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Role of dyslipidemia in impairment of energy metabolism, oxidative stress, inflammation and cardiovascular disease in chronic kidney disease

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Abstract Advanced chronic kidney disease (CKD) results in a constellation of dysregulation of lipid metabolism, oxidative stress, and inflammation which are causally interconnected and participate in a vicious cycle. The CKD-associated lipid disorders are marked by impaired clearance of very low density lipoprotein and chylomicrons, hypertriglyceridemia, formation of small dense low-density lipoprotein (LDL), oxidative modification of LDL, intermediate density lipoprotein and chylomicron remnants, and high-density lipoprotein deficiency and dysfunction. This review provides a brief overview of the role of CKD-induced lipid disorders in the pathogenesis of oxidative stress, inflammation, cardiovascular disease, impaired exercise capacity, cachexia and wasting syndrome.

Keywords End-stage renal disease · Oxidative stress · Impaired exercise capacity · Skeletal muscle · Adipose tissue · Lipid metabolism · Malnutrition

Background

Advanced chronic kidney disease (CKD) results in a triad of oxidative stress, inflammation and dyslipidemia which form a vicious circuit that promotes progression of kidney disease, cachexia, diminished exercise capacity, cardiovascular disease, and numerous other complications [1]. Patients with end-stage renal disease (ESRD) maintained on hemodialysis have elevated serum triglyceride, very

low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), chylomicron remnants, and oxidized lipoproteins. This is frequently accompanied by reduced plasma ApoA1 and high-density lipoprotein (HDL) cholesterol concentrations, and low or normal serum total cholesterol and low-density lipoprotein (LDL) cholesterol concentrations [2–4]. LDL in these patients consists of highly atherogenic small dense particles which contain abnormal levels of residual triglycerides [4–6]. In addition serum level of lipoprotein(a) [Lp(a)], particularly its low molecular forms is increased and contributes to cardiovascular disease in this population [7]. However, due to concomitant genetic or other disorders a minority of ESRD patients have elevated HDL and or LDL cholesterol levels.

Mechanisms of CKD-induced lipid/lipoprotein disorders

Nascent VLDL and chylomicrons are, respectively, packaged by the liver and intestine and released in the circulation for delivery of lipid fuels and construction material to the myocytes, adipocytes and various other cells for generation and storage of energy and incorporation into the cellular structures. Maturation of nascent VLDL and chylomicrons, lipolysis of their triglyceride cargos, conversion of IDL to LDL, and removal of chylomicron remnants by the liver are impaired in CKD [2–4]. Several factors contribute to these abnormalities. Maturation of the nascent VLDL and chylomicrons depends on acquisition of ApoC and ApoE from cholesterol ester-rich HDL-2 which are scarce in CKD [8]. Since ApoE is necessary for endothelial binding of VLDL and chylomicrons and ApoC-II is necessary for activation of lipoprotein lipase (LPL), their defective transfer from HDL limits lipolysis of triglyceride

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contents of VLDL and chylomicron. This is compounded by CKD-induced reduction in skeletal muscle, adipose tissue and myocardial LPL [9–11] which is, in part, due to down-regulation of the adaptor molecule glycosylphosphatidylinositol-anchored binding protein 1 (GPIHBP1) [12]. Consequently deficiencies of LPL and GPIHBP1 in CKD severely impair VLDL and chylomicron metabolism.

After undergoing lipolysis by LPL, VLDL and chylomicrons are transformed to IDL and chylomicron remnants and released into the circulation. Chylomicron remnants and a portion of IDL are then removed by the liver via LDL receptor-related protein (LRP) [13]. However, CKD results in down-regulation of hepatic LRP [14] leading to accumulation of oxidation-prone and atherogenic chylomicron remnants in the plasma.

Normally IDL is converted to cholesterol ester-rich LDL which is readily cleared by the liver via LDL receptor. The IDL conversion to LDL requires removal of its triglyceride cargo and expansion of its cholesterol ester content. This is accomplished by cholesteryl ester transfer protein (CETP)-mediated exchange of triglycerides for cholesterol ester between IDL and HDL2 and hydrolysis of the triglyceride and phospholipid contents of IDL by hepatic lipase. However, although serum CETP level is normal in ESRD patients [15], this process is impaired due to the scarcity of HDL-2 and hepatic lipase deficiency [16–18]. These abnormalities lead to accumulation of IDL and formation of CE-poor, triglyceride-rich small dense LDL which has low binding affinity for LDL receptor and is highly oxidation prone and atherogenic.

A fraction of plasma VLDL is cleared via VLDL receptor-mediated endocytosis by myocytes and adipocytes [19]. CKD results in down-regulation of skeletal muscle and adipose tissue VLDL receptor [20, 21] which can contribute to elevation of plasma VLDL.

Mechanisms of CKD-induced HDL abnormalities

In addition to its role in reverse cholesterol transport, normal HDL limits uptake of oxidized lipoproteins by macrophages, prevents monocyte adhesion/infiltration in the artery wall, exerts antioxidant and anti-inflammatory actions, facilitates endothelial repair and regeneration, and inhibits platelet adhesion. Via these actions, normal HDL protects against atherosclerosis, restores endothelial function, and attenuates oxidative stress and systemic inflammation. HDL cholesterol is reduced, maturation of CE-poor to CE-rich HDL-2 is impaired [8] and antioxidant, anti-inflammatory and reverse cholesterol transport activities of HDL are impaired in most ESRD patients [22, 23]. These abnormalities are due to (a) reduced production and oxidative modification of ApoAI [8, 24, 25] which lead to

HDL deficiency and impaired HDL binding to the gateway of cholesterol efflux (ATP binding cassette A1), (b) upregulation of acyl-CoA cholesterol acyltransferase (ACAT) [26–29] which limits release of intracellular cholesterol, (c) lecithin cholesterol acyltransferase (LCAT) deficiency [30] which impairs HDL maturation, and (d) paraoxonase and glutathione peroxidase deficiencies [28] which limit the ability of HDL to reduce oxidized LDL.

Under normal conditions, CE-rich HDL-2 unloads its cholesterol and triglyceride cargos in the liver by binding to the HDL docking receptor, scavenger receptor-B1 (SRB-1). In contrast the CE-poor HDL particles which constitute the majority of HDL particles in most ESRD patients have low affinity for SRB-1 and high affinity for the hepatic HDL endocytic receptor (ATP synthase beta) which mediates their removal and degradation [31]. Collectively these abnormalities contribute to HDL deficiency and dysfunction in CKD. In addition HDL-2 plays a major role in metabolism of chylomicrons and VLDL by donating ApoE and ApoC and by enabling CETP-mediated exchange of cholesterol ester for triglyceride which is essential for IDL conversion to LDL. Thus, CKD-induced abnormalities of HDL structure and function have a wide range of adverse consequences far beyond the impairment of the reverse cholesterol transport process.

Role of lipid disorders in wasting and impaired energy metabolism

In addition to causing hypertriglyceridemia, impaired clearance of triglyceride-rich lipoproteins contributes to cachexia, malnutrition, reduced exercise capacity, and altered energy metabolism in CKD patients [1]. In this context the CKD-induced LPL and VLDL receptor deficiencies limit the supplies of lipid fuel and construction material to the skeletal muscles, myocardium and adipose tissues [32]. Limitation of available lipid fuel can, in turn, contribute to muscle weakness, diminished exercise capacity and myocardial dysfunction which are common in CKD patients. Similarly the reduction in delivery of fatty acids to the adipose tissue limits the capacity to store energy and contributes to weight loss, wasting and cachexia in this population.

Role of dyslipidemia in oxidative stress and systemic inflammation

The scarcity of cholesterol ester-rich HDL together with LPL, hepatic lipase and LRP deficiencies in CKD leads to elevation of plasma IDL and chylomicron remnants and

generation of small dense LDL. The small dense LDL, chylomicron remnants, and IDL are highly prone to oxidation which is accelerated by the CKD-associated HDL deficiency and dysfunction and oxidative stress. This phenomenon accounts for elevated plasma oxidized LDL and lipid peroxidation products in CKD patients. Formation and accumulation of the oxidized forms of LDL, IDL, and chylomicron remnants, in turn, amplifies inflammation by binding to oxidized LDL receptor-1 (LOX-1), scavenger receptor A-1 (SRA-1) and oxidized phospholipid receptors on monocytes and macrophages, and the consequent release of pro-inflammatory cytokines and chemokines [33, 34]. By virtue of their presence in the circulating blood, these pro-inflammatory particles serve as vehicles which readily spread inflammation throughout the body. Moreover, via lipid peroxidation chain reaction, these floating oxidized particles contribute to dissemination of oxidative stress in the CKD patients. Therefore, the alteration of lipid metabolism contributes to CKD-associated systemic inflammation and oxidative stress which promote cardiovascular disease, CKD progression, anemia, cachexia, malnutrition and various other morbidities.

Role of lipid disorders in atherosclerosis

Patients with CKD exhibit accelerated atherosclerosis and cardiovascular disease which are the primary cause of death in this population [35, 36]. Besides the classic risk factors for atherosclerosis several other conditions influence the development of cardiovascular disease in CKD/ESRD patients. In particular, ESRD patients exhibit medial calcification of the arteries, arteriosclerosis, endothelial dysfunction, cardiomyocyte/capillary mismatch, dilated cardiomyopathy, myocardial fibrosis, and sudden cardiac death [37–39]. These events are primarily driven by phosphate retention, reduced nitric oxide availability (due to oxidative stress and elevation of asymmetrical dimethylarginine), hypertension, hypervolemia, electrolyte imbalance, myocardial ischemia and fibrosis, and drug toxicities among other conditions.

The primary cause of accelerated atherosclerosis in CKD is oxidative stress and inflammation [40]. In contrast to the general population low serum cholesterol level is associated with increased risk of cardiovascular disease and overall mortality [41] whereas higher serum total and LDL cholesterol values are associated with greater survival in the ESRD population [42]. The lack of the significant role of cholesterol level, per se, as a cause of atherosclerotic cardiovascular disease in the majority of the ESRD population is clearly illustrated by the failure of randomized clinical trials of various statins to lower cardiovascular

events in hemodialysis patients [43–45]. The association between low serum cholesterol with higher mortality in this population is undoubtedly related to systemic inflammation which has a cholesterol-lowering effect. Conditions that increase influx or impair efflux of cholesterol in the macrophages can lead to atherosclerosis and cardiovascular disease independent of plasma cholesterol level. The influx of cholesterol in the macrophages in the ESRD population is facilitated by oxidation of chylomicron remnants, IDL and small dense LDL and defective HDL antioxidant and anti-inflammatory properties. This is compounded by impaired HDL-mediated reverse cholesterol transport due to oxidation of apoA1 (which interferes with HDL binding to ABCA1, the gateway of cholesterol efflux), LCAT deficiency (which limits cholesterol carrying capacity of HDL), and upregulation of ACAT (which favors retention of cholesterol ester within the artery wall). The constellation of these abnormalities drives the relentless progression of the atherogenic process in CKD patients independent of plasma cholesterol level.

In conclusion, besides promoting cardiovascular disease the CKD-induced dysregulation of lipid metabolism plays a major role in the pathogenesis of oxidative stress, inflammation, CKD progression, impaired exercise capacity, cachexia, and wasting syndrome in this population.

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