids and proteins that can be modified in disease conditions. In patients with chronic kidney disease (CKD), the accumulation of uremic toxins, high oxidative stress, and chronic micro-inflammatory conditions contribute to changes in the HDL composition and may also account for protein/lipid modifications. These conditions are associated with a decreased protective function of HDL. Therefore, the HDL quantity and the functional quality of the particle must be considered.

This review summarizes the current knowledge of dyslipidemia in CKD patients, the effects of lipid-modulating therapy, and the structural modifications of HDL that are associated with dysfunction.

**Keywords**

Chronic kidney disease • Dyslipidemia • High-density lipoprotein • Uremia • Uremic toxin

**Abbreviations**

- ABCA1: ATP-binding cassette subfamily A
- ADMA: Asymmetric dimethylarginine
- AGE: Advanced glycated end product
- AIM-HIGH: Atherothrombosis intervention in metabolic syndrome with low HDL/high triglycerides: impact on global health outcomes
- ALERT: Assessment of LEscol in Renal Transplantation
- apo: Apolipoprotein
- AURORA: A study to evaluate the use of rosvastatin in subjects on regular hemodialysis: an assessment of survival and cardiovascular events
- CETP: Cholesterol ester transfer protein
- CKD: Chronic kidney disease
- cLDL: Carbamylated low-density lipoprotein
- 4D: Deutsche Diabetes Dialyse Studie
- DEFINE: Determining the Efficacy and Tolerability of CETP inhibition with Anacetrapib
- DMA: Dimethylarginine
- eGFR: Estimated glomerular filtration rate
- EPIC: European Prospective Investigation into Cancer and Nutrition
- ESRD: end-stage renal disease
- GFR: Glomerular filtration rate
- HD: Hemodialysis
- HDL: High-density lipoprotein
- HDL-C: High-density lipoprotein cholesterol
- HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A
- HPS2-THRIVE: Treatment of HDL to Reduce the Incidence of Vascular Events
- IDL: Intermediate-density lipoprotein
1 Introduction

Plasma lipoproteins are composed of non-covalent aggregates of different lipids and proteins. They transport water-insoluble substances in the blood by building micelle-like structures. These structures are classified by their density into the...
following groups: very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL).

In previous years, several clinical studies have found that HDL cholesterol (HDL-C) plasma levels were inversely correlated with cardiovascular risk, whereas high LDL-C levels were related to increased cardiovascular mortality (Di Angelantonio et al. 2009; Gordon et al. 1977; Mori et al. 1999). Initially, due to the crucial role of HDL in reverse cholesterol transport (RCT), HDL was associated with a decreased cardiovascular risk. Therefore, the theory of the “good HDL” and “bad LDL” emerged. Further studies, primarily in vitro or animal studies, identified the pleiotropic cardiovascular protective effects of HDL in addition to its RCT function: HDL has anti-atherosclerotic, anti-inflammatory, antioxidative, antithrombotic, and endothelial-protective properties (Navab et al. 2011). Accordingly, there is growing interest in the study of HDL metabolism and the cellular and the molecular signaling pathways involved in its vascular protective effects.

Therefore, enhancing HDL plasma levels has been a principal approach for the reduction of cardiovascular risks in different patient cohorts. Pharmacologically active substances, such as cholesterol ester transfer protein (CETP) inhibitors, fibrates, and niacin, have been tested in large clinical trials to evaluate the occurrence of cardiovascular endpoints (Longenecker et al. 2005; van Capelleveen et al. 2014). However, raising HDL-C plasma levels did not protect against cardiovascular events in all patient cohorts tested. In addition, despite a significant HDL-C increase in patients, large clinical trials were terminated because of a lack of positive effects or, in some cases, an increase in the rate of cardiovascular events.

These findings indicate that a better understanding of lipoprotein modifications in disease conditions is necessary to establish possible indications and target mechanisms in the therapy of cardiovascular diseases. Patients with chronic kidney disease (CKD) suffer from a dramatic increase in cardiovascular morbidity and mortality. The disease condition is associated with dyslipidemia and/or modifications in lipoprotein composition and function (Keane et al. 2013; Vaziri 2006).

This review summarizes current knowledge regarding the structural and functional changes of HDL in the context of renal dysfunction. A brief overview of CKD epidemiology and pathophysiology is presented, followed by aspects of dyslipidemia and its therapy in CKD patients. Subsequently, CKD-dependent structural and functional changes of HDL are summarized.

2 Chronic Kidney Disease: Epidemiology and Pathophysiology

Kidney disease is defined as an abnormality of kidney structure or function. The criteria for abnormalities include: albuminuria, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by
Kidney disease can occur abruptly, and it can either resolve or become chronic. CKD is defined as kidney damage that persists for more than 3 months (Levey et al. 2005). CKD is one of the major medical concerns associated with premature morbidity and mortality, especially due to cardiovascular complications. The epidemic of CKD is globally driven by demographic aging, as well as an increase in other risk factors leading to CKD (e.g., diabetes mellitus, hypertension, and obesity).

CKD is divided into different stages, which are summarized in Fig. 1, based on the glomerular filtration rate (GFR) (Levey et al. 2005). CKD patients have a high occurrence of cardiovascular disease. In recent years, several studies have implicated an inverse correlation of kidney function and cardiovascular mortality (Tonelli et al. 2006). Thereby, the cardiovascular phenotype of the CKD population is heterogeneous, and the cardiovascular risk depends on the CKD stage. In addition to traditional risk factors, such as hypertension, diabetes mellitus, and smoking, nontraditional risk factors also contribute to cardiovascular diseases. In CKD patients, the nontraditional risk factors of anemia and enhanced oxidative stress or uremic toxins play a major role in cardiovascular disease progression (Mizobuchi et al. 2009). Under normal conditions, uremic toxins are cleared by the kidneys, and many of these toxins have been recently identified (Duranton et al. 2012). Uremic toxins are classified as water-soluble molecules with low molecular weight (e.g., uric acid), middle molecules (e.g., parathyroid hormone), and protein-bound toxins (e.g., hippuric acid) (Duranton et al. 2012). A number of different uremic toxins are elusive, and biological functions have not been identified for all toxins. Clinical studies have shown that cardiovascular morbidity and mortality in CKD patients are associated with uremic toxin accumulation, which leads to a progression of vascular alterations. Recently, Moradi et al. summarized the influence of uremic toxins on vascular cells and pathological pathways in the vascular wall (Moradi et al. 2013). The activation of leukocytes;
endothelial damage, for example, by the disruption of glycocalyx and production of reactive oxygen species (ROS); the proliferating effects on smooth muscle cells; and platelet activation are only some of the described effects (Moradi et al. 2013). In addition, uremic toxins influence lipoprotein modifications. Urea induces the formation of carbamylated LDL (cLDL) (Apostolov et al. 2010). Some uremic toxins are lipid-bound and may occur in a different subfraction of lipoproteins. Additionally, HDL function may be affected by the accumulation of uremic toxins.

Nonetheless, further studies are necessary to characterize the impact of different compounds on cardiovascular outcome and the precise signaling pathways involved. The therapeutic goal should be to remove the solutes associated with the highest cardiovascular risk to minimize fatal cardiovascular outcomes in patients with CKD. To date, cardiovascular morbidity in patients with CKD remains high despite the utility of dialysis and renal transplantation (Foley et al. 1998).

3 Dyslipidemia, Lipid-Modulating Therapy, and Cardiovascular Risk in CKD Patients

In the general population, plasma lipid levels correlate with the level of cardiovascular risk (Di Angelantonio et al. 2009). Increased LDL-C levels have been associated with cardiovascular mortality. LDL-C is a primary risk biomarker for cardiovascular disease in the general population; however, it loses its prognostic association in CKD patients (Kilpatrick et al. 2007), especially for patients with end-stage renal disease (ESRD) (Baigent et al. 2011; Kovesdy et al. 2007). In addition, traditional risk factors, such as hypercholesterolemia, hypertension, and obesity, no longer appear to be related to the level of cardiovascular risk in ESRD patients. One explanation might be the accumulation of nontraditional risk factors in CKD patients (Appel 2004; Coresh et al. 1998; Muntner et al. 2004). Presumably, the complexity of traditional and nontraditional risk factors determines patient outcome. An alternative explanation may be that patient outcome is determined by the numerous quantitative and qualitative lipid abnormalities in triglycerides, phospholipids, and lipoproteins that are observed in CKD patient cohorts (Keane et al. 2013; Vaziri 2006).

3.1 Dyslipidemia in CKD Patients

Several studies have demonstrated a characteristic switch in the lipid phenotype at different stages of CKD. Data from the “Multi-Ethnic Study of Atherosclerosis” (MESA) have indicated an elevation of triglyceride-rich lipoproteins (Lamprea-Montealegre et al. 2013). Triglyceride-rich VLDL or other apoB-rich lipoproteins accumulate in patients with ESRD as a consequence of increased triglyceride levels (Vaziri and Norris 2011). The VLDL particle increase depends on the CKD stage and is aggravated by a decline in kidney function (Lamprea-Montealegre
et al. 2013). Hypertriglyceridemia is caused by reduced lipoprotein lipase (LPL) levels (Vaziri 2006; Vaziri et al. 2012) and results in the limited delivery of triglyceride-rich fuel lipoproteins to adipocytes and myocytes (Vaziri et al. 2012). The enrichment of triglyceride-containing lipoprotein particles results in a higher susceptibility to oxidative modifications. These particles are highly pro-inflammatory (Vaziri 2013). In addition, other apoB-rich lipoproteins, such as small dense LDL or IDL-C, are commonly increased in patients with CKD (Saland and Ginsberg 2007; Vaziri 2006). The reduced clearance rate of LDL particles contributes to the increase in LDL levels (Ikewaki 2013).

Lipoprotein a (Lp(a)), which consists of apoA and apoB and is similar to LDL-C, is increased in CKD patients (Longenecker et al. 2005; Muntner et al. 2004). Lp(a) serves as an independent biomarker that predicts cardiovascular complications (Jacobson 2013; Thompson and Seed 2013).

Dyslipidemia is further enhanced by hyperparathyroidism, which frequently occurs in CKD patients (Moe and Sprague 2012). Normal lipid metabolism depends on proper parathyroid function, and hyperparathyroidism tends to result in hypertriglyceridemia (Liang et al. 1998) as well as in a deficiency in lipid metabolism enzymes, such as hepatic lipase and LPL (Klin et al. 1996). The enrichment of apoB-containing lipoproteins is correlated with decreased HDL-C levels (Saland and Ginsberg 2007; Vaziri 2006).

The lipid profile is altered in CKD patients compared with healthy subjects and differs depending on the stage of CKD progression (e.g., stage I to V, pre/post-dialysis, and time on dialysis) and the dialysis procedure (e.g., hemodialysis (HD) or peritoneal dialysis (PD)). As a consequence, the lipid profiles of the CKD population are heterogeneous. Extrinsic factors, including drug administration for kidney disease and associated disorders (hypertension, diabetes mellitus, and malnutrition), contribute to dyslipidemia in this patient cohort.

To overcome the complex dyslipidemia in CKD patients, diverse clinical trials have addressed the influence of lipid-modulating therapies on cardiovascular outcomes. The results of these therapies in the general population suggest that the incidence of cardiovascular events in CKD patients is expected to decrease (van Capelleveen et al. 2014).

3.2 Lipid-Modulating Therapy in CKD Patients

Currently, drugs that treat dyslipidemia are in use or under investigation. Statins, which primarily lower the LDL-C level; peroxisome proliferator-activated receptor (PPAR) agonists; inhibitors of lipid metabolism (CETP, niacin); and apoAI mimetics have been evaluated in preclinical and/or clinical studies. The currently established lipidemic drugs have been reviewed elsewhere; therefore, this article summarizes aspects of therapy related to CKD. Although lipid-modulating therapies have had a positive impact on the cardiovascular outcome in patients with normal kidney function, the effect in CKD patients has been disappointing. These observations have originated predominantly from statin trials.
Statin treatment leads to a reduction in LDL-C through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the initial enzyme in endogenous cholesterol biosynthesis. In several clinical trials, it has been clearly demonstrated that for patients without renal disease, a reduction of LDL-C upon statin therapy is associated with a decreased cardiovascular mortality rate (The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group 1998; Scandinavian Simvastatin Survival Study Group 1994; Baigent et al. 2005; Collins et al. 2003; LaRosa et al. 2005; Sever et al. 2003). Due to the substantially high cardiovascular risk in CKD patients, the effect of statin therapy was also evaluated in three large clinical trials (>1,000 patients included): the “Deutsche Diabetes Dialyse Studie” (4D) (Wanner et al. 2005), “A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events” (AURORA) (Fellstrom et al. 2009a), and “Study of Heart and Renal Protection” (SHARP) (Baigent et al. 2011). The “Prevention of Renal and Vascular End-Stage Disease Intervention Trial” (PREVEND-IT) (Asselbergs et al. 2004; Brouwers et al. 2011) has also addressed the effect of statin therapy in a smaller cohort (<1,000 patients) but included a longer follow-up period. The “Assessment of LEscol in Renal Transplantation” (ALERT) (Holdaas et al. 2003) trial investigated cardiovascular outcomes in renal transplant recipients. The 4D study consisted of a randomized control trial that examined Western HD patients with diabetes (Wanner et al. 2005). No benefits in the primary endpoints were observed in a follow-up period of approximately 4 years (Wanner et al. 2005) (Table 1). A subsequent subgroup analysis of the 4D study cohort showed a reduction in cardiovascular disease after statin treatment in patients with LDL-C >145 mg/dL (Marz et al. 2011). The 4D trial with 1,225 patients was followed by the larger AURORA trial, which enrolled 2,776 HD patients with and without diabetes mellitus. Nonetheless, the reduction in LDL-C that was observed did not have an effect on cardiovascular outcomes (Fellstrom et al. 2009a). Another large randomized trial, the SHARP trial, enrolled HD patients and CKD patients in stages III to V: (Baigent et al. 2011). The combination therapy of simvastatin and ezetimibe lowered the LDL-C level but did not reduce the overall vascular mortality (Baigent et al. 2011). However, the risk for atherosclerotic events was reduced in a wide range of CKD patients (Baigent et al. 2011). The longest follow-up period, up to 9.5 years, was in the PREVEND-IT trial (Asselbergs et al. 2004; Brouwers et al. 2011). Here, patients with microalbuminuria were enrolled and treated with pravastatin and fosinopril. In the follow-up period of 46 months, pravastatin treatment had no effect on cardiovascular endpoints (Asselbergs et al. 2004). The extended follow-up period of 9.5 years showed that elevated urinary albumin excretion was associated with increased cardiovascular morbidity and mortality (Brouwers et al. 2011).

Thus, the large clinical trials examining statin therapy in CKD patients failed to show a significant reduction in overall cardiovascular mortality for patients undergoing dialysis treatment (Table 1). Based on the data from the US Renal Data System, the majority of cardiovascular deaths in CKD patients are due to chronic heart failure and are not influenced by statin treatment (Collins et al. 2013).
| Study     | Follow-up (years) | Drug Treatment | Patients | Outcome | Outcome Details | References |
|-----------|-------------------|----------------|----------|---------|----------------|------------|
| Statins   |                   |                |          |         |                |            |
| 4D        | 3.9               | Atorvastatin (20 mg daily) | 1,255 patients, DM type II on HD | Decreased rate of all cardiac events, increased rate of fatal stroke | Decreased rate of all cardiac events, increased rate of fatal stroke | Wanner et al. (2005) |
| AURORA    | 3.2               | Rosuvastatin (10 mg daily) | 2,776 patients, HD with and without DM | No reduction of cardiovascular mortality, nonfatal MI, nonfatal stroke | No reduction of cardiovascular mortality, nonfatal MI, nonfatal stroke | Fellstrom et al. (2004), Holdaas et al. (2011) |
| PREVEND-IT| 9.5               | Pravastatin (40 mg daily), fosinopril (20 mg daily) | 864 patients with microalbuminuria | No effect on cardiovascular events | No effect on cardiovascular events | Asselbergs et al. (2004), Brouwers et al. (2011) |
| SHARP     | 4.9               | Ezetimibe (10 mg daily) in combination with simvastatin (20 mg daily) | 9,270 CKD patients (stage III to V, including dialysis) | 17 % reduction in major atherosclerotic events, 15 % reduction in major vascular events | Fewer cardiac deaths and nonfatal MIs, no reduction in mortality | Baigent et al. (2011) |
| ALERT     | 5-6               | Fluvastatin | 2,104 renal transplant recipients with stable graft function | No reduction of overall mortality, decreased cardiovascular events or death | No reduction of overall mortality, decreased cardiovascular events or death | Holdaas et al. (2003) |
| VA-HIT    | 5-7               | Gemfibrozil (1,200 mg daily) | 1,046 CKD patients with creatinine clearance <75 ml/min | No reduction of cardiovascular events or death | No reduction of cardiovascular events or death | Rubins et al. (1995), Tonelli et al. (2004) |
| Fibrates and fatty acids | | | | | | Svennson et al. (2006) |

For full study names, please see text.

CKD, chronic kidney disease; HD, hemodialysis; DM, diabetes mellitus; n3-PUFA, n3-polyunsaturated fatty acids; MI, myocardial infarction.
Therefore, other uremia-related pathways and/or the previously existing vascular damage may contribute to the increase in cardiovascular risk. A trial that investigated the effect of statin therapy in renal transplant recipients observed similar effects. In the ALERT trial (Holdaas et al. 2003), statin therapy reduced the LDL-C plasma concentration in treated patients (Holdaas et al. 2003). Although fewer cardiac deaths and nonfatal MIs were observed, no significant reduction in the primary endpoint was achieved (Holdaas et al. 2003).

Based on the findings of the current clinical trials with CKD patients, the therapies tested had either no real impact on cardiovascular outcome or resulted in fatal effects (Kilpatrick et al. 2007). Interestingly, despite a robust reduction in the LDL-C level, only negative or neutral effects on acute cardiovascular events were measured (Baigent et al. 2011; Fellstrom et al. 2009b; Wanner et al. 2005). Effective prevention of cardiovascular events was only documented in patients with mild to moderate CKD (Baigent et al. 2011).

In addition to statins, which primarily lower LDL-C plasma levels, other lipid-modulating drugs are currently used in non-renal-insufficient patients. Here, different targets in HDL metabolism have been identified to overcome dyslipidemia. Initial studies addressed the effect of enzyme inhibition on lipid metabolism, such as CETP inhibition. PPAR agonists, niacin, and apoAI mimetics are other therapeutic options that have been tested in clinical and/or preclinical studies. However, these studies often excluded patients with CKD from recruitment. Therefore, further studies are necessary to determine the effects of these therapies on patients with renal insufficiency.

CETP is responsible for the shuttling of cholesteryl esters between HDL and apoB-containing lipoprotein particles. Inhibition of this enzyme results in a dramatic increase in HDL levels. Torcetrapib was the first CETP inhibitor examined in a large clinical trial, “Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events” (ILLUMINATE) which included approximately 15,000 patients (Barter et al. 2007). The treatment increased the HDL concentration by more than 50% (Barter et al. 2007). However, the study was prematurely terminated because an increased risk of cardiovascular events was observed (e.g., increase in arterial blood pressure) (Barter et al. 2007). In the ILLUMINATE trial, patients with severe CKD were not enrolled. The mean eGFR in patients included in the study was 79.5 ml/min/1.73 m² with creatinine concentration of 1 mg/dL (Barter et al. 2007). In subsequent trials with other CETP inhibitors, which attempted to overcome the off-target effects of torcetrapib, CKD patients were excluded. The “Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib” (DEFINE) study (Cannon et al. 2010) investigated anacetrapib, and a key exclusion criteria in this study was an eGFR <30 ml/min/1.73 m² or severe renal impairment (Cannon et al. 2010). In the dal-OUTCOMES trial with dalcetrapib (Schwartz et al. 2009, 2012), the exclusion criteria was a creatinine level of >2.2 mg/dL (Schwartz et al. 2009). For the “Randomized Evaluation of the Effects of Anacetrapib Through Lipid-Modification” (REVEAL) study, patient recruitment is ongoing, and the study is expected to be completed in 2017 (Gutstein et al. 2012). On the basis of the current CETP inhibitor studies, the effects of CETP...
inhibition on cardiovascular mortality cannot be determined, and patients with severe CKD were excluded from all studies.

Niacin treatment most effectively raises HDL-C levels and decreases triglyceride, LDL-C, and Lp(a) levels. The mechanism underlying the influence of niacin on HDL metabolism is unknown (Linsel-Nitschke and Tall 2005). The beneficial effects on lipoprotein levels and the corresponding cardiovascular outcome have been described in several small-scale clinical trials. Unfortunately, the large-scale trials AIM-HIGH (AIM-HIGH Investigators 2011; Boden et al. 2011) and HPS2-THRIVE (2013), in which patients were treated with niacin in combination with a statin, were prematurely terminated because of a high prevalence of side effects. In both studies, no patients with severe CKD were included. In AIM-HIGH, the mean eGFR was 82.8 ml/min/1.72 m² (2011), and in HPS2-THRIVE, severe renal insufficiency was an exclusion criteria for patient recruitment (2013).

The family of PPAR transcription factors is involved in the regulation of fatty acid metabolism and influences lipid levels. The family consists of three members: PPAR-α, PPAR-γ, and PPAR-δ. PPAR-γ agonists, such as rosiglitazone and pioglitazone, are high-affinity agonists at the receptor site (Linsel-Nitschke and Tall 2005), and their effects on cardiovascular outcome have been tested. However, only a minimal benefit or an increase in heart failure rates was observed in a study population with diabetes in the “Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes” (RECORD) trial (Home et al. 2009). The mean serum creatinine level in the study cohort was approximately 62 μmol/L (Home et al. 2009). The activation of PPAR-α via fibrates, which are weak agonists of this receptor (Linsel-Nitschke and Tall 2005), results in reductions in LDL-C and triglycerides, whereas HDL-C plasma levels are moderately increased (Linsel-Nitschke and Tall 2005; Sahebkar et al. 2014). The “Veterans’ Affairs High-Density Lipoprotein Intervention Trial” (VA-HIT) (Tonelli et al. 2004) investigated the effects of the fibrate gemfibrozil in a cohort of individuals with CKD. Gemfibrozil treatment did not reduce overall mortality, but the rate of major cardiovascular events and nonfatal myocardial infarctions (MIs) was significantly reduced in patients with mild to moderate CKD (Tonelli et al. 2004). Currently, there are no synthetic ligands for PPAR-δ in clinical use (Sahebkar et al. 2014).

In the secondary prevention of cardiovascular disease, there is evidence that n3-polyunsaturated fatty acids (n3-PUFAs) are effective (Studer et al. 2005). A study with HD patients failed to show a reduction in cardiovascular events or death after treatment with an n3-PUFA (Svensson et al. 2006). However, a significant reduction of MIs was observed in this patient cohort (Svensson et al. 2006).

Additional pharmacotherapeutic strategies are currently under development. apoAI-based drugs and reconstituted/engineered HDL particles have been tested in animal and human studies. Recently, van Capelleveen et al. summarized current knowledge of these novel therapeutics (van Capelleveen et al. 2014). The human trials were completed with a limited patient number (<200 patients) and a short follow-up period (several weeks). However, the clinical impact of these novel drugs is highly interesting and must be evaluated in larger clinical trials. Several trials are
currently under way (van Capelleveen et al. 2014); however, the high treatment costs may limit their use in routine clinical practice. After the promising results in animal studies, treatment with apoAI mimetics did not improve biomarkers that were selected to describe HDL function (Watson et al. 2011).

To date, the benefit of apoAI-based therapy for CKD patients remains elusive. The studies described indicate that with a decline in renal function, lipid-modulating therapies lose their capacity to prevent the occurrence of cardiovascular nonfatal and fatal events. Consequently, the lipid compositional and corresponding functional changes that occur with declining renal function are not fully understood. In Table 1, the different therapeutic approaches in patients with variable renal function and the effects on cardiovascular outcome are summarized.

Recent guidelines for the management of lipid disorders in patients with chronic renal failure recommend lipid-lowering therapy only in patients with CKD who are not undergoing renal replacement therapy (National Kidney Foundation 2003; Tonelli and Wanner 2013). The guidelines clearly indicate our inadequate understanding of how to address the complex lipid changes in CKD patients.

### 3.3 Protective Effects of HDL on the Kidney

Based on the current evidence, the causal association between the HDL level, HDL function, and cardiovascular outcome in CKD patients is not fully understood. Dysregulated HDL metabolism might be caused by reduced kidney function. Abnormalities in lipid metabolism enzymes and transport processes have been described (Hirano 2013; Pahl et al. 2009; Vaziri and Norris 2011). The changes involve enrichment of free cholesterol, triglycerides, and fatty acids as well as the depletion of cholesterol esters within HDL. However, there is evidence that HDL might be an independent protective factor for kidney function. Epidemiologic data from a multi-study cohort demonstrated an association between a low HDL-C level and reduced kidney function (Odden et al. 2013). Additional trials addressed the question of whether HDL-C is associated with the progression of CKD. A recent study, which included 3,303 patients with CKD stages III to V and a median follow-up period of 2.8 years, supports the hypothesis that dyslipidemia is independently associated with rapid renal progression (Chen et al. 2013). Two meta-analyses suggest that statin therapy has a benefit on GFR and inhibits GFR decline (Fried et al. 2001; Sandhu et al. 2006). However, other studies found no impact on renal outcome with statin treatment (Atthobari et al. 2006; Rahman et al. 2008). Focusing on HDL-C, Baragetti and coworkers observed an association between low HDL-C and earlier entry in dialysis or doubling of the plasma creatinine in a patient cohort of 176 subjects with mild to moderate kidney dysfunction (Baragetti et al. 2013). Moreover, a cross-sectional analysis of 4,925 patients with normal kidney function strengthened the association between HDL-C and eGFR (Wang et al. 2013). Confounders (e.g., age, blood pressure, and lipid parameters) influenced the relationship (Wang et al. 2013). Furthermore, malnutrition and hypoalbuminemia,
which are frequently present in patients with CKD (Kaysen 2009; Peev et al. 2014), affected the HDL level and functionality (Khovidhunkit et al. 2004). Further studies are necessary to determine whether HDL-targeted therapies are beneficial for renal outcome. The difference in the HDL quantity and functional quality in CKD patients must be considered. The results of clinical trials, such as ILLUMINATE (Barter et al. 2007) and HPS2-THRIVE (2013), suggest that increasing HDL-C plasma levels is not an optimal therapeutic target. Furthermore, as shown in the “European Prospective Investigation into Cancer and Nutrition” (EPIC) study and the MESA study, intima/media thickness and cardiovascular events had a stronger association with HDL particle number compared with HDL cholesterol levels (Arsenault et al. 2009; El Harchaoui et al. 2009; Mackey et al. 2012). Figure 2 summarizes the potential protective effects of HDL on kidney function.

Additional studies that address the structure-dependent functions of the heterogeneous HDL particles are necessary to assess the benefit of HDL-increasing therapy for different disease conditions.
4 Structural and Functional Modifications of HDL in CKD Patients

In the last several years, HDL and its structural composition in disease conditions, especially cardiovascular, metabolic, and renal diseases, have been a focus of experimental research. Compositional changes of the proteome, alterations of the lipid moiety, and posttranslational modifications of HDL isolated from these patient cohorts contribute to a lower protective function of the lipoprotein particle (Annema and von Eckardstein 2013). The following section summarizes the current knowledge of the HDL changes identified in patients with reduced renal function. It is important to keep in mind that the investigations were performed in a heterogeneous group of patients with different stages of renal failure. Therefore, it is often difficult to define the role of uremia on the functionality of HDL.

The HDL particle contains hundreds of different lipids and a multitude of proteins that form a lipoprotein with different shapes, sizes, and densities throughout its metabolism (Camont et al. 2011; Shah et al. 2013). Because of its amphipathic character and the presence of specific binding proteins, HDL serves as cargo for vitamins, hormones, toxins, and microRNA (Vickers and Remaley 2014). There is evidence of biological activity for many of the lipid and protein components. These components can bind to specific receptors and activate signaling pathways in vascular cells, thereby influencing atherogenesis, thrombosis, apoptosis, oxidative reactions, endothelial properties, and inflammatory reactions (Calabresi et al. 2003; Navab et al. 1991; Nofer et al. 2004; Watson et al. 1995). The functions of the associated proteins and lipids in the vascular wall have been characterized in vitro and in animal studies, as well as in clinical trials. It has been shown that compositional changes are related to functionality and are influenced by uremic toxins. For example, (1) the dysregulation of proteins in the HDL metabolism affects HDL plasma level and cholesterol clearance. Furthermore, (2) changes in HDL apolipoprotein composition occur, and finally (3) the loss of proteins with a protective function or (4) the accumulation of substances with a fatal function within HDL influences its vascular protective properties. The compositional changes may not only result in a decrease in function but may also lead to increased dysfunction (Fig. 3), and both are associated with an increased cardiovascular risk profile.

4.1 Dysregulation of Proteins in HDL Metabolism

As discussed in the preceding paragraph, CKD is associated with a decreased HDL-C plasma concentration and dyslipidemia. The uremic condition is responsible for the disrupted protein metabolism (Vaziri 2006) due to uremic-induced liver damage (Yeung et al. 2013). Many proteins important in HDL metabolism are predominantly produced within the liver, and their production is dysregulated in uremia. For proper HDL maturation and metabolism, enzymes such as LCAT and CETP are responsible. Furthermore, diverse receptors on intestinal and peripheral cells, as well as hepatic cells, are necessary for cholesterol transport via HDL to the
liver for biliary excretion (Fig. 4). There is evidence that the expression of enzymes and receptors in HDL metabolism is altered in patients who suffer from kidney disease. To date, most studies have been completed with CKD stage V patients dependent on dialysis (ESRD), and less information on enzyme expression has been obtained from patients prior to dialysis. LCAT is important for HDL maturation. In ESRD patients, the LCAT enzyme concentration and activity were reduced (Miida et al. 2003; Moradi et al. 2009; Pahl et al. 2009; Shoji et al. 1992; Tolle et al. 2012).

**Fig. 3** Functional vs. dysfunctional HDL particles. Depending on the substances that accumulate within the HDL, the particle may exert functional or dysfunctional properties.

**Fig. 4** Dysregulation in HDL metabolism under uremic conditions. ↓ decrease, ↑ increase, ↔ no effect. For references, refer to the text.
The association between the plasma levels of cholesterol transport proteins, such as CETP and CKD, remains unclear. Some studies have failed to show any significant changes in the CETP protein level or activity (Pahl et al. 2009), whereas other studies have identified an increased (Dullaart et al. 1993) or decreased (Miida et al. 2003) CETP level. These controversial data may result from the heterogeneity of CKD patients and the analysis of different patient subgroups: increased levels were identified in proteinuric patients (Dullaart et al. 1993), and unchanged or decreased levels were identified in HD patients with different lengths of minimum dialysis treatment (minimum of 3 months vs. 1 year) (Miida et al. 2003; Pahl et al. 2009). The expression of receptors important for RCT appears to be affected by kidney dysfunction. In nephrectomy animal models, SR-BI (Liang and Vaziri 1999) and ABCA1 (Zuo et al. 2009) receptor expression is decreased. A reduction of these receptors in humans would subsequently be associated with altered HDL metabolism in CKD patients.

4.2 Changes of HDL Apolipoproteins (Modifications and Levels)

HDL contains different apolipoproteins. Under uremic conditions, the composition of the proteins within HDL changes: some protein levels decrease, whereas other protein levels increase. The main apolipoprotein of HDL under normal physiological conditions is apoAI. The presence of altered apoAI levels in CKD patients remains controversial. Some studies have identified decreased apoAI levels in dialysis patients (Holzer et al. 2011a; Moradi et al. 2009; Vaziri et al. 1999, 2009), whereas other studies did not identify a significant change in apoAI concentration (Shoji et al. 1992; Tolle et al. 2012). While apoAII and apoCI levels decreased in CKD patients (Holzer et al. 2011a), apoCII (Holzer et al. 2011a; Weichhart et al. 2012) and apoCIII (Holzer et al. 2011a) increased. ApoAIV was not identified in the HDL obtained from healthy subjects, but was detected in dialysis patients via mass spectrometry analysis (Holzer et al. 2011a). No significant difference was found in apoD and apoE levels, whereas apoM levels decreased (Holzer et al. 2011a). Table 2 summarizes the main apolipoprotein changes in CKD patients. Currently, most identified changes are based on studies with HD patients. The discrepancy in apolipoprotein levels may be a result of the heterogeneous patient population (e.g., CKD stage, time on dialysis, medication, or secondary disease), different HDL isolation protocols (e.g., one-step vs. multistep ultracentrifugation, chromatography, or differentiation between HDL2/3), and different apolipoprotein detection methods (e.g., enzyme-linked immunosorbent assay vs. mass spectrometry).

In addition to changes in the apolipoprotein levels, modifications of the proteins within HDL occurred, which were closely connected to altered functionality. To date, oxidative modifications, carbamylation, and glycosylation have been detected. These effects may be a consequence of the high level of ROS in patients with renal failure.
Patients with CKD suffer from increased reactive oxygen stress (Sung et al. 2013; Tucker et al. 2013). The pro-oxidant state is multifactorial but is related to high amounts of uremic toxins. Uremic toxins are directly involved in the oxidative response, e.g., phenyl acetic acid is a strong inducer of ROS (Schmidt et al. 2008), and indoxyl sulfate has a dual role that consists of pro-oxidant properties in the uremic condition and antioxidative properties under normal physiological conditions (Miyamoto et al. 2011). The increase in highly reactive radicals contributes to the oxidation of proteins and lipids. For example, the oxidation of LDL is known to occur in CKD patients (Ribeiro et al. 2012; Samouilidou et al. 2012). Furthermore, oxidative modifications of apoAI have been identified (Nicholls et al. 2005; Undurti et al. 2009; Zheng et al. 2004). ApoAI oxidation is dependent on the binding activity between apoAI and its receptors ABCA1 (Zheng et al. 2004) and SR-BI (Undurti et al. 2009). Therefore, ox-apoAI impairs HDL metabolism. In addition, an association between oxidative modifications of HDL and a higher risk for cardiovascular events in dialysis patients has been identified (Honda et al. 2012).

Another reactive compound that leads to protein modification is reactive cyanate, which induces the carbamylation of proteins. Cyanates emerge from the degradation of urea or via myeloperoxidase (MPO) at the sites of inflammation (Holzer et al. 2012; Sirpal 2009). CKD patients are prone to carbamylated proteins because urea levels are increased in the uremic condition, and these patients experience increased inflammation. MPO associates with HDL (Nicholls et al. 2005); thus, HDL proteins in addition to LDL proteins (Apostolov et al. 2005) become targets for carbamylation. Carbamylation impairs HDL function by decreasing the cholesterol efflux capacity of HDL from macrophages (Hadfield et al. 2013; Holzer et al. 2011b).

CKD patients are also prone to glycated protein modifications caused by insulin resistance, which is a condition that is frequently observed with reduced renal function (DeFronzo et al. 1981; Kobayashi et al. 2005). Insulin resistance appears

| Apolipoprotein | Change in the HDL in CKD patients | References |
|----------------|----------------------------------|------------|
| apoAI          | ↓ ↔                             | Holzer et al. (2011a), Moradi et al. (2009), Shoji et al. (1992), Tolle et al. (2012), Vaziri et al. (1999), Vaziri et al. (2009) |
| apoAII         | ↓                               | Holzer et al. (2011a) |
| apoAIV         | ↑                               | Holzer et al. (2011a) |
| apoCII         | ↑                               | Holzer et al. (2011a), Weichhart et al. (2012) |
| apoCIII        | ↑                               | Holzer et al. (2011a) |
| apoD           | ↔                               | Holzer et al. (2011a) |
| apoE           | ↔                               | Holzer et al. (2011a) |
| apoM           | ↓                               | Holzer et al. (2011a) |

Table 2 Differences in apolipoprotein composition within the HDL in CKD patients compared with healthy control subjects (↑ increase, ↓ decrease, ↔ no change vs. healthy control)
to be associated with a high burden of oxidative stress. The reduction of oxidative stress by treatment with a superoxide dismutase/catalase mimetic reduces not only ROS production but also insulin resistance in a CKD mouse model (D’Apolito et al. 2010). The modified proteins are advanced glycated end products (AGEs), which are usually found at high levels in CKD patients. Glycated apoAI is likely an AGE (Lapolla et al. 2008). It has been speculated that these modified apoAIs have reduced RCT activity.

Additional proteins are also associated with HDL under physiological and pathophysiological conditions. Many proteins within HDL have been identified using a proteomic approach. Some proteins are increased, whereby other proteins are decreased in HD patients (Holzer et al. 2011a; Weichhart et al. 2012). However, an association between all of the proteins identified by proteome analysis and HDL functionality/dysfunctionality in the vessel wall could not be identified. Retinol-binding protein 4 (RBP4) was detected in the HDL from CKD patients, whereas it was not found within the HDL of healthy controls (Holzer et al. 2011a). Plasma levels of RBP4 were increased in dialysis patients (Frey et al. 2008), and the increase was dependent upon the CKD stage (Henze et al. 2010). Furthermore, surfactant protein B and α-1-microglobulin/bikunin precursor proteins were significantly increased in ESRD patients (Weichhart et al. 2012). Transthyretin was not identified within the HDL from healthy controls, but was detectable in the HDL from dialysis patients (Holzer et al. 2011a). An overview of the identified proteins was recently presented (Holzer et al. 2011a; Weichhart et al. 2012).

4.3 Loss of Protective Proteins or Lipids

Oxidative stress participates in the pathogenesis and progression of CKD and was increased in CKD patients (Mimic-Oka et al. 1999; Puchades et al. 2013). This results from an imbalance of pro-oxidative and antioxidative signals that is favored by uremic toxins (Mimic-Oka et al. 1999). Navab et al. postulated that HDL itself can become pro-inflammatory (Navab et al. 2006). In this condition, serum lipoproteins are prone to oxidative modification. The enzymes linked to HDL that have an antioxidative capacity are thought to facilitate oxidative protection. A higher pro-inflammatory index of HDL in CKD patients resulted in a higher adjusted death hazard ratio (Kalantar-Zadeh et al. 2007). Furthermore, it was shown that the in vitro antioxidative function of HDL was impaired in CKD patients (Moradi et al. 2009). The primary antioxidative HDL-linked enzymes are PON and glutathione peroxidase, and of these two enzymes, PON is the most studied one. The PON family consists of three members: PON1, PON2, and PON3. In contrast to PON2, PON1 and PON3 are secreted in the blood and are associated within HDL (Macharia et al. 2012). PON1 remains the best-studied enzyme of this family in cardiovascular disease and kidney dysfunction. In CKD patients, proteomic analysis did not indicate a significant difference in PON1 compared with healthy individuals (Holzer et al. 2011a), whereas its enzyme activity was reduced in CKD patients (Dantoine et al. 1998; Kennedy et al. 2013;
Moradi et al. 2009). The reduction negatively correlated with the CKD stage (Dantoine et al. 1998). For glutathione peroxidase, decreased concentration and activity were identified in dialysis patients (Moradi et al. 2009).

The loss of this antioxidative capacity combined with an increased level of pro-oxidative molecules (see below) may, at least in part, account for the increased oxidative stress in CKD patients.

A component that contributes to several of the protective functions of HDL is sphingosine-1-phosphate (S1P) (Nofer et al. 2004, 2007; Schuchardt et al. 2011; Theilmeier et al. 2006). HDL-associated apoM binds S1P (Christoffersen et al. 2011). In CKD patients, apoM levels are decreased (Holzer et al. 2011a), which may lead to higher levels of S1P free from HDL. There are several indications that non-HDL-bound S1P signaling differs compared with HDL-bound S1P (Schuchardt et al. 2011).

4.4 Increase of Molecules within HDL with a Fatal Function in the Vascular Wall

In vitro and in vivo studies and/or clinical trials have identified proteins that accumulate within HDL. Interestingly, the albumin content in HDL from uremic patients was elevated, and apolipoprotein displacement may occur (Holzer et al. 2011a).

The acute phase protein serum amyloid A (SAA), which is secreted by the liver during inflammation, is primarily transported by HDL within the blood (Uhlar and Whitehead 1999). In uremic patients, elevated SAA (Holzer et al. 2011a; Tolle et al. 2012; Weichhart et al. 2012; Zimmermann et al. 1999) is a sign of a chronic inflammatory status. This is closely related to an increased cardiovascular risk in humans (Zimmermann et al. 1999). In vitro studies support these findings, as the accumulation of SAA in HDL was correlated with a reduced anti-inflammatory capacity of HDL and a pro-inflammatory potential (Tolle et al. 2012; Weichhart et al. 2012). Furthermore, the cholesterol efflux capacity was decreased when the SAA level dramatically increased during acute sepsis (Annema et al. 2010). In addition, SAA accumulation results in the replacement of apoAI and influences HDL remodeling and metabolism. Nonetheless, the replacement was not identified in all patient cohorts (Tolle et al. 2012), which may be because of the different experimental settings. A displacement of other protective proteins during the acute phase response by SAA was also observed for PON1 and PAF-AH (Van Lenten et al. 1995). Thus, SAA enrichment within HDL affects the anti-inflammatory response. Recently, a pro-inflammatory response of SAA-rich HDL in CKD patients was observed (Tolle et al. 2012; Weichhart et al. 2012). The effects of SAA accumulation on the cholesterol efflux function of HDL remain controversial. In some experiments, a reduction of the cholesterol efflux capacity of HDL was observed if it was enriched with SAA (Artl et al. 2000; Marsche et al. 2007), whereas other studies found normal efflux capacity even with SAA-rich HDL (Banka et al. 1995; van der Westhuyzen et al. 2005).
Furthermore, phospholipases (PLA) associated with cardiovascular mortality are elevated in uremic patients. For example, lipoprotein-associated PLA (Lp-PLA) 2 was increased in uremic patients (Holzer et al. 2011a). The secreted PLA 2 (sPLA2) concentration and activity were also higher in ESRD patients. This elevation contributes to excessive oxidative stress in these patients (van der Giet et al. 2010a).

Dimethylarginines (DMAs), such as asymmetric dimethylarginine (ADMA) and its structural isomer symmetric DMA (SDMA), have been correlated with cardiovascular risk factors. As uremic toxins, they have been associated with cardiovascular outcomes and renal dysfunction (Duranton et al. 2012; Kielstein et al. 2006). DMAs originate from protein proteolysis and are mainly excreted in the urine. DMAs influence nitric oxide (NO) synthesis and negatively influence its vascular protective effects (Bode-Boger et al. 2006). The accumulation of SDMA in HDL from CKD patients and its association with decreased NO have recently been demonstrated (Speer et al. 2013).

MPO is another protein associated with the pathogenesis of cardiovascular disease because of its pro-oxidative and carbamylating potential (Nicholls et al. 2005; Undurti et al. 2009; Zheng et al. 2004). As discussed earlier, MPO associates with HDL (Nicholls et al. 2005) and contributes to reduced RCT in inflammatory diseases (Annema et al. 2010; Zheng et al. 2004). Furthermore, MPO-derived oxidative products modify apoAI (Hadfield et al. 2013). The modifications induced by MPO result in a pro-inflammatory HDL particle (Undurti et al. 2009). In patients with diabetes mellitus type 2, MPO activity was increased in HDL (Sorrentino et al. 2010). Interestingly, in a CKD cohort, the MPO plasma level decreased with advancing renal failure (Madhusudhana Rao et al. 2011). Further studies are necessary to determine the role of MPO in HDL dysfunction in a CKD cohort.

The HDL from ESRD patients on HD was less effective at accepting cholesterol from macrophages compared with the HDL from healthy subjects (Holzer et al. 2011a; Yamamoto et al. 2012). The reverse cholesterol transport may be affected in uremic patients.

5 Possibility of Functional Restoration of HDL

HDL function has been a recent focus of experimental research. With respect to weak effects on cardiovascular outcome after an increase of HDL quantity in CKD patients, HDL function capacity appears important for the design of new therapeutic approaches. Therefore, the question arose whether structural modifications and associated dysfunctions under uremic conditions are reversible. The best approach to test this hypothesis in the case of renal function is to study patients after successful renal transplantation. A limitation of this model is that these patients often require immunosuppressive drugs, which may affect lipid metabolism and function (Badiou et al. 2009). Some investigations have attempted to observe changes in HDL function after renal transplantation. Dantoine and coworkers
reported that the PON enzyme activity in patients after kidney transplantation was comparable to that in control subjects, whereas in dialysis patients, it was decreased (Dantoine et al. 1998). Furthermore, the anti-inflammatory capacity of HDL from ESRD patients compared with healthy controls increased after successful renal transplantation (van der Giet et al. 2010b). The observed effect appears to be related to a decreased SAA level in transplant recipients. Other indicators of the reversibility of HDL dysfunction are based on studies with chronic heart failure patients. In this cohort, exercise training, which is an accepted intervention strategy to decrease cardiovascular risk in heart failure patients, resulted in increased HDL. The authors demonstrated that changes in HDL function induced by exercise training correlated with improved endothelial function (Adams et al. 2013).

According to these data it has been suggested that a restoration of HDL is possible. The lipid metabolism and the composition of different lipoprotein particles are primarily influenced by the metabolic condition. To date, little information is available regarding whether the CKD stage before transplantation is dependent on the HDL functionality after kidney transplantation or whether a point-of-no-return exists for functional restoration, vessel damage, and cardiovascular risk.

### 6 Laboratory Tests to Measure HDL Function

According to previous clinical and experimental trials, it has become clear that HDL particle modifications in disease conditions are associated with reduced HDL function; specific factors that determine HDL functionality remain unclear. It is known that various structural features are associated with HDL function, which can be measured by in vitro studies. A limitation arises in the difficulty of comparing experimental results. The standardization of the experimental design for HDL isolation, separation of proteins/lipids, sample preparation for proteomic approaches, and detection methods for components within HDL would help to overcome certain limitations that may result in discrepancies between findings. In addition, in vitro functionality assays are very complex and further hamper comparability. The complexity and cost preclude these tests from routine clinical laboratory analyses, thus limiting the validation of experimental findings of functionality in large clinical trials. Standardization, validation, and optimization for high throughput must first be established.

Recently, an overview of the laboratory tests that measure HDL subclasses (shape, density) and several HDL functions was described (Eren et al. 2012). There is a growing need to identify an optimal biomarker that describes HDL functionality. The development of reproducible, standardized, and validated methods to assess HDL function for routine use is of substantial interest. The knowledge regarding individual HDL function can help identify patients who may benefit from HDL-C increasing therapy or patients with a normal HDL-C level but at particularly high risk for cardiovascular events.
**Conclusion and Perspective**

HDL is a plasma lipoprotein with many pleiotropic protective functions in the vascular wall, including anti-atherosclerotic properties. Emerging evidence from clinical and laboratory studies indicates that HDL-C plasma levels in humans do not adequately represent HDL function. The pleiotropic protective effects of HDL depend on its composition, which is influenced by pathophysiological conditions. With the decline of renal function, HDL modifications occur. Evidence suggests that HDL composition, rather than plasma level, may be an important determinant for its pleiotropic protective function in the vascular wall. The goal is to identify robust biomarkers that describe HDL functionality and are measurable in validated, standardized assays that can be used routinely. Improvement of HDL functionality may serve as an interesting therapeutic target in the future for populations beyond CKD patients.

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