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Chapter

Lipid Disorders in Uremia

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Abstract

Lipoprotein has important physiologic functions within the human body. Many enzymes, enzyme activators, and protein parts, such as apolipoproteins and specific hepatic and extrahepatic receptors, are involved in their metabolism. Renal failure is associated with an increased risk of cardiovascular disease. One of the main mechanisms underlying this increased cardiovascular risk is dyslipidemia. Abnormal lipoprotein profiles are generally a combination of abnormalities of all fractions. Uremic lipoprotein profile includes increased triglyceride-rich lipoproteins, small dense LDL particles, increased lipoprotein (a), and decreased HDL. Enhanced oxidative stress and uremic environment can strongly modify plasma lipoproteins, changing their interactions with biological functions and especially cardiovascular physiology. This profound lipoprotein disorder has led to the formulation of an accelerated atherogenesis hypothesis and has been commonly linked with their metabolic alteration associated with uremia.

Keywords: chronic uremia, lipoproteins, dyslipidemia, cardiovascular risk

1. Introduction

Urea cycle is one of the most important pathways in the human body. The continuous degradation and synthesis of cellular proteins occur in all forms of life. High rates of protein degradation occur in tissue undergoing structural rearrangements.

Approximately 75% of liberated amino acids are reutilized. Since the excess amino acids are not stored, those not immediately incorporated into new proteins are degraded rapidly. The excess nitrogen from amino acids forms urea. As a hydrosoluble compound, urea is excreted by the kidney. Uremia is a clinical syndrome marked by elevated concentrations of urea in the blood and is associated with many metabolic disorders such as acidosis, abnormalities in lipids, mineral and homocysteine metabolism, oxidative stress, chronic inflammation, insulin and erythropoietin resistance, vitamin D deficiency, and malnutrition. Uremia more commonly develops with chronic kidney disease (CKD), but it also may occur with acute kidney injury if loss of renal function is rapid. Nearly all body organs and systems are affected by the toxicity of uremic compounds retained in the course of renal dysfunction. According to the European Uremic Toxin Work Group, uremic toxins are defined as accumulated solutes, normally excreted by the kidneys, that interact negatively with biological functions [1]. This has shown the need for the search for new uremic compounds, combining them into panels of substances involved in the pathophysiological processes. As example we can mention uridine adenosine, a strong vasoconstrictor, which is considered as a new uremic toxin. It has been demonstrated that uremic patients have increased levels of uridine adenosine, which can influence blood pressure, proliferation rate of vascular smooth

muscle cells, and vascular calcification [2]. All these effects correlated with vascular dysfunctions and development of atherosclerosis. As uremic toxins are considered some components, which concentrations are not directly associated with glomerular filtration, but interacts negatively with vascular physiology. Several acute-phase proteins, IL-1, IL-6, IL-12, α2-macroglobulin, fibrinogen, and myeloperoxidase, together with endothelium-related proteins, such as vascular cell adhesion molecule 1, vascular endothelial growth factor 1, and soluble vascular endothelial growth factor receptor, increased in CKD and play a crucial role in endothelium dysfunction promoting the development of atherosclerosis. Renal failure is associated with an increased risk of cardiovascular disease [3, 4]. One of the main mechanisms underlying this increased cardiovascular risk is dyslipidemia [2]. In uremic environment lipids are affected by oxidative stress. The end products of lipid peroxidation process affect the circulating lipoproteins, lipidic and proteinic, leading to profound alterations of their biological properties, changing their interactions with biological functions and especially cardiovascular physiology. For this reason, lipoproteins, in renal failure, can be also considered as uremic toxins.

In the human body, dietary lipids absorbed from intestine and lipids synthesized by the liver and adipose tissue must be transported between the various tissues and organs for utilization and storage. Since lipids are insoluble in water, the problem on how to transport them in aqueous blood plasma is solved by associating nonpolar lipids (triacylglycerol and cholesterol esters) with amphipathic lipids (phospholipids and cholesterol) and proteins, to form water-soluble particle known as lipoproteins.

The plasma lipoproteins are classified as chylomicrons and very-low-density (VLDL), intermediate-density (IDL), low-density (LDL), and high-density (HDL) lipoproteins, according to their ultracentrifugation characteristics. Chylomicrons and VLDL serve as vehicles to transport triglycerides to the sites of consumption, as myocytes and suprarenal glands or storage in adipocytes. HDL fraction serves as a vehicle to transport surplus cholesterol from peripheral tissues to the liver for disposal. Many enzymes, enzyme activators, and protein parts, such as apolipoproteins and specific hepatic and extrahepatic receptors, are involved in lipoprotein metabolism.

Apolipoproteins (Apo), the protein part of lipoproteins, are present in each lipoprotein and carry out several roles. They can be part of the structure of lipoproteins, serve as an enzyme cofactors or inhibitors, and finally act as ligands for interaction with lipoprotein receptor in tissue. Apolipoproteins of HDL are designated as A (A-I, A-II, A-IV). Apo A-I is an activator of enzyme lecithin-cholesterol acyltransferase (LCAT) and serves as a ligand for HDL binding to specific scavenger receptor B1 (SR-B1). Apo A-II is an inhibitor of enzyme lipoprotein lipase. The main apolipoprotein of LDL and VLDL is Apo B-100, while the chylomicrons contain Apo B-48. Apo B-100 acts as ligand of LDL for LDL receptors in the liver and extrahepatic tissue. Apo B-48 is part of the structure of chylomicrons. Apo E is found in chylomicrons, VLDL, and HDL, and its role is to uptake the remnant of chylomicrons by a receptor specific for apolipoprotein E, in the liver. Apo C-I, Apo C-II, and Apo C-III are transferable between several different lipoproteins. Apo C-II is activator, whereas Apo C-III is an inhibitor for enzyme lipoprotein lipase. The Apo C-I is an inhibitor for enzyme cholesteryl ester transfer protein (CETP).

The main enzymes involved in lipoprotein metabolism are lipoprotein lipase (EC 3.1.1.34), hepatic lipase (EC 3.1.1.3), lecithin-cholesterol acyltransferase (EC 2.3.1.43), and acyl-CoA cholesterol acyltransferase (ACAT) (EC 2.3.1.26).

Lipoprotein lipase is located on the walls of blood capillaries of the heart, adipose tissue, spleen, lung, renal medulla, aorta, lactating mammary gland, and diaphragm. It is abundantly produced as an inactive enzyme by myocytes, adipocytes,

and several other cell types. The inactive enzyme requires sequential glycation and cleavage of a 27-amino acid peptide to become functionally active. The role of lipoprotein lipase is the hydrolysis of triglyceride-rich lipoproteins, as chylomicrons and VLDL. Apo C-II and phospholipids are cofactors for enzyme activity, while Apo A-II and Apo C-III act as inhibitors.

Hepatic lipase is bound to the surface of hepatic cells. Hepatic lipase catalyzes hydrolysis and removal of the triglyceride content of HDL and chylomicron remnant. Accordingly, hepatic lipase plays a central role in the metabolism of chylomicron remnants and HDL.

LCAT is the enzyme of HDL, which is activated by Apo A-I, the structural protein of HDL. The enzyme plays an important role in HDL-mediated cholesterol uptake from the extrahepatic tissues and, as such, serves as a main determinant of HDL maturation and plasma HDL cholesterol level.

The formation of cholesteryl esters from cholesterol and long-chain fatty-acyl-coenzyme A catalyzes the enzyme called ACAT. It is a membrane-bound protein and, at the single-cell level, serves as a regulator of intracellular cholesterol homeostasis. In addition, ACAT supplies cholesteryl esters for lipoprotein assembly in the liver and small intestine.

Cholesteryl ester transfer protein is a hydrophobic glycoprotein that is secreted mainly from the liver and circulates in the plasma, bounded mainly to HDL [5]. It mediates cholesterol ester transfer from HDL to IDL in exchange for triglycerides. CETP promotes the transfer of cholesteryl esters from anti-atherogenic HDLs to pro-atherogenic Apo B-containing lipoproteins, including VLDL, VLDL remnants, IDL, and LDL. In this way CETP transfers lipids from one lipoprotein particle to another in a process that results in equilibration of lipids between lipoprotein fractions.

2. Lipoprotein metabolism

2.1 The metabolism of chylomicrons

The exogenous pathway of lipid metabolism begins with chylomicrons. Chylomicrons are responsible for the transport of all dietary lipids into the circulation. They are produced within the enterocytes containing triglycerides, cholesterol ester, and phospholipids. Apo B-48 is essential for chylomicron formation. The nascent chylomicrons, from the small intestine, are released into the circulation via the lymphatic system. In the circulation, the nascent chylomicrons acquire Apo E and Apo C-II, which are in the surface of HDL. Apo C-II is an activator for enzyme lipoprotein lipase. The endothelium binding accommodates interaction of chylomicrons with the endothelium-bound lipoprotein lipase. Reaction with lipoprotein lipase results in the loss of approximately 90% of triglycerides in chylomicrons. The majority of fatty acids released diffuse into the adjacent myocytes for energy production or into adipocytes for energy storage. After hydrolysis chylomicron remnants are subsequently cleared by the liver and other tissues. Uptake is mediated by a receptor specific for Apo E. Both the LDL (Apo B-100 and Apo E) receptor and LDL receptor-related protein (LRP), specific for Apo E, are believed to take part. Chylomicron remnants return the borrowed Apo C- II and Apo E to HDL before their uptake by the liver and other tissues (**Figure 1**).

2.2 The metabolism of VLDL, IDL and LDL

VLDL particles are produced by the liver and are precursor of IDL and LDL. VLDL serves as the vehicle for delivery of endogenous lipids, endogenous

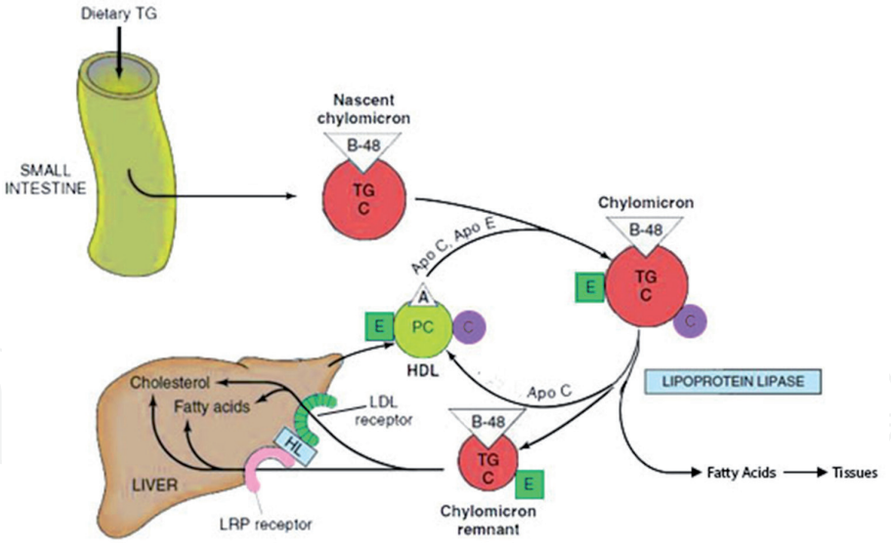

Figure 1.
Chylomicron metabolism. Chylomicrons, from the small intestine, are released into the circulation by apolipoprotein B-48 (B48). Nascent chylomicrons acquire apolipoprotein (Apo) E (green square) and C-II (purple circle), which are in the surface of HDL. Apo A-I (white triangle marked with a) is a main apolipoprotein of HDL. Apo E and Apo C-II are necessary for activation of lipoprotein lipase and for uptakes of remnant chylomicrons by an LDL receptor and LDL receptor-related protein. TG-triglycerides, C-cholesterol, P-phospholipids.

triglycerol, and cholesterol, to the peripheral tissues. Nascent VLDL is formed within the hepatocyte and Apo B-100. Those are triglyceride-rich lipid droplet, followed by the addition of Apo E, Apo A-I, and Apo A-II. The triglycerides and cholesterol ester used by hepatocytes for incorporation into VLDL are generated by the enzymes acyl-CoA diacylglycerol acyltransferase (DGAT; EC 2.3.1.20) and ACAT. Apo C-II and Apo E, borrowed from HDL, are important for subsequent metabolism of VLDL by lipoprotein lipase and the VLDL receptor. Enzyme lipoprotein lipase is activated by the apolipoprotein C-II, and this is followed from the hydrolysis of VLDL triglycerides by the activated enzyme, leading to release fatty acids, which diffuse into the adjacent myocytes or adipocytes for energy production or storage. Lipolysis of VLDL results in reduction in their triglyceride content and detachment and release of a remnant particle, known as IDL. IDL particles may undergo further lipolysis via hepatic triglyceride lipase. Apo E serves as a ligand for remnant VLDL or IDL binding to specific receptors in the liver. This leads to the extraction of nearly all remaining triglycerides from IDL by the liver and formation of cholesterol-rich LDL. LDL particles are then removed via LDL (Apo B-100) receptor by the liver, as well as extrahepatic tissue (**Figure 2**).

2.3 The metabolism of HDL

HDL is synthesized and secreted from the liver and intestine. A major function of HDL is to act as a repository for the Apo C-II and Apo E, for metabolism of triglyceride-rich lipoproteins, chylomicrons, and VLDL. Also, the primary function of HDL is retrieval and transport of cholesterol from the tissue to the liver which is known as reverse cholesterol transport. This cycle is very important for cellular cholesterol homeostasis. The principal apolipoprotein constituents of HDL are Apo A-I and Apo A-II. As the main structural constituent of HDL, Apo A-I is the activator of enzyme LCAT. LCAT system is involved in HDL-mediated removal of excess unesterified cholesterol from triglyceride-rich lipoproteins and tissues. Apo A-II serves as an activator of hepatic lipase, which plays a central role in the removal of HDL triglycerides by the liver. HDL-mediated removal of surplus

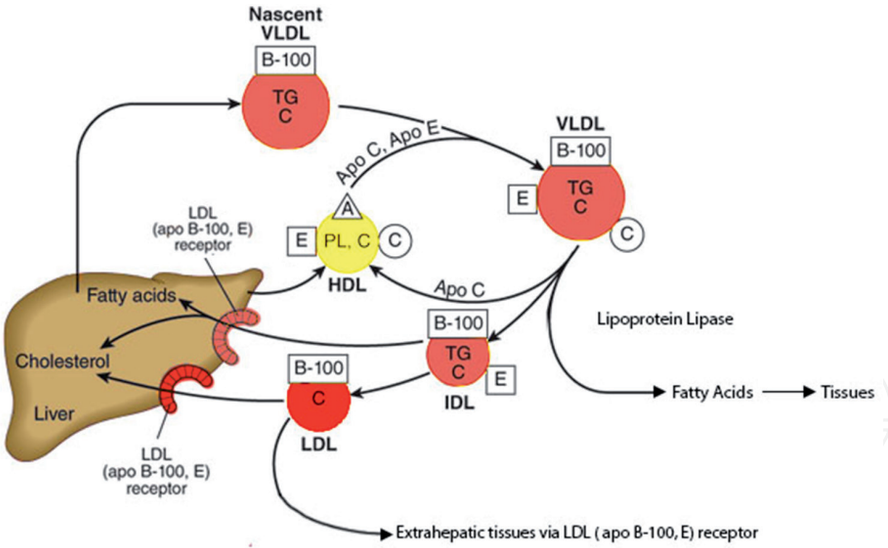

Figure 2.
Very-low-density lipoprotein metabolism. In circulation VLDL are transformed into intermediate-density lipoprotein after lipoprotein lipase activation by apolipoprotein C-II. IDL are removed by hepatic LDL receptors specific for apolipoprotein B and E. Apo E and Apo C-II are borrowed from high-density lipoprotein. A, Apolipoprotein a; B-100, Apolipoprotein B-100; C, Apolipoprotein C; E, Apolipoprotein E; LDL, low-density lipoproteins; TG, triglycerides; C, cholesterol; P, phospholipids.

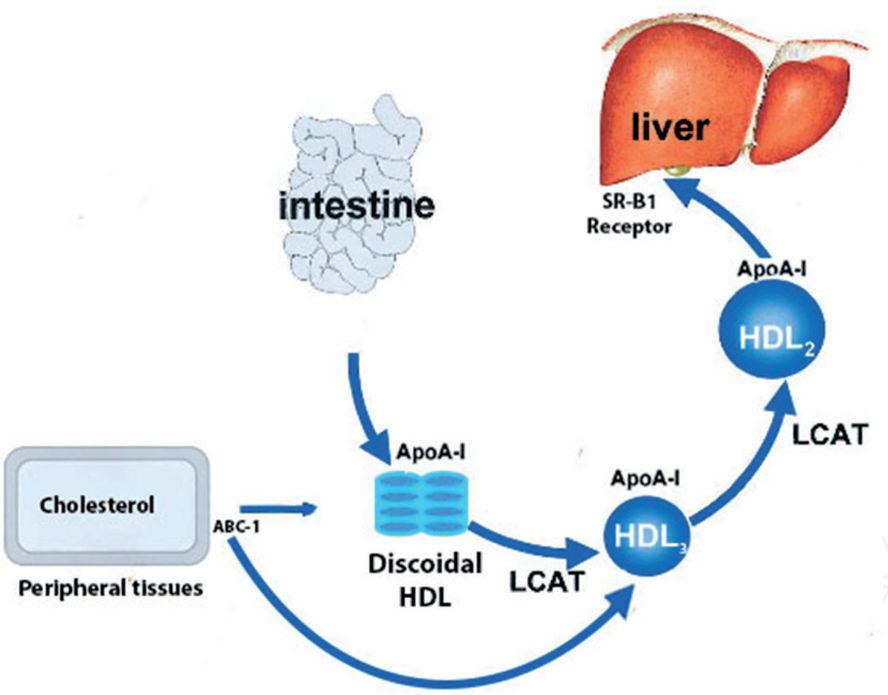

Figure 3.
High-density lipoprotein metabolism. As the main structural constituent of HDL, apolipoprotein A-I (Apo A-I), is the activator of enzyme lecithin-cholesterol acyltransferase. LCAT system is involved in HDL-mediated removal of excess unesterified cholesterol from tissues and its esterification. Scavenger receptor B1,and ATP-binding cassette transporter type I.

cholesterol from extrahepatic tissues requires attachment of nascent HDL to the ATP-binding cassette transporter type I (ABCA1). Binding to ABCA1 appears to trigger active transfer of phospholipids to nascent HDL, a step which is necessary for efficient translocation of free cholesterol from adjacent caveolae to the surface of HDL. Free cholesterol reaching the surface of HDL moves to the core of HDL. In this process nascent discoidal HDL is transformed into spherical HDL 3. After being accepted by HDL3, the free cholesterol is then esterified by LCAT to

cholesterol esters, increasing the size of the particles to form the less dense HDL2. In the next step, HDL2, released in circulation, participates in a series of elaborate exchanges of apoproteins and lipids with the Apo B-containing lipoproteins such as chylomicrons, VLDL, and IDL, before reaching the liver. Actually, HDL in circulation receives triglycerides from Apo B-containing lipoproteins in exchange for cholesterol esters, a process catalyzed by CETP. Finally, HDL-2, via Apo A-I, binds to the scavenger receptor B1, which has been identified as a HDL receptor in the liver. The cycle is completed by the reformation of HDL 3, either after selective delivery of cholesteryl esters to the liver via SR-B1 or by hydrolysis of HDL2 phospholipids and triglycerides by hepatic lipase. Released, free Apo A-I forms preβ-HDL with the minimum amount of phospholipid and cholesterol. Preβ-HDL is considered the most potent form of HDL in inducing cholesterol efflux from the tissues to form discoidal HDL (**Figure 3**).

3. Oxidative stress, lipid peroxidation, and lipoprotein modifications

CKD is associated with increased oxidative stress, which promotes covalent modifications of lipids and lipoproteins. Oxidative stress is an imbalance in the reactive oxygen species (ROS) production and their degradation ratio. ROS include various compounds such as superoxide anions, hydroperoxide, and hydroxyl radical. These compounds are produced under physiologic conditions, during energy production in mitochondria by reducing oxygen during aerobic respiration.

But excessive ROS levels may have a harmful effect on tissue function and structure, because of their interaction with different biomolecules in the human body, such as nucleic acids, proteins, and lipids. This interaction results with oxidative modifications of these biomolecules.

Under physiologic conditions, the production of ROS is balanced by antioxidant mechanisms that protect the cells from oxidative damages. The antioxidant mechanisms include enzymes; superoxide dismutase (SOD, EC 1.15.1.1) which catalyzes the dismutation of $O2^{\bullet-}$ into H_2O_2; and glutathione peroxidase (GPX, EC 1.11.1.9), which detoxifies H_2O_2 and other hydroperoxides. Reduced glutathione (GSH), as a non-enzymatic antioxidant, allows the scavenging of OH. The redox reactions are catalyzed by glutathione peroxidase. In antioxidant mechanisms also included several compounds such as HDL, albumin, tocopherols, ferritin, ceruloplasmin, transferrin, ubiquinol, flavonoids, and carotenoids.

HDL is well known for its protective antioxidant properties. Protein paraoxonase-1 (PON1, EC 3.1.8.1), bound to HDL, exhibited antioxidant effects, against lipid peroxidation. Selenium Glutathione-peroxidase 3, also known as glutathione peroxidase 3 (GPX3, EC 1.11.1.9), is another antioxidant enzyme, which is associated with HDL. Besides many functions in the human body, albumins are known for the antioxidant function too. In the first place concerning the lipid peroxidation, albumin can scavenge hypochlorous acid, responsible for chlorination of proteins mediated by myeloperoxidase, and through its reduced cysteine residue can scavenge hydroxyl radicals. One of the physiological functions of albumins is the transportation of insoluble components, through the blood plasma. In this way, albumins bind the long-chain fatty acids (LCFA), polyunsaturated fatty acids (PUFAs), and cholesterol and in the circulation, preventing them from oxidative modifications. Albumins bind also the ligands such as copper, iron, α-tocopherol, bilirubin, and homocysteine and prevent their antioxidant damages. Tocopherol is an important antioxidant in the human body, because of its ability to intercept intermediary radicals during the lipid peroxidation process. Most antioxidant mechanisms described above are decreased in patients with renal failure, leading to

a higher sensitivity to oxidative stress. These patients have low activity and concentration of Glutathione, low concentration of HDL, PON-1 and GPX3 enzymes, albumins and antioxidant vitamins such as vitamin E, D and C. This decreased antioxidant status, enhanced oxidative stress, and affected lipids and proteins leading to lipoproteins modifications and dysfunction. Lipids are one of the compounds mostly attached to oxidative stress. The peroxidation of lipids began with the reaction between a free radical with a polyunsaturated fatty acid containing more than two double bounds and formation of a lipid radical. In the next reaction, lipid radical can create lipid peroxyl radicals ($LOO^{\bullet}$) in reaction with oxygen, which can further react with other lipids forming new lipid radicals and lipid hydroperoxide (LOOH). Malondialdehyde (MDA) and 4-OH-2,3 alkenals are the end products of lipid hydroperoxide degradation. MDA covalently binds to proteins and nucleic acids, interfering with their normal biological functions. Binding to nucleic acids, MDA induce mutations and base-pair substitutions [6].

Binding to lysine amino group of protein part of lipoproteins, MDA created toxic adducts known as advanced lipoxidation end products (ALEs). In general, ALEs exhibit several pro-inflammatory effects and are involved in atherosclerosis [7]. These ALEs on Apo B result with oxidative modification of [8]. 4-OH-2,3 alkenals can also react with proteins, exactly with histidine, cysteine, and lysine residues and, create ALEs [9], which generate modified LDL. In this modified form, LDL can activate macrophages and increase the upregulation of class A scavenger receptors involved in the transformation of LDL into foam cells [10]. Another end product of lipid peroxidation is F2α-isoprostanes. Oxidation of arachidonic acid by a cyclooxygenase-independent pathway generates F2α-isoprostanes, known for atherogenic properties, because of their implication on platelet aggregation via Thromboxane A2 receptor, vasoconstrictive effects on smooth muscle cells, and endothelial cell proliferation and endothelin-1 secretion [11]. These three end products are routinely used for in vivo evaluation of lipid peroxidation level [12].

4. Lipid disorders in chronic uremia

Renal failure is characterized by specific metabolic abnormalities of plasma lipoproteins [13]. These abnormalities involve all lipoprotein classes and show variations depending on the degree of renal impairment. Uremic lipid profile includes increased VLDL, IDL, small dense LDL particles, lipoprotein (a), and decreased HDL. Besides the changes in their concentration and structure, as stated above, uremic environment can strongly modified circulating lipoproteins leading to profound alterations of their biological properties and toxic effects in different cells and tissues. This has led to the formulation of an accelerated atherogenesis hypothesis and has been commonly linked with the lipid metabolic alteration associated with uremia.

4.1 Chylomicrons and VLDL

Hypertriglyceridemia is common a disorder in uremic patients. Several studies have shown increased concentration of triglycerides even though serum creatinine levels are within normal range [14]. The predominant mechanism responsible for increased concentration of triglyceride-rich lipoproteins, including chylomicrons, VLDL, and their remains, is delayed catabolism and increased synthesis Apo B-48, the essential for chylomicrons metabolism. There are evidences that Apo B-48 levels are increased and inversely correlated with glomerular filtration and proteinuria [15]. In circulation, triglyceride-rich lipoproteins acquire Apo E and Apo C-II,

which are in the surface of HDL. In uremic patients, concentrations of Apo E and Apo C-II, which are necessary for activation of lipoprotein lipase and for uptakes of remnant chylomicrons and VLDL by a receptor specific for Apo E, are reduced. Such defect leads to a reduced release of triglycerides in peripheral tissues and to an accumulation of triglycerides. Delayed catabolism of triglyceride-rich lipoproteins occurs probably because of a decreased activity of hepatic triglyceride lipase and lipoprotein lipase. Moreover, significant evidence showed that enzyme lipoprotein lipase is lacking in renal failure [16]. There are evidences that diminished activity of enzyme is a consequence of the downregulation of the enzyme gene [17]. There is also downregulation of hepatic lipase expression [18].

The presence of lipoprotein lipase inhibitors also contributes to delayed triglyceride-rich lipoprotein catabolism. Apolipoprotein C-II is an activator, whereas apolipoprotein C-III is a direct lipoprotein lipase inhibitor. A decrease in apolipoprotein C-II/ apolipoprotein C-III ratio due to a disproportionate increase in plasma apolipoprotein C-III may be the cause of lipoprotein lipase inactivation, which further contributes to hypertriglyceridemia [19].

As it is mentioned above, triglyceride-rich lipoproteins, chylomicrons, and VLDL,need apolipoprotein C-II and apolipoprotein E for their maturation, which are delivered by HDL-2. In uremic patients HDL metabolism is impaired and HDL-3 are not maturated into HDL-2 due to a LCAT deficiency [20].

In healthy persons, VLDL and chylomicrons are transformed into IDL and chylomicron remnants after lipolysis in peripheral tissue. Chylomicron remnants are removed by the specific receptors of the liver, via LDL (Apo B-100 and Apo E) receptor and LDL receptor-related protein. It has been demonstrated that LDL receptor protein is downregulated in uremic patients [21] which leads to increasing levels of exogenous triglycerides. In physiological conditions, surplus IDL is transformed into LDL by the removal of their triglycerides by the hepatic lipase and enrichment in cholesteryl esters from HDL-2 by CETP. But the lack of HDL-2 impedes this process and leads to the accumulation of pro-atherogenic IDL [22]. There is a downregulation of hepatic lipase expression [18]; thus hepatic lipase deficiency which decreased conversion of IDL to LDL and lack of HDL work in concert to rise plasma concentration of IDL. A part of VLDL is removed by VLDL receptors, but in chronic uremia, the expression of VLDL receptors in tissues is also downregulated [23]. This makes impossible the VLDL binding with VLDL receptors in adipocytes and myocytes and their removal from the circulation (**Figure 4**). Insulin resistance is often associated with chronic uremia and seems to be responsible for a hepatic VLDL overproduction [24]. Secondary hyperparathyroidism, in renal failure, may play an additional role in triglyceride-rich lipoprotein catabolism impairment.

The predominant mechanism responsible for delayed metabolism of chylomicrons and very-low-density lipoproteins is increased synthesis apolipoprotein (Apo B-48) and low activity of lipoprotein lipase (LPL). Decrease concentration of high-density lipoproteins in renal failure results with decreased Apo E and Apo C-II, which are necessary for activation of LPL and for uptakes of remnant chylomicrons and intermediate-density lipoproteins by a receptor specific for Apo E. Such defect, together with the downregulation of LDL receptor protein and hepatic lipase (HL), leads to accumulation of chylomicron remnants and IDL, reducing the release of fatty acids into peripheral tissues. In physiological conditions, surplus IDL is transformed into LDL by the removal of their triglycerides and enrichment in cholesteryl esters from HDL-2 by CETP. But the lack of HDL-2 impedes this process and leads to the accumulation of pro-atherogenic IDL. Increased activity of CETP contributed in reducing HDL concentration. The presence of lipoprotein lipase inhibitor, Apo C-III, also contributes to delayed triglyceride-rich lipoprotein metabolism.

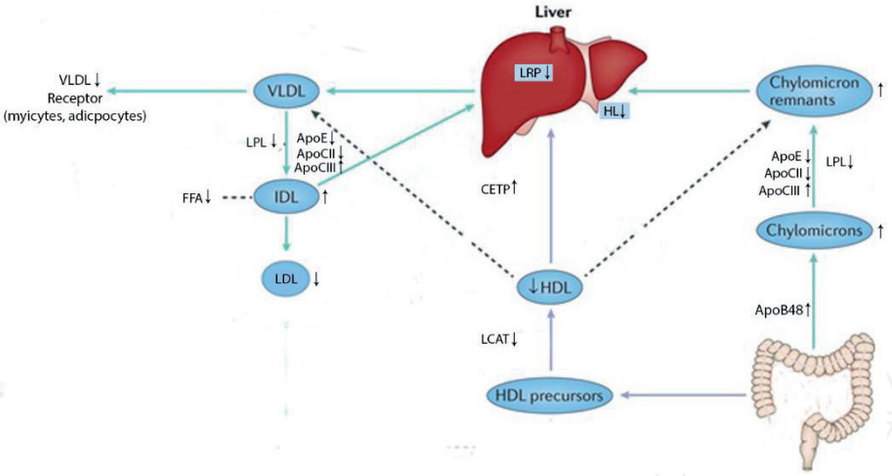

Figure 4.
Changes in chylomicrons and VLDL metabolism in renal failure.

4.2 HDL cholesterol

Uremic patients have decreased HDL in comparison with healthy population [25, 26]. Several mechanisms, working in concern, may underlie the reduction in HDL levels, which is usually indicative of impaired reverse cholesterol transport. Specifically, maturation of HDL is impaired and its composition is altered. Thus, uremic patients usually exhibit decreased levels of apolipoproteins A-I and A-II (the main protein constituents of HDL), diminished activity of LCAT, the enzyme responsible for the esterification of free cholesterol in HDL particles, as well as increased activity of CETP that facilitates the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins. One of the mechanisms for impaired HDL metabolism in uremia is the increased activity of enzyme ACAT which is responsible for intracellular cholesterol esterification. In physiological conditions, Apo A-I and Apo A-II, in the circulation, are loaded with cholesterol and phospholipids to form nascent HDL. Then, nascent HDL binds to the ABCA-1 receptor on circulating macrophages and activates cholesterol ester hydrolase allowing their loading with cholesterol. ACAT limits this reverse efflux of cholesterol from macrophages by catalyzing the esterification of intracellular cholesterol. Oxidative modification of Apo A-I can limit HDL binding on macrophages [27] and upregulation of hepatic ACAT [28] contributing in impaired cholesterol efflux. Therefore, an increase in ACAT activity can potentially limit HDL-mediated cholesterol uptake and contribute to the reduction in plasma HDL cholesterol and impaired maturation of HDL. Although the effect of chronic renal failure on ACAT expression and activity in the extrahepatic tissues is not known, chronic renal failure has been recently shown to markedly raise hepatic ACAT-2 mRNA and protein abundance, as well as total ACAT activity [29].

On the other hand, the activity of enzyme LCAT is decreased [30, 31]. Apo A-I is the activator of LCAT, the essential enzyme for the HDL-mediated cholesterol retrieval from extrahepatic tissues and as well as ligand for the SR-B1 and HDL-binding protein (ABCA1 transporter). Apo A-II serves as an activator of hepatic lipase, which plays a central role in the removal of HDL triglycerides by the liver. As mentioned above, in patients with impaired kidney function, Apo A-I and Apo A-II levels are decreased. This reduction contributes to diminished HDL concentration and impaired HDL maturation. Until recently, it was not clear whether the reported reduction in plasma LCAT activity is caused by the reduction in its hepatic production and plasma concentration or is a consequence of its inhibition by an

unknown uremic toxin [32]. Another enzyme with diminished activity is CETP. The enzyme mediates transfer of cholesterol ester from HDL to IDL in exchange for triglycerides. Increased activity of CETP in uremic patients facilitates the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins, reducing the HDL cholesterol ester and elevation of HDL triglycerides. The mechanism responsible for the elevation of CETP is unknown, but some investigation connected its increased synthesis with proteinuria. Probably the same mechanism is responsible for the dysregulation of hepatic SR-B1. Hepatic SR-B1 is the primary pathway for the disposal of HDL-borne cholesterol ester and triglycerides, and dysregulation of this protein can impact HDL metabolism. Heavy glomerular proteinuria has been shown to significantly reduce hepatic SR-B1 protein expression in experimental animals [29]. HDL has a protective effect against inflammation, platelet adhesion, and LDL oxidation. Those protective functions of HDL can be attributed to HDL-associated enzymes on its surface. Paraoxonase-1 is considered as the main antioxidant enzyme bound to HDL. Mainly expressed in the liver and the kidney, this enzyme exhibited antioxidant properties against lipid peroxidation as it binds to HDL and in a minor part to VLDL [33]. Glutathione seleno-peroxidase 3, also known as glutathione peroxidase 3, is another antioxidant enzyme associated with HDL [34].

One of main anti-atherogenic properties of HDL is a reverse cholesterol transport from circulating macrophages. HDL also increases the production of nitric oxide (NO), through the activation of the endothelial NO synthase in endothelial cells resulting in a vasorelaxant phenotype. In CKD the production of NO by endothelial cells is significantly reduced with HDL [28]. HDL also inhibits the expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1), which prevent the attachment of circulating monocytes to endothelial cells. In uremic patients, HDL promotes an enhanced expression of VCAM-1 and ICAM-1 on endothelial cells [35, 36]. Moreover, CKD-HDL upregulates the expression of pro-inflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1), interleukin-1ß (IL-1ß), and tumor necrosis factor α (TNF-α) [36, 37]. And finally normal HDL exhibit anti-apoptotic effects on endothelial cells through the downregulation of caspase-3 (a member of the cysteine-aspartic acid protease) activity [38]. All these diminished protective functions of HDL can contribute to accelerated atherogenesis [39]. HDL is very sensitive in oxidative stress and posttranslational modifications. Renal failure is associated with an enhanced activity of enzyme myeloperoxidase (MPO, EC 1.11.2.2) that plays a crucial role in the generation of posttranslational modification derived products (PTMDPs). MPO catalyzed the oxidative reactions and formation of a variety of chlorinated protein and lipid adducts. MPO-modified ApoA-1 results in decreased reverse cholesterol efflux and a reduced binding with ABCA-1 receptor, which disturbed cholesterol homeostasis (**Figure 5**). 3-chlorotyrosine, an oxidation product of MPO, impairs the activity of enzymes, LCAT, and PON-1, resulting with decreased anti-inflammatory effects of HDL. And through the activation of SR-B1 in macrophages, MPO-modified HDL directly contributes in atherosclerosis (**Figure 5**).

In renal failure, decreased activity of lecithin-cholesterol acyltransferase impaired the transformation of nascent cholesterol into HDL3 and then into HDL2. Increased activity of cholesteryl ester transfer protein facilitates the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins, reducing HDL concentration. Removal of free cholesterol from macrophages proceeds by scavenger receptor 1. Nascent HDL is generated when Apo A-I interacts with ATP-binding cassette transporter type 1 (ABCA1). Than nascent HDL activates cholesterol ester hydrolase allowing their loading with cholesterol. ACAT limits this reverse efflux of cholesterol from macrophages by catalyzing the esterification of intracellular

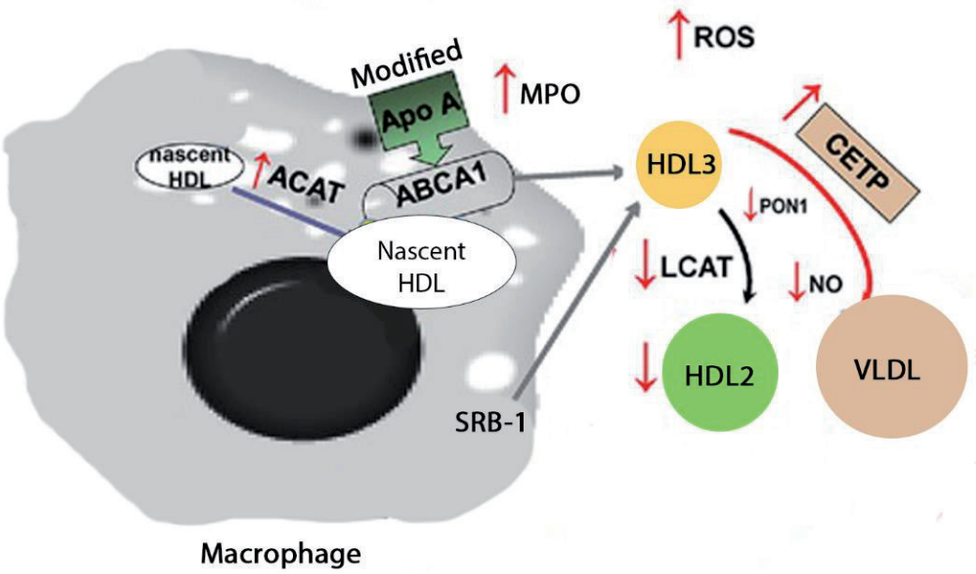

Figure 5.
HDL metabolism in renal failure.

cholesterol. Increased activity of ACAT, in renal failure, participates in impaired cholesterol efflux. Antioxidative and anti-inflammatory functions of HDL are impaired due to reduced activity of HDL enzyme PON1. HDL from patients with renal failure loses its vasoprotective properties, inhibiting nitric oxide production. Oxidative modification of Apo A-I decreases HDLs binding to macrophages. Myeloperoxidase-modified Apo A-I decrease reverse cholesterol efflux, reduce binding with ABCA1, and impair HDLs anti-apoptotic properties.

4.3 LDL cholesterol

Beyond atherogenic risk of LDL level itself, renal failure leads to various structural modifications of LDL particles. The lipoproteins found in uremic patients are disproportionately modified, with LDL that is enriched in triglycerides. These modified LDL particles tend to be smaller and denser in their form. Small dense LDL is believed to be markedly pro-atherogenic, and this is attributed to its ability to infiltrate the vessel wall and its increased susceptibility to oxidative modification. Because of the significantly modified lipid subfraction turnover, residence time of lipoproteins in the circulation is prolonged. Thus, lipoproteins are at risk of posttranslational modification. LDL receptor-mediated cholesterol uptake plays an important role in cholesterol homeostasis. Modified LDL have reduced affinity for the classic LDL receptors and are taken up by the scavenger receptors on the surface of the macrophages. These receptors are increased in chronic uremia. High affinity for macrophages results in the accumulation of cholesterol and the formation of foam cells in the vascular walls, resulting in the development of atherosclerotic plaques [40, 41]. Heavy proteinuria alone or in combination with chronic uremic state results in acquired LDL receptor deficiency and plays a central role in the genesis of the atherosclerosis and cardiovascular diseases. Several levels of LDL oxidation can coexist in the bloodstream and lead to the activation of several pathways involved in atherosclerosis through their binding to scavenger receptors [42] and smooth muscle cell proliferation. There is an evidence that OxLDL are accumulated in uremic patients and are correlated with the intensity of peripheral arterial disease [43]. Oxidized epitopes of LDL can activate immunity and then lead to the formation of antibodies directed against OxLDL. OxLDL/antibodies against OxLDL ratio were also correlated with carotid atherosclerosis

and cardiovascular events [44]. Formation of OxLDL is a consequence of oxidative stress. As mentioned above, the breakdown of polyunsaturated fatty acids produces highly reactive molecules, such as MDA and 4-OH-2,3 alkenals. MDA and 4-OH-2,3 alkenals can form Schiff bases and covalent Michael-type adducts, with lysine residues of Apo B-100, in LDL (**Figure 6**). The oxidized fatty acid fragments which can remain attached via ester bridges, may also contain terminal reactive phospholipids which may form adducts with Schiff base lysine residues of Apo B-100. Similarly with HDL modifications, increased levels of MPO are involved in LDL modifications. MPO can modify LDL through several mechanisms. MPO initiated the reaction between hypochlorous acid and tyrosine residues of Apo B-100, protein part of LDL, resulting with 3-chlorotyrosine formation, which is known for pro-atherogenic properties through its binding with lectin-like oxidized LDL receptor 1. MPO also generated reactive nitrogen species, converting LDL into a nitrosilated-LDL form. This reaction resulted in nitration of Apo B-100 tyrosyl residues of LDL. Carbamylated LDL (cLDL) is another modified form of LDL, initiated by MPO. In this reaction MPO catalyzed the addition of thiocyanate, derived from the decomposition of urea to the lysine residues of LDL, and leads to the formation of carbamylated LDL [45, 46]. The carbamylation occurs by spontaneous, nonenzymatic chemical modification of Apo B-100, by thiocyanate. It is a irreversibly reaction of thiocyanate with free amino groups and ε-NH2 of lysine residues in protein part of LDL (**Figure 7**). cLDL have pro-atherogenic effects such as the transformation of macrophages into foam cells [47] through their binding to the pro-atherogenic CD36 receptor [48, 49]. cLDL are associated with endothelial toxicity [50, 51] through lectin-like oxidized LDL receptor 1 [52] (**Figure 8**). cLDL levels are raised by chronic uremia [53, 54].

Modified forms of LDL; carbamylated LDL and oxidized LDL; activated lectin-like oxidized LDL receptor 1, on endothelial cells; and initiated formation of macrophages and smooth muscle cell proliferation.

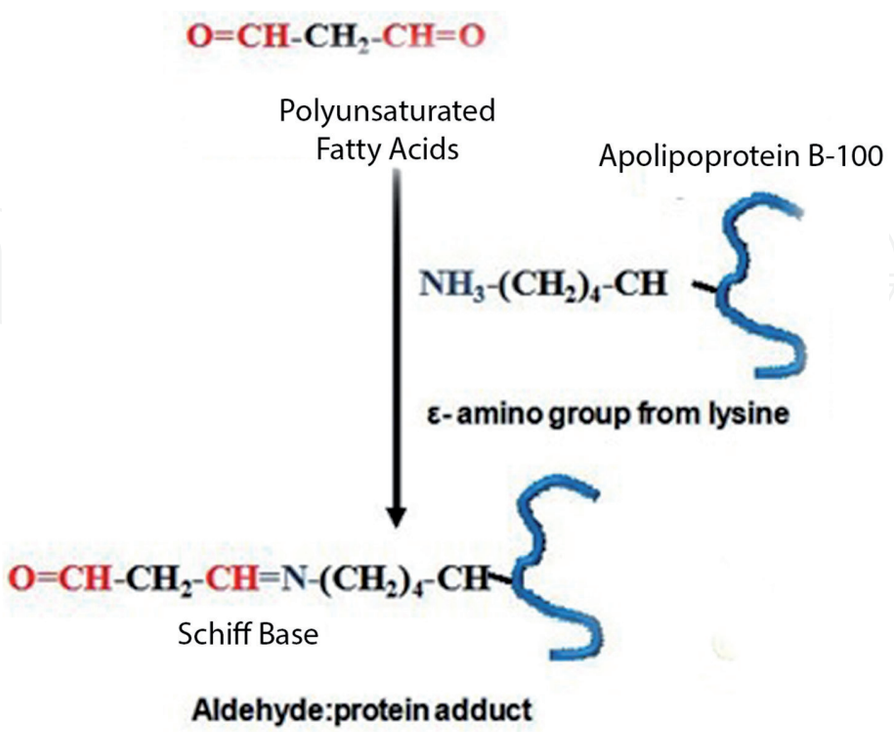

Figure 6.
Formation of oxidized LDL.

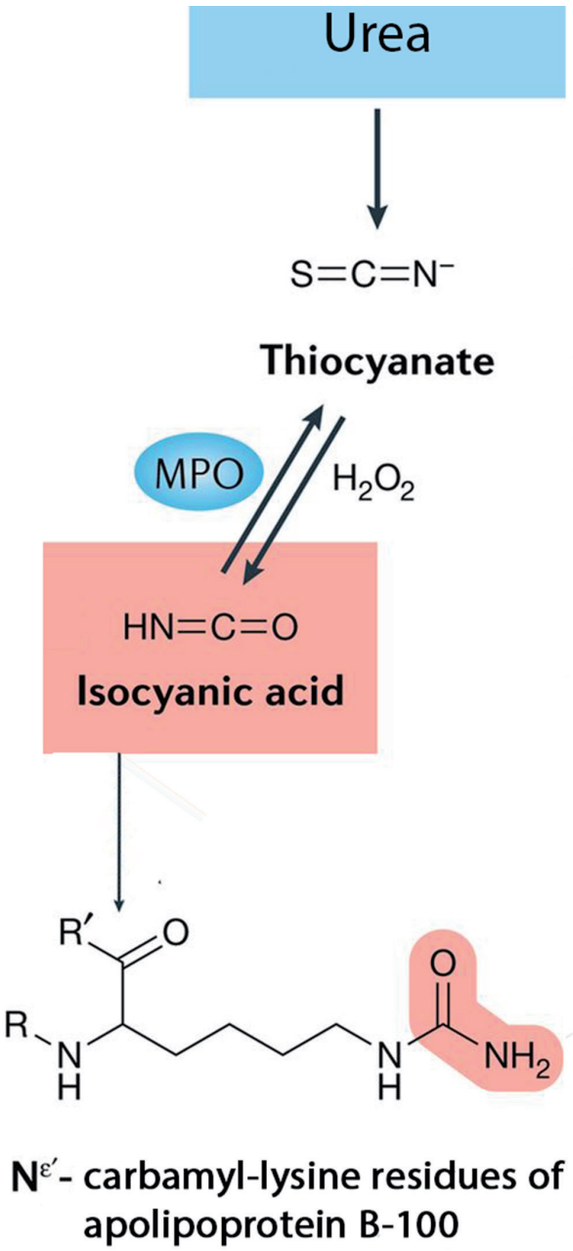

Figure 7.
Formation of carbamylated LDL.

4.4 Lipoprotein (a)

The contribution of cardiovascular events to the extraordinary high mortality in CKD has generated some interest in nontraditional atherosclerotic cardiovascular disease risk factors, which are prevalent in this population, such as Lipoprotein (a) [Lp (a)]. Lp (a) is an LDL-like lipoprotein containing a unique apolipoprotein called Apo(a). Serum levels of Lp(a) are determined largely by genetic variation in the gene encoding for Apo(a). Apo(a) is very homologous to plasminogen [55] and exhibits an extreme size polymorphism with the Apo(a) isoproteins, ranging in size from 420 to 840 kDa. Inherited in an autosomal codominant fashion, the Apo(a) isoprotein is closely correlated with serum Lp(a) concentrations, with an inverse correlation between the size of the Apo(a) isoprotein and the serum Lp(a) concentrations. Lp(a) has been implicated in the regulation of plasminogen activator inhibitor-1 expression in endothelial cells and shown to inhibit endothelial cell surface fibrinolysis to

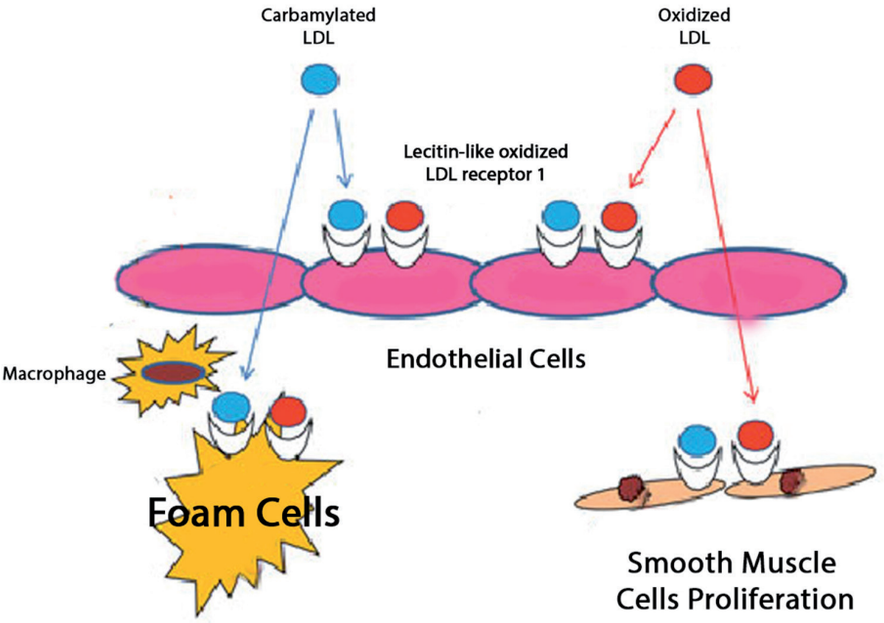

Figure 8.
Oxidized LDL and carbamylated LDL effects.

attenuate plasminogen binding to platelets and to bind to plaque matrix components. Autopsy studies in humans have documented the presence of Lp(a) in aortic and coronary atherosclerotic plaques and an apparent colocalization with fibrinogen [56]. Lp(a) levels are frequently elevated in uremic patients with CKD [57] and have been associated with a frequency distribution of apolipoprotein (a)-Lp(a) isoforms, similar to those found in general population. This indicates that elevated Lp(a) levels in these patients are not due to the genetic origin [58]. It has been suggested that kidneys have an important role in Lp(a) metabolism [59]. In CKD, Lp(a) occurs at high concentrations, largely because of reduced clearance or as a result of increased hepatic synthesis, induced by an acute-phase reaction or by protein losses from proteinuria [60]. Uremia can be considered to be a state of activated acute-phase response, and in the micro-inflammatory milieu, a number of atherogenic proteins like Lp(a) are acting as an acute-phase reactant. Based in all these properties, Lp(a) is a prototype candidate to be classified as a uremic toxin.

5. Conclusion

Chronic uremia causes profound alteration in lipoprotein metabolism, promoting the development of atherosclerosis and cardiovascular disease. Besides the changes in their concentration, enhanced oxidative stress and uremic environment can strongly modify circulating lipoproteins leading to profound alterations of their biological properties and can be considered as uremic toxins. Uremic lipoprotein profile is directly involve in glomerular capillary endothelial damage and in the progression of renal disease. This "reverse epidemiology" shows the importance of lipid control to prevent the progression of renal failure.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

ABCA1	ATP-binding cassette transporter type I
ACAT	acyl-CoA cholesterol acyltransferase
α-TNF	alpha tumor necrosis factor
ALEs	advanced lipoxidation end products
Apo A,B,C,E	apolipoprotein A,B,C,E
Apo (a)	apolipoprotein
CETP	cholesteryl ester transfer protein
CKD	chronic kidney disease
cLDL	carbamylated low-density lipoprotein
DGAT	acyl-CoA diacylglycerol acyltransferase
GPX	glutathione peroxidase
GPX3	glutathione peroxidase 3
HDL	high-density lipoproteins
IDL	intermediate-density lipoproteins
ICAM-1	intercellular adhesion molecule-1
IL-1ß	interleukin-1ß
LCAT	lecithin-cholesterol acyltransferase
LDL	low-density lipoproteins
Lp(a)	lipoprotein (a)
LRP	LDL related protein
MCP-1	monocyte chemoattractant protein-1
mRNA	messenger ribonucleic acid
MDA	malondialdehyde
MPO	myeloperoxidase
NO	nitric oxide
OxLDL	oxidized-LDL
LCFA	long chains fatty acids
$LOO^{\bullet}$	peroxyl radicals
LOOH	lipid hydroperoxide
PON1	paraoxonase 1
PTMDPs	posttranslational modification derived products
PUFAs	polyunsaturated fatty acids
ROS	reactive oxygen species
SOD	superoxide dismutase
SR-B1	scavenger receptor B1
VCAM	vascular adhesion molecule-1
VLDL	very-low-density lipoprotein

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References

[1] Florens N, Calzada C, Lyasko E, Juillard L. Modified lipids and lipoproteins in chronic kidney disease: A new class of uremic toxins. Toxins (Basel). 2016;**8**(12):376. DOI: 10.3390/toxins8120376

[2] Duranton F, Cohen G, De Smet R, Rodriguez M, Jankowski J, Vanholder R, et al. On behalf of the European uremic toxin work group Normal and pathologic concentrations of uremic toxins. Journal of the American Society of Nephrology. 2012;**23**:1258-1270. DOI: 10.1681/ASN.2011121175

[3] McCullough PA, Agrawal V, Danielewicz E, Abela GS. Accelerated atherosclerotic calcification and Monckeberg's sclerosis: A continuum of advanced vascular pathology in chronic kidney disease. Clinical Journal of the American Society of Nephrology. 2008;**3**:1585-1598. DOI: 10.2215/CJN.01930408

[4] Schiffrin EL, Lipman ML, Mann JFE. Chronic kidney disease: Effects on the cardiovascular system. Circulation. 2007;**116**:85-97. DOI: 10.1161/CIRCULATIONAHA.106.678342

[5] Tall AR. Plasma cholesteryl ester transfer protein. Journal of Lipid Research. 1993;**34**:1255-1274

[6] VanderVeen LA, Hashim MF, Shyr Y, Marnett LJ. Induction of frameshift and base pair substitution mutations by the major DNA adduct of the endogenous carcinogen malondialdehyde. PNAS. 2003;**100**:14247-14252. DOI: 10.1073/pnas.2332176100

[7] Negre Salvayre A, Coatrieux C, Ingueneau C, Salvayre R. Advanced lipid peroxidation end products in oxidative damage to proteins. Potential role in diseases and therapeutic prospects for the inhibitors. British Journal of Pharmacology. 2008;**153**:6-20. DOI: 10.1038/sj.bjp.0707395

[8] Palinski W, Ord VA, Plump AS, Breslow JL, Steinberg D, Witztum JL. ApoE-deficient mice are a model of lipoprotein oxidation in atherogenesis. Demonstration of oxidation-specific epitopes in lesions and high titers of autoantibodies to malondialdehyde-lysine in serum. Arteriosclerosis, Thrombosis, and Vascular Biology. 1994;**14**:605-616. DOI: 10.1161/01.ATV.14.4.605

[9] Petersen DR, Doorn JA. Reactions of 4-hydroxynonenal with proteins and cellular targets. Free Radical Biology and Medicine. 2004;**37**:937-945. DOI: 10.1016/j.freeradbiomed.2004.06.012

[10] Hoff HF, O'Neil J, Chisolm GM, Cole TB, Quehenberger O, Esterbauer H, et al. Modification of low density lipoprotein with 4-hydroxynonenal induces uptake by macrophages. Arteriosclerosis, Thrombosis, and Vascular Biology. 1989;**9**:538-549. DOI: 10.1161/01.ATV.9.4.538

[11] Yura T, Fukunaga M, Khan R, Nassar GN, Badr KF. Free-radical-generated F2-isoprostane stimulates cell proliferation and endothelin-1 expression on endothelial cells. Kidney International. 1999;**56**:471-478. DOI: 10.1046/j.1523-1755.1999.00596.x

[12] Grotto D, Santa Maria LD, Boeira S, Valentini J, Charão MF, Moro AM, et al. Rapid quantification of malondialdehyde in plasma by high performance liquid chromatography-visible detection. Journal of Pharmaceutical and Biomedical Analysis. 2007;**43**:619-624. DOI: 10.1016/j.jpba.2006.07.030

[13] Tsimihodimos V, Dounousi E, Siamopoulos KC. Dyslipidemia in chronic

kidney disease an approach to pathogenesis and treatment. American Journal of Nephrology. 2008;**28**:958-973

[14] Sechi LA, Catena C, Zingaro L, Melis A, De Marchi S. Abnormalities of glucose metabolism in patients with early renal failure. Diabetes. 2002;**51**:1226-1232

[15] Okubo M, Hanada H, Matsui M, Hidaka Y, Masuda D, Sakata Y, et al. SerumapolipoproteinB-48concentration is associated with a reduced estimated glomerular filtration rate and increased proteinuria. Journal of Atherosclerosis and Thrombosis. 2014;**21**:974-982. DOI: 10.5551/jat.23309

[16] Vaziri ND, Yuan J, Ni Z, Nicholas SB, Norris KC. Lipoprotein lipase deficiency in chronic kidney disease is accompanied by down-regulation of endothelial GPIHBP1 expression. Clinical and Experimental Nephrology. 2012;**16**:238-243. DOI: 10.1007/s10157-011-0549-3

[17] Vaziri ND, Liang K. Down-regulation of tissue lipoprotein lipase expression in experimental chronic renal failure. Kidney International. 1996;**50**:1928-1935

[18] Sato T, Liang K, Vaziri ND. Protein restriction and AST-120 improve lipoprotein lipase and VLDL receptor in focal glomerulosclerosis. Kidney International. 2003;**64**:1780-1786. DOI: 10.1046/j.1523-1755.2003.00281.x

[19] Chan DT, Dogra GK, Irish AB, et al. Chronic kidney disease delays VLDL apoB-100 particle catabolism: Potential role of apo C-III. Journal of Lipid Research. 2009;**50**:2524-2531

[20] Moradi H, Pahl MV, Elahimehr R, Vaziri ND. Impaired antioxidant activity of high-density lipoprotein in chronic kidney disease. Translational Research. 2009;**153**:77-85. DOI: 10.1016/j.trsl.2008.11.007

[21] Kim C, Vaziri ND. Down-regulation of hepatic LDL receptor-related protein (LRP) in chronic renal failure. Kidney International. 2005;**67**:1028-1032. DOI: 10.1111/j.1523-1755.2005.00166.x

[22] Hirowatari Y, Homma Y, Yoshizawa J, Homma K. Increase of electronegative-LDL-fraction ratio and IDL-cholesterol in chronic kidney disease patients with hemodialysis treatment. Lipids in Health and Disease. 2012;**11**(1). DOI: 10.1186/1476-511X-11-111

[23] Sato T, Liang K, Vaziri ND. Down-regulation of lipoprotein lipase and VLDL receptor in rats with focal glomerulosclerosis. Kidney International. 2002;**64**:1780-1786. DOI: 10.1046/j.1523-1755.2003.00281.x

[24] Tsimihodimos V, Mitrogianni Z, Elisaf M. Dyslipidemia associated with chronic kidney disease. Open Cardiovascular Medicine Journal. 2011;**5**:41-48

[25] Attman PO, Samuelsson O, Alaupovic P. Lipoprotein metabolism and renal failure. American Journal of Kidney Diseases. 1993;**21**:573-592

[26] Vaziri ND, Deng G, Liang K. Hepatic HDL receptor, SR-B1 and Apo A-I expression in chronic renal failure. Nephrology, Dialysis, Transplantation. 1999;**14**:1462-1466

[27] Shao B, Oda MN, Oram JF, Heinecke JW. Myeloperoxidase: An inflammatory enzyme for generating dysfunctional high density lipoprotein. Current Opinion in Cardiology. 2006;**21**:322-328. DOI: 10.1097/01.hco.0000231402.87232.aa

[28] Liang K, Vaziri ND. Upregulation of acyl-CoA: Cholesterol acyltransferase in chronic renal failure. American Journal of Physiology. Endocrinology and Metabolism. 2002;**283**:676-681. DOI: 10.1152/ajpendo.00364.2001

[29] Blaton V. Dyslipidemia at chronic renal failure. EJIFCC. 2009;**20**(1):59-66

[30] Shoji T, Nishizawa Y, Nishitani H, Yamakawa M. Impaired metabolism of high density lipoprotein in uremic patients. Kidney International. 1992;**41**:1653-1661. DOI: 10.1038/ki.1992.238

[31] Vaziri ND, Liang K, Parks JS. Down-regulation of hepatic lecithin: Cholesterol acyltransferase gene expression in chronic renal failure. Kidney International. 2001;**59**:2192-2196. DOI: 10.1046/j.1523-1755.2001.00734.x

[32] Vaziri ND. Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences. American Journal Of Physiology. Renal Physiology. 2006;**290**(2):F262-F272. DOI: 10.1152/ajprenal.00099.2005

[33] Litvinov D, Mahini H, Garelnabi M. Antioxidant and anti-inflammatory role of paraoxonase 1: Implication in arteriosclerosis diseases. North American Journal of Medical Sciences. 2012;**4**:523-532

[34] Maddipati KR, Marnett LJ. Characterization of the major hydroperoxide-reducing activity of human plasma. Purification and properties of a selenium-dependent glutathione peroxidase. The Journal of Biological Chemistry. 1987;**262**(36):17398-17403

[35] Shroff R, Speer T, Colin S, Charakida M, Zewinger S, Staels B, et al. HDL in children with CKD promotes endothelial dysfunction and an abnormal vascular phenotype. Journal of the American Society of Nephrology. 2014;**25**:2658-2668. DOI: 10.1681/ASN.2013111212

[36] Kaseda R, Jabs K, Hunley TE, Jones D, Bian A, Allen RM, et al. Dysfunctional high-density lipoproteins in children with chronic kidney disease. Metabolism. 2015;**64**:263-273. DOI: 10.1016/j.metabol.2014.10.020

[37] Yamamoto S, Yancey PG, Ikizler TA, Jerome WG, Kaseda R, Cox B, et al. Dysfunctional high-density lipoprotein in patients on chronic hemodialysis. Journal of the American College of Cardiology. 2012;**60**:2372-2379. DOI: 10.1016/j.jacc.2012.09.013

[38] Kimura T, Sato K, Malchinkhuu E, Tomura H, Tamama K, Kuwabara A, et al. High-density lipoprotein stimulates endothelial cell migration and survival through sphingosine 1-phosphate and its receptors. Arteriosclerosis, Thrombosis, and Vascular Biology. 2003;**23**:1283-1288. DOI: 10.1161/01.ATV.0000079011.67194.5A

[39] Kwan BCH, Kronenberg F, Beddhu S, Cheung AK. Lipoprotein metabolism and lipid management in chronic kidney disease. Journal of the American Society of Nephrology. 2007;**18**:1246-1261

[40] Shurraw S, Tonelli M. Statins for treatment of dyslipidemia in chronic kidney disease. Peritoneal Dialysis International. 2006;**26**:523-539

[41] Piecha G, Adamczak M, Ritz E. Dyslipidemia in chronic kidney disease. Polskie Archiwum Medycyny Wewnętrznej. 2009;**119**:487-492

[42] Levitan I, Volkov S. Oxidized LDL: Diversity, patterns of recognition, and pathophysiology. Antioxidants and Redox Signaling. 2010;**13**:39-75. DOI: 10.1089/ars.2009.2733

[43] Takenaka T, Takahashi K, Kobayashi T, Oshima E, Iwasaki S, Suzuki H. Oxidized low density lipoprotein (ox-LDL) as a marker of atherosclerosis in hemodialysis (HD) patients. Clinical Nephrology. 2002;**58**:33-37. DOI: 10.5414/CNP58033

[44] Pawlak K, Myśliwiec M, Pawlak D. Oxidized LDL to autoantibodies against oxLDL ratio—The new biomarker associated with carotid atherosclerosis and cardiovascular complications in dialyzed patients. Atherosclerosis. 2012;**224**:252-257. DOI: 10.1016/j.atherosclerosis.2012.07.011

[45] Shiu SWM, Xiao SM, Wong Y, Chow WS, Lam KSL, Tan KCB. Carbamylation of LDL and its relationship with myeloperoxidase in type 2 diabetes mellitus. Clinical Science. 2013;**126**:175-181. DOI: 10.1042/CS20130369

[46] Exner M, Hermann M, Hofbauer R, Hartmann B, Kapiotis S, Gmeiner B. Thiocyanate catalyzes myeloperoxidase-initiated lipid oxidation in LDL. Free Radical Biology and Medicine. 2004;**37**:146-155. DOI: 10.1016/j.freeradbiomed.2004.04.039

[47] Apostolov EO, Ok E, Burns S, Nawaz S, Savenka A, Shah SV, et al. Carbamylated-oxidized LDL: Proatherosclerotic effects on endothelial cells and macrophages. Journal of Atherosclerosis and Thrombosis. 2013;**20**:878-892. DOI: 10.5551/jat.14035

[48] Park YM. CD36, a scavenger receptor implicated in atherosclerosis. Experimental and Molecular Medicine. 2014;**46**:e99. DOI: 10.1038/emm.2014.38

[49] Chmielewski M, Bryl E, Marzec L, Aleksandrowicz E, Witkowski JM, Rutkowski B. Expression of scavenger receptor CD36 in chronic renal failure patients. Artificial Organs. 2005;**29**:608-614. DOI: 10.1111/j.1525-1594.2005.29097.x

[50] Carracedo J, Merino A, Briceno C, Soriano S, Buendia P, Calleros L, et al. Carbamylated low-density lipoprotein induces oxidative stress and accelerated senescence in human endothelial progenitor cells. The FASEB Journal. 2011;**25**:1314-1322. DOI: 10.1096/fj.10-173377

[51] Speer T, Owala FO, Holy EW, Zewinger S, Frenzel FL, Stähli BE, et al: Carbamylated low-density lipoprotein induces endothelial disfunction. Eur Heart J. 2014;**35**(43):3021-32

[52] Son JN, Lho Y, Shin S, Kwon S-H, Moon KC, Ha E. Carbamylated low-density lipoprotein increases reactive oxygen species (ROS) and apoptosis via lectin-like oxidized LDL receptor (LOX-1) mediated pathway in human umbilical vein endothelial cells. International Journal of Cardiology. 2011;**146**:428-430. DOI: 10.1016/j.ijcard.2010.10.098

[53] Apostolov EO, Ray D, Savenka AV, Shah SV, Basnakian AG. Chronic uremia stimulates LDL carbamylation and atherosclerosis. American Society of Nephrology. 2010;**21**:1852-1857. DOI: 10.1681/ASN.2010040365

[54] Apostolov EO, Basnakian AG, et al. Carbamylated low-density lipoprotein: Nontraditional risk factor for cardiovascular events in patients with chronic kidney disease. Journal of Renal Nutrition. 2012;**22**:134-138. DOI: 10.1053/j.jrn.2011.10.023

[55] Kirmizis D, Tsiandoulas A, Pangalou M, et al. Validity of plasma fibrinogen, D-dimer, and the von Willebrand factor as markers of cardiovascular morbidity in patients on chronic hemodialysis. Medical science monitor international medical journal of experimental and. Clinical Research. 2006;**12**:55-62

[56] Costa E, Rocha S, Rocha-Pereira P, et al. Cross-talk between inflammation, coagulation/fibrinolysis and vascular access in hemodialysis patients. The Journal of Vascular Access. 2008;**9**(4):248-253

[57] Shibata T, Magari Y, Kamberi P, et al. Significance of urinary fibrin/fibrinogen degradation products (FDP) D- dimer measured by a highly sensitive

ELISA method with a new monoclonal antibody (D-D E72) in various renal diseases. Clinical Nephrology. 1995;**44**(2):91-95

[58] Péquériaux NC, Fijnheer R, Gemen EF, et al. Plasma concentration of von Willebrand factor predicts mortality in patients on chronic renal replacement therapy. Nephrology, Dialysis, Transplantation. 2012;**27**(6):2452-2457

[59] Longenecker C, Klag M, Marcovina S, et al. High lipoprotein(a) levels and small Apolipoprotein(a) size prospectively predict cardiovascular events in dialysis patients. American Society of Nephrology. 2005;**16**:1794-1802

[60] Dieplinger H, Lackner C, Kronenberg F. Elevated plasma concentrations of lipoprotein(a) in patients with end stage renal disease are not related to the size polymorphism of apolipoprotein(a). The Journal of Clinical Investigation. 1993;**91**(2):397-401