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Review

Mechanisms and consequences of hypertriglyceridemia and cellular lipid accumulation in chronic kidney disease and metabolic syndrome

Hyun Soon Lee
Department of Pathology, Seoul National University College of Medicine, Seoul, Korea

Summary. Hypertriglyceridemia and intracellular lipid overload are commonly present in both the chronic kidney disease (CKD) and metabolic syndrome. Hypertriglyceridemia in the metabolic syndrome arises mostly from increased lipoprotein synthesis, while that in the CKD is mainly caused by decreased catabolism. In metabolic syndrome, enhanced plasma levels of free fatty acids and triglyceride (TG) may lead to intracellular fatty acid accumulation in the kidney. However, the mechanisms by which intracellular lipid accumulation occurs in the dieased glomeruli have not been established. I provide evidence that binding/uptake of TG-rich very low-density lipoprotein by glomerular cells is increased in CKD, leading to increased endocytic accumulation of TG. I also provide evidence that cellular damage by fatty acid accumulation in the kidney is particularly severe in podocytes, leading to apoptosis and resulting in glomerulosclerosis. Collectively, these data bring new mechanistic insights into cellular lipid overload and lipotoxicity in CKD.

Key words: Free fatty acids, Glomerulosclerosis, Lipogenesis, Lipolysis, Lipotoxicity

Introduction

Lipoprotein abnormalities are common features of nephrotic syndrome and uremia. Dyslipidemia and renal accumulation of lipids may play a role in the progression of original renal disease to glomerulosclerosis and tubulointerstitial fibrosis (Joles et al., 2000; Keane, 2000; Okamura et al., 2007; Lee and Song, 2009; Ruan et al., 2009). Furthermore, the presence of renal dyslipidemia signifies an increased risk for cardiovascular morbidity. Moorhead et al. (1982) initially suggested that nephrotic hyperlipidemia resulting from a compensatory increase in hepatic synthesis of lipoproteins could aggravate glomerular and tubulointerstitial disease. Progression of chronic kidney disease (CKD) (Samuelsson et al., 1998; Ruan et al., 2009) or intraglomerular lipid deposition (Lee et al., 1991; Joles et al., 1995), however, is independent of hypercholesterolemia. Rather, hypertriglyceridemia is emerging as a risk factor for progression of glomerular disease (Samuelsson et al., 1998; Syrianen et al., 2000; Tozawa et al., 2002; Lee et al., 2009; Rutledge et al., 2010). Furthermore, hypertriglyceridemia, combined with the accumulation of partially catabolized triglyceride (TG)-rich lipoproteins in the form of remnant lipoprotein particles, is considered to be highly atherogenic (Cohn et al., 1995; Masuda et al., 2009).

Metabolic syndrome, according to the new International Diabetes Federation definition, is defined as having central obesity plus any two of four additional factors, such as hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hypertension, and hyperglycaemia (Alberti et al., 2006). Metabolic syndrome is considered to be a risk factor in the development of CKD (Chen et al., 2004). In many regards, dyslipidemia in metabolic syndrome resembles that of CKD, which is characterized by hypertriglyceridemia and decreased plasma levels of HDL cholesterol (Barrett and Watts, 2003; Barista et al., 2004). Hypertriglyceridemia in metabolic syndrome arises mostly from increased lipoprotein synthesis, in which high plasma TG and free fatty acid levels lead to increased import of free fatty acids into non-adipose tissues, resulting in generalized steatosis (Unger, 2002, 2003; Unger et al., 2010). By contrast, hypertriglyceridemia in nephrotic syndrome or CKD is mainly caused by decreased catabolism (Furukawa et al., 1990;

Offprint requests to: Hyun Soon Lee, M.D., Department of Pathology, Seoul National University College of Medicine, Chongno-gu, Yongon-dong 28, Seoul 110-799, Korea. e-mail: hyunsoon@plaza.snu.ac.kr

Yoshino et al., 1993; Hirano et al., 1994; de Sain-van der Velden et al., 1998; Shearer et al., 2001), with reduced plasma levels of free fatty acids (Shearer et al., 2001). Mayrhofer et al. (2009) recently reported that impaired fatty acid utilization as shown in the metabolic syndrome may contribute to intracellular fatty acid accumulation in damaged podocytes of rats with puromycin aminonucleoside (PA) nephrosis. In fact, intracellular lipid accumulation is frequently detected by electron microscopy in the diseased glomeruli (Lee et al., 1991; Lee and Lee, 1993). So far, the mechanisms by which intracellular lipid accumulation occurs in the diseased glomeruli have not been established. Nor is it clear whether a similar alteration in renal lipid metabolism, as shown in metabolic syndrome, could mediate the progression of CKD.

This review will discuss the recent findings on the mechanisms and consequences of hypertriglyceridemia and lipid overload on kidney and cell function in CKD and metabolic syndrome. The relationship of experimental animal models and cell culture studies to human pathophysiology will also be discussed.

Lipoprotein metabolism

In the plasma, lipids are carried by water-soluble particles known as lipoproteins. Lipoproteins consist of an outer envelope of free cholesterol, phospholipids, and apolipoproteins (apo) surrounding a disorganized core of hydrophobic cholesteryl esters and TG. Lipoprotein transport can be broken down into three major pathways: the exogenous pathway for transport of dietary lipids to the liver and periphery, the endogenous pathway for transport of hepatically synthesized lipids to the periphery, and reverse cholesterol transport pathway via HDL.

In the exogenous pathway, fatty acids and monoacylglycerol are taken up by the intestinal cells, converted back to TG, and together with $apoB_{48}$ packaged into chylomicrons. In the circulation, nascent chylomicron acquires apoC-II and apoE from HDL-2, which are necessary for activation of lipoprotein lipase (LpL) and chylomicron binding to the endothelial surface, respectively. Chylomicron core TGs are hydrolyzed to free fatty acids and remnant particles on the vascular endothelium by LpL (Santamarina-Fojo and Haudenschild, 2000). The chylomicron remnants are rapidly taken up by hepatocytes through a process mediated primarily by apoE. As TGs are removed, the resultant surface lipids and apoproteins transfer to HDL particles.

In the endogenous pathway, very low-density lipoprotein (VLDL) is formed in the liver from endogenous TG and cholesterol in combination with $apoB_{100}$, apoE, and apoC-II. In the circulation, VLDL TGs are catabolized to free fatty acids and remnant particles on the vascular endothelium by LpL. Smaller VLDL and intermediate-density lipoprotein (IDL) are referred to as VLDL remnants. About half of the VLDL remnants are cleared directly by the liver through apoE-mediated processes. The remainder is converted to low-density lipoprotein (LDL) containing only $apoB_{100}$. LDL receptor binds $apoB_{100}$-containing lipoproteins, LDL and VLDL. There is a direct link between functional LDL receptor expression and $apoB_{100}$ degradation. LDL receptor mediates even presecretory degradation of the major VLDL protein, $apoB_{100}$, inhibiting its secretion (Twisk et al., 2000; Gillian-Daniel et al., 2002). In addition, the LDL receptor binds and internalizes apoE-containing lipoproteins, ß-migrating VLDL (ß-VLDL), and a cholesterol-induced HDL particle (Mehta et al., 1991). VLDL receptor, one of the LDL receptor family members, is implicated in both neuronal development and lipid metabolism (Hong et al., 2010), and binds apoE-containing lipoproteins, VLDL, ß-VLDL, and IDL (Takahashi et al., 1992).

Reverse cholesterol transport recycles cholesterol in the periphery back to the liver via HDL. In the peripheral tissues, HDL removes surplus cholesterol via ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1) whose expression is regulated by liver X receptor (LXR). ABCA1 and ABCG1 mediate transfer of cellular cholesterol and phospholipids to lipid-poor HDL and mature HDL, respectively (Oram and Vaughan, 2006).

Lipid homeostasis

The primary, essential role of fatty acids is to form the phospholipid bilayers of the cell membranes and the phospholipid messengers that transmit vital intracellular signals. In mammalian cells, free fatty acids are generated through the de novo synthetic pathway and are liberated when TGs and phospholipids are hydrolyzed by cellular lipases.

Free fatty acids can also be imported into mammalian cells by both protein- and non-protein-mediated mechanisms, either when cellular demands are high or when extracellular free fatty acid concentrations are high (Schaffer, 2002; Huang et al., 2009).

Fatty acids are used for mitochondrial energy conversion (van der Vusse et al., 2002). On activation to their respective coenzyme A (CoA) esters in cytoplasm, fatty acids are degraded to acetyl CoA in the mitochondrial matrix by ß-oxidation, which functions either to directly produce ATP or to produce ketone bodies for ATP generation (Bartlett and Eaton, 2004).

Regulation of intracellular fatty acid homeostasis

Normal cellular fatty acid homeostasis reflects a balance between processes that generate or deliver fatty acids and processes that utilize these molecules. Long-chain fatty acids (LCFAs) are the major source of energy in non-adipose cells, and imbalance in their uptake and oxidation may elicit lipotoxic effects.

Lipogenesis

Sterol regulatory element binding proteins (SREBPs) have been shown to be master regulators of lipid homeostasis. SREBPs are a family of transcription factors that reside in the membrane and, when proteolytically cleaved, translocate to the nucleus and stimulate expression of the target genes. The three SREBP isoforms, SREBP-1a, SREBP-1c and SREBP-2, have different roles in lipid synthesis. In vivo studies using knockout and transgenic mice suggest that SREBP-1c is involved in fatty acid and TG synthesis and insulin-induced glucose metabolism (particularly in lipogenesis), whereas SREBP-2 activates the LDL receptor gene and various genes required for cholesterol synthesis. The SREBP-1a isoform seems to be implicated in both pathways (Horton et al., 2002). Target lipogenic enzymes regulated by SREBP-1c include acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), which together produce palmitate (C16:0). Other SREBP-1c-responsive genes encode an enzyme of long chain fatty acyl elongase, which converts palmitate to stearate (C18:0); stearoyl-CoA desaturase (SCD), which converts stearate to oleate (C18:1); and glycerol-3-phosphate acyl transferase (GPAT), the first committed enzyme in TG and phospholipid synthesis (Horton et al., 2002) (Fig. 1). SREBP-2-responsive genes in the cholesterol synthetic pathway include those for the enzymes 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthase, HMG-CoA reductase, and farnesyl pyrophosphate, geranylgeranyl pyrophosphate and squalene synthase (Horton et al., 2002) (Fig. 1).

Carbohydrate response element binding protein (chREBP) functions as a regulator of de novo lipid synthesis in response to elevated serum glucose in the liver (Uyeda and Repa, 2006).

Peroxisome proliferator-activated receptors (PPAR) are ligand-activated nuclear hormone receptors and transcription factors. Three PPAR isoforms, PPAR-α, -ß/δ, and -γ, have been identified. PPAR-γ is a key transcription factor in adipogenesis, and overactive PPAR-γ may contribute to the pathogenesis of obesity. PPAR-γ regulates key cholesterol synthesis genes in alveolar macrophages (Baker et al., 2010). PPAR-γ agonists, such as thiazolidinediones, activate PPAR-γ, and seem to have beneficial effects in CKD (Fogo, 2011).

In addition, LXR activators are shown to stimulate lipogenesis via SREBP-1c, leading to liver steatosis and hypertriglyceridemia, although their agonists possess antidiabetic properties (Baranowski, 2008).

Fatty acid transport and uptake

Serum free fatty acids are liberated by LpL-mediated hydrolysis of TG, and they are bound to albumin for cellular delivery. After dissociation from albumin, they enter the endothelial cell layer and basement membrane. At high extracellular free LCFA concentrations, import occurs by spontaneous flip-flop. At low concentrations, however, protein-mediated LCFA permeation occurs (Schaffer, 2002), by interaction of the free fatty acids with fatty acid transport protein complexes with or without previous binding to cell-surface proteins, such as fatty acid translocase (FAT/CD36) (Doege and Stahl, 2006; Masuda et al., 2009). Recently, Hagberg et al. (2010) reported that vascular endothelial growth factor B targets the local endothelium and promotes fatty acid

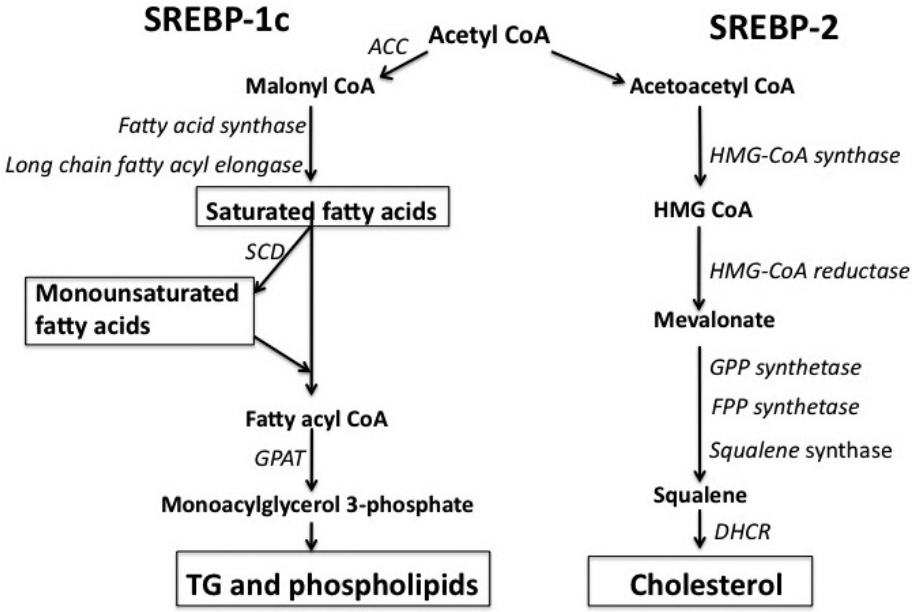

Fig. 1. Biosynthetic pathways used to generate fatty acids, triglyceride (TG), and cholesterol. Sterol regulatory element binding protein (SREBP)-1c preferentially activates genes of fatty acid and TG synthesis, whereas SREBP-2 preferentially activates genes of cholesterol synthesis. ACC, acetyl-CoA carboxylase; DHCR, 7-dehydrocholesterol reductase; FPP, farnesyl pyrophosphate; GPAT, glycerol-3-phosphate acyltransferase; GPP, geranyl-geranyl pyrophosphate; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; SCD, stearoyl-CoA desaturase.

transport from the blood, across the endothelial cell layer, to fat-burning tissues.

ß-oxidation

LCFAs are esterifed or are transported into the mictochondria for oxidation and subsequent energy production. The carnitine palmitoyltransferase (CPT) system is mainly involved in the movement of LCFAs across the mitochondrial membranes. CPT1 catalyzes the trans-esterification of fatty acyl-CoA to acylcarnitine. The acylcarnitine can then be translocated to the inner mitochodrial membrane and finally is regenerated to acyl-CoA by the latent CPTII in the mitochondrial matrix (Kerner and Hoppel, 2000). PPAR-α is highly expressed in tissues that posses high mitochondrial and ß-oxidation activity, such as liver, renal cortex and heart. It is the transcription factor for enzymes of fatty acid oxidation, CPT1 and acyl-CoA oxidase (ACO). PPAR-α activation also increases fatty acid uptake, decreases TG level, and promotes TG-VLDL lipolysis, exerting beneficial metabolic effects on lipid metabolism (Guan, 2004).

Role of leptin

Leptin is an adipocyte-derived liporegulatory hormone that controls lipid homeostasis via central nervous system receptors during periods of overnutrition to attenuate appetite (Ahima and Flier, 2000; Unger, 2002). Leptin stimulates fatty acid oxidation in non-adipose tissues, so as to minimize ectopic fatty acid spillover (Unger et al., 2010). It also downregulates SREBP-1c, thereby reducing the expression of lipogenic enzymes, such as ACC, FAS, and GPAT (Unger, 2003). By promoting fatty acid oxidation and deterring lipogenesis, hyperleptinemia maintains the non-adipose tissue content of lipids at a near-normal level. When this capacity is exceeded, resultant lipid-induced cellular dysfunction or cell death is termed lipotoxicity (Unger, 2002, 2003; Unger et al., 2010).

Disorders of lipid homeostasis in association with overnutrition: metabolic syndrome

Mutations of the leptin or leptin receptor genes

Obese *fa/fa* Zucker rats with mutation of the fa-gene, encoding the leptin receptor, are considered as a model for metabolic syndrome (Iida et al., 1996; Phillips et al., 1996). VLDL represents the predominant form of lipoprotein in the Zucker *fa/fa* rats with progressive elevation of serum free fatty acid and TG levels (Zhou et al., 2000). Lack of a functional leptin receptor in *db/db* mice (Lee et al., 1996) also results in extreme obesity due to hyperphagia and type 2 diabetes. Plasma levels of TG and cholesterol are increased in *db/db* mice (Deb et al., 2010).

In human subjects with hyperphagia and severe early-onset obesity, the prevalence of pathogenic leptin receptor mutations is not so rare (Farooqi et al., 2007).

Diet-induced obesity

Diet-induced obesity is considered a major generator of metabolic syndrome. Whereas adipocytes have a unique capacity to store excess free fatty acids in the form of TG in lipid droplets, non-adipose tissues, such as cardiac myocytes and pancreatic ß-cells, have a limited capacity for storage of lipids. Increased abdominal fat mass yields high circulating free fatty acids, which drives intracellular fatty acid accumulation in non-adipose tissues, causing insulin resistance and lipotoxicity (Bagby, 2004).

In patients or animals with diet-induced obesity, renal expression of SREBP-1 and/or SREBP-2 is increased, together with renal accumulation of lipids and glomerulosclerosis (Sun et al., 2002; Jiang et al., 2005; Wu et al., 2006; Kume et al., 2007). In SREBP-1c$^{-/-}$ mice with high fat diet, the renal accumulation of TG was prevented, suggesting that renal SREBP-1c-mediated de novo lipogenesis is a major contributor to renal lipid accumulation in diet-induced obesity (Jiang et al., 2005). Furthermore, fatty acid uptake is generally increased in metabolic syndrome (Karmi et al., 2010), together with decreased cellular ß-oxidation (Mancuso et al., 2010). Normally, early in obesity, adipocytes increase leptin secretion and, therefore, oxidative metabolism of surplus lipids is upregulated in non-adipose tissues (Unger, 2003). Long-term exposure of leptin, however, decreased ß-oxidation, despite increased uptake of fatty acids in cardiomyocytes, leading to intracellular lipid accumulation (Palanivel et al., 2006).

In summary, the elevation of circulating free fatty acid and TG levels, together with increased fatty acid uptake and impaired intracellular fatty acid oxidation may lead to intracellular fatty acid accumulation in non-adipose tissues, including renal cells in the metabolic syndrome (Fig. 2).

Alterations in lipid metabolism in nephrotic syndrome and chronic renal failure

In nephrotic patients, levels of LDL, VLDL and IDL cholesterol are frequently increased, while HDL is decreased (Barista et al., 2004). The typical features of CKD-associated dyslipidemia are high levels of plasma TGs and decreased levels of HDL-cholesterol. Chronic renal failure (CRF) is commonly associated with hypertriglyceridemia and elevated plasma VLDL level (Attman et al., 1993).

Elevated TG levels can be associated with the formation of small dense LDL particles (Berneis et al., 2009). Reduced clearance and increased plasma levels of small dense LDL particles facilitates their entrance into arterial walls, where accelerated oxidation of small dense LDL causes renal and vascular damage due to reduced antioxidant activity of these particles (Rizzo et

al., 2009).

Mechanisms of hypertriglyceridemia in nephrotic syndrome and CRF

Nephrotic syndrome

Although initial serum TG levels were increased in nephrotic rats, TG synthesis was actually reduced as compared with controls when mean VLDL TG secretion rates were measured using Triton WR 1339 (Shearer et al., 2001). Thus, increased TG synthesis does not contribute to hypertriglyceridemia in nephrotic rats (Yoshino et al., 1993; Shearer et al., 2001). Hypertriglyceridemia in nephrotic syndrome is primarily a result of decreased catabolism (Furukawa et al., 1990; Yoshino et al., 1993; Hirano et al., 1994; de Sain-van der Velden et al., 1998; Shearer et al., 2001).

VLDL is hydrolyzed by LpL on the vascular endothelium, releasing free fatty acids. The heparin-releasable or endothelial-bound LpL pool is greatly reduced in nephrotic syndrome. Nagase analbuminemic rats, which cannot synthesize albumin, exhibit some aspects of nephrotic syndrome, despite a lack of proteinuria, including elevated plasma TG and cholesterol and reduced heparin-releasable LpL (Davies et al., 1990; Shearer and Kaysen, 2006). Thus, hypoalbuminemia in nephrotic syndrome seems to reduce the biologically active LpL pool, contributing to defective VLDL catabolism (Shearer et al., 2001; Shearer and Kaysen, 2006).

In addition, proteinuria alters the structure of VLDL and HDL. The lipolytic rate for nephrotic VLDL by LpL is significantly lower than that for normal VLDL (Furukawa et al., 1990). The low lipolytic rate of VLDL-TG improved when VLDL from nephrotic rats was preincubated with HDL from normal rats (Furukawa et al., 1990). VLDL acquires apoE from HDL, which is necessary for VLDL binding to the endothelial surface. HDL from nephrotic rats is poor in apoE. Proteinuria appears to cause reduced apoE in HDL in nephrotic rats, resulting in poor binding of VLDL to endothelial-bound LpL and reduced TG lipolysis, contributing to hypertriglyceridemia (Shearer et al., 2001). In Imai rats with features of nephrotic syndrome, reduced LpL activity and spontaneous focal segmental glomerulosclerosis (FSGS) formation, amelioration of proteinuria can slow progression of renal disease by restoration of LpL activity and VLDL handling (Sato et al., 2003).

An impaired catabolism of VLDL apoB_{100} may also play an important role in nephrotic hyper-triglyceridemia (de Sain-van der Velden et al., 1998).

Liang and Vaziri (1997) reported that VLDL receptor levels are reduced in nephrotic animals, suggesting that the reduced endothelial binding of lipoproteins to VLDL receptor contributes to elevated serum TG. VLDL receptor deficient mice, however, showed normal plasma lipoprotein levels on a normal chow diet (Frykman et al., 1995; Goudriaan et al., 2001, 2004), suggesting that VLDL receptor may not be actively involved in VLDL uptake. Furthermore, VLDL particles are removed through the action of LDL receptors, and VLDL receptor may instead play a role in the delivery of VLDL-derived fatty acids to peripheral tissues (Goudriaan et al., 2001). In this regard, a reduced VLDL receptor number may not be closely related to hypertriglyceridemia in nephrotic animals.

Together, hypertriglyceridemia in nephrotic syndrome appears to be caused by decreased clearance of VLDL resulting from decreased endothelial-bound LpL and proteinuria-induced reduced apoE in HDL, while the VLDL receptor-mediated process may not play an important role in VLDL clearance (Fig. 2, Table 1).

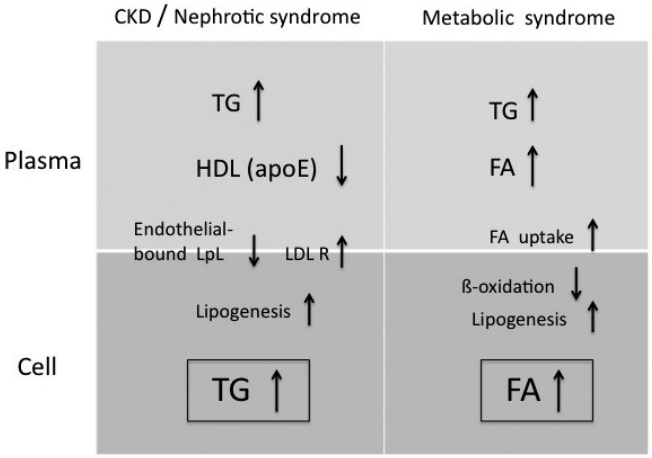

Fig. 2. Mechanisms of hypertriglyceridemia and intracellular lipid accumulation in chronic kidney disease (CKD)/nephrotic syndrome and metabolic syndrome. In nephrotic syndrome, decreased endothelial-bound lipoprotein lipase (LpL) and reduced apolipoprotein E (apoE) in high-density lipoprotein (HDL) may lead to decreased lipolysis of triglyceride (TG), resulting in hypertriglyceridemia. Increased uptake of TG-rich very low-dense lipoprotein (VLDL) via low-dense lipoprotein receptors (LDL R), as with enhanced lipogenesis by glomerular cells in CKD may lead to endocytic accumulation of TG. In the metabolic syndrome, however, elevation of circulating free fatty acid and TG levels, together with increased lipid synthesis and fatty acid uptake and decreased ß-oxidation may lead to intracellular fatty acid accumulation in glomerular cells.

CRF

Reduced enzyme activity of LpL in humans and animals with CRF may lead to the decreased catabolism of TG-rich lipoproteins (Attman et al., 1993; Vaziri and Liang, 1996). Furthermore, CRF causes a true LpL deficiency (Vaziri and Liang, 1996; Vaziri, 2006). A decrease in LpL activity, however, may not be a prerequisite for the hypertriglyceridemia of uremia (Arnandottir et al., 1995). Expression of fatty acid-producing enzymes is increased in the white adipose tissue or remnant kidney of uremic rats, suggesting that enhanced production of fatty acid or TG contributes to uremic hypertriglyceridemia (Szolkiewicz et al., 2002;

Rutkowski et al., 2003; Korczyska et al., 2004; Kim et al., 2009). In fact, endogenous fatty acid synthesis is markedly increased in LpL-deficient mice, possibly as a compensatory response to diminished fatty acid entry into the adipose tissue (Weinstock et al., 1997).

To sum up, hypertriglyceridemia in CRF may be caused by reduced LpL activity or increased synthesis of fatty acid and TG (Fig. 2).

Mechanisms of intracellular lipid overload in nephrotic syndrome and CKD

Intracellular lipid accumulation is commonly present in the diseased glomeruli (Lee et al., 1991; Lee and Lee, 1993). Furthermore, oxidized LDL (Ox-LDL) is demonstrated in the glomeruli of patients with nephrotic syndrome and CKD (Lee and Kim, 1998). Murine mesangial cells have a large number of specific receptors for Ox-LDL, generating foam cells. In contrast, the receptors for Ox-LDL are almost negligible in human mesangial cells (Lee and Koh, 1994). In this regard, reactive aldehydes within the Ox-LDL, which react directly with matrix tissue or cell surface proteins (Uchida, 2000), seem to be responsible for the effects of Ox-LDL on the oxidative stress pathway in human mesangial cells (Lee and Song, 2009).

In a variety of experimental renal diseases, hypercholesterolemia aggravates glomerular and interstitial macrophage accumulation (Lee et al., 1997; Okamura et al., 2007). Macrophages have a large number of scavenger receptors and can internalize substantial quantities of cholesterol ester from Ox-LDL in diseased glomeruli and interstitium, leading to foam cell formation. Once converted to foam cells, internalized lipid peroxide products can activate the cells to produce inflammatory cytokines, chemokines, and growth factors, culminating in renal fibrosis (Abrass, 2004; Lee and Song, 2009).

In CKD or nephrotic syndrome, liberation of free fatty acids from TG lipolysis is reduced in plasma, yet several mechanisms may be responsible for lipid overload in the glomerular cells.

CKD

CKD is associated with low-grade, long-term and chronic inflammatory stress. Elevated plasma levels of cytokines are often associated with CKD (Deboer et al., 2008; Ruan et al., 2009). Inflammatory cytokines, interleukin-1ß and tumor necrosis factor-α, induced enhanced levels of nuclear SREBP-1 protein or SREBP-2 mRNA, and LDL receptor mRNA overexpression, as

Table 1. Proposed mechanisms for hypertriglyceridemia in nephrotic syndrome.

Proposed mechanisms	References
Low lipolytic rate of VLDL-TG, due to	
-reduced endothelial-bound LpL	Davies et al. (1990); Shearer et al. (2001); Shearer and Kaysen (2006)
-reduced apoE in HDL	Furukawa et al. (1990); Shearer et al. (2001)
Catabolic defect of VLDL $apoB_{100}$	de Sain-van der Velden et al. (1998)
Reduced VLDL receptor levels	Liang and Vaziri (1997)

apo, apolipoprotein; HDL, high-density lipoprotein; LpL, lipoprotein lipase; TG, triglyceride; VLDL, very low-density lipoprotein.

Table 2. Proposed mechanisms for lipid accumulation in glomerular cells in chronic kidney disease/nephrotic syndrome.

Mesangial cells or podocytes	References
Increased LDL receptor expression	Ruan et al. (2001); Chen et al. (2007)
Increased binding of VLDL to LDL receptor	Dergunov et al. (2000)
Increased uptake of triglyceride	Berfield and Abrass (2002); Berfield et al. (2006)
Increased lipogenesis	
-increased SREBP-1, SREBP-2	Ruan et al. (2001); Chen et al. (2007)
-increased FAS, chREBP, ACC	Kim et al. (2009)
-increased HMG-CoA reductase	Johnson et al. (2003)
Increased fatty acid uptake	Mayrhofer et al. (2009)
Reduced ß-oxidation	Mayrhofer et al. (2009)

ACC, acetyl-CoA carboxylase; chREBP, carbohydrate response element binding protein; FAS, fatty acid synthase; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; LDL, low-density lipoprotein; SREBP, sterol regulatory element binding protein; VLDL, very low-density lipoprotein.

well as intracellular lipid accumulation in cultured human mesangial cells (Ruan et al., 2001; Chen et al., 2007). SREBPs stimulate LDL receptor expression, in addition to increased lipid synthesis (Brown and Goldstein, 1997). Thus, inflammatory cytokine-induced SREBPs may stimulate both lipid synthesis and LDL receptor expression by mesangial cells leading to foam cell formation in CKD. Although Ruan et al. (2001) suggested that unregulated intracellular accumulation of LDL is responsible for cytokine-induced foam cell formation, the proposal was not confirmed due to lack of binding and uptake experiments.

Ruan et al. (1999) also reported that phorbol myristate acetate and angiotensin II (Ang II) induced scavenger receptors in cultured human mesangial cells. These observations suggest that human mesangial cells may express an inducible scavenger receptor during inflammation, through which Ox-LDL can accumulate in these cells in CKD.

Insulin-like growth factor-1 (IGF-1) has been implicated as a cytokine that contributes to the development of glomerulosclerosis. Abrass and colleagues observed that rat mesangial cells cultured with IGF-1 become foam cells containing neutral lipids (Berfield and Abrass, 2002; Berfield et al., 2006). Their first attempt to demonstrate the LDL receptor- or scavenger receptor-mediated increased uptake of cholesterol by these cells failed. Instead, they found that IGF-1 induces heavy accumulation of TG in mesangial cells (Berfield et al., 2006). Both LDL and VLDL from the circulation are removed by LDL receptor (Horton et al., 2002). When plasma levels of TG are high, affinity of LDL to the LDL receptor is decreased, while binding of hypertriglyceridemic VLDL to the LDL receptor is increased (Dergunov et al., 2000). Thus, LDL receptor overexpression and hypertriglyceridemia in CKD may lead to increased binding and uptake of TG-rich VLDL by glomerular cells, resulting in enhanced endocytic accumulation of TG from VLDL (Fig. 2).

In the remnant kidney of uremic rats, fatty acid biosynthesis is increased with upregulation of FAS, chREBP and ACC (Kim et al., 2009), which may contribute to intracellular fatty acid overload.

In summary, increased uptake of TG-rich VLDL via LDL receptor and enhanced lipid synthesis by glomerular cells in CKD may lead to intracellular lipid accumulation, mainly of TG (Fig. 2; Table 2).

Nephrotic syndrome

In the early stage of PA nephrosis, enzymes of the mitochondrial ß-oxidation pathway are downregulated, while expression of CD36 and albumin precursor is increased. Similar results are also obtained in PA-treated podocytes in culture, in which CD36 is predominantly localized to the plasma membrane (Mayrhofer et al., 2009). In murine cardiomyocytes, leptin immediately increased fatty acid uptake and oxidation, yet oxidation decreased over time, leading to intracellular lipid accumulation (Palanivel et al., 2006). Thus, similar to metabolic syndrome, enhanced fatty acid uptake together with depressed ß-oxidation in damaged podocytes in the nephrotic syndrome may result in intracellular lipid accumulation (Mayrhofer et al., 2009).

HMG-CoA reductase is a key enzyme that mediates cholesterol synthesis. When the intracellular levels of cholesterol are increased, the activity of HMG-CoA reductase is decreased. In experimental glomerulopathy, however, despite increased renal cortical cholesterol levels, expression of HMG-CoA reductase is significantly increased, contributing to a cell cholesterol overload state (Johnson et al., 2003).

Together, increased uptake of fatty acid and lipid synthesis, as well as decreased ß-oxidation by damaged glomerular cells, may contribute to intracellular lipid accumulation in nephrotic syndrome (Table 2).

Pathophysiology of lipid overload in kidney

Role of cellular TG accumulation in the diseased glomeruli

Cellular TG accumulation itself is not initially toxic. Rather, TG may serve a cytoprotective role in lipid overload states in the heart (Liu et al., 2009). In pathologic states, lipotoxicity may occur over time, when either the cellular capacity for TG storage is exceeded or when TG pools are hydrolyzed, resulting in increased cellular free fatty acid levels (Listenberger et al., 2003).

In cultured mesangial cells, TG-rich VLDL induces proliferation and cytokine expression (Stevenson et al., 2001). TG-rich mesangial foam cells show impaired contraction in response to Ang II with abnormal phagocytosis (Berfield and Abrass, 2002; Berfield et al., 2006). The role of cellular TG accumulation in the diseased glomeruli is not clearly determined, yet it is conceivable that long-term accumulation of TG in the glomerular cells may exert lipotoxicity due to degradation of TG molecules to free fatty acids, which may contribute to progression of CKD.

Fatty acid-induced glomerular pathology

Lipotoxicity in diet-induced obesity is caused by excess intracellular fatty acid and its metabolite. In obese *fa/fa* Zucker rats, progressive renal disease is characterized by early injury to podocytes, but not mesangial cells (Coimbra et al., 2000), and this podocyte injury eventually leads to progression of FSGS (Gassler et al., 2001). In patients or animals with diet-induced obesity, high fat diet induces glomerular lipid accumulation and glomerulosclerosis (Sun et al., 2002; Jiang et al., 2005; Wu et al., 2006; Kume et al., 2007). Severe obesity in humans is associated with the eventual development of FSGS (Kambham et al., 2001; Praga et al., 2001).

Fatty acid-induced tubulointerstitial injury

Rats injected with free fatty acid-carrying bovine serum albumin had significantly greater macrophage infiltration in the outer cortex, tubular cell apoptosis, and cortical cell proliferation than control rats. Thus, free fatty acids carried by filtered albumin in the setting of proteinuria appear to play a role in the development of tubulointerstitial injury (Thomas et al., 2002).

Ang II increased plasma TG levels (Ran et al., 2004) and renal expression of SREBP-1 and FAS, together with transforming growth factor-ß1 mRNA expression in lipid-positive tubular epithelial cells in rats (Saito et al., 2005). These observations suggest that there is a link between Ang II and TG/fatty acid and tubular damage.

Mechanisms of fatty acid-induced cell injury and glomerulosclerosis

Role of ceramide

Increased intracellular fatty acids lead to nonoxidative metabolic pathway, such as ceramide synthesis in non-adipose tissues. Ceramide is a potent regulator of cell proliferation, activation, and apoptosis, and plays an important role in lipoprotein aggregation and foam cell formation in atherosclerosis (Williams and Tabas, 1995). Ceramide attenuates endothelium-dependent vasorelaxation in small coronary arteries via NAD(P)H oxidase-mediated superoxide production and subsequent peroxynitrite formation (Zhang et al., 2003). Long-chain saturated fatty acids, but not unsaturated fatty acids, induce apoptosis (Maedler et al., 2001; Listenberger et al., 2003; Mishra and Simonson, 2005; Henique et al., 2010).

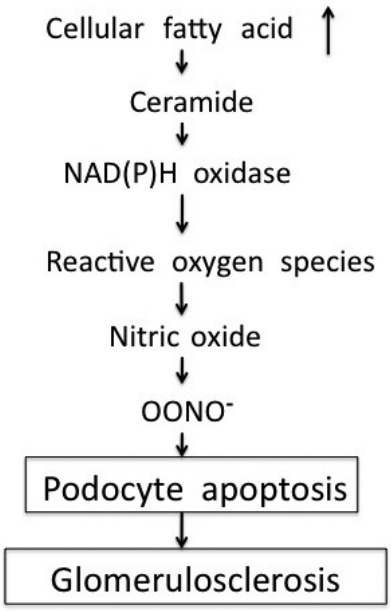

Fig. 3. Proposed model for the fatty acid-induced podocyte injury. Increased intracellular fatty acids leads to ceramide synthesis in podocytes, which activates NAD(P)H oxidase with increased reactive oxidative species generation. This process leads to the formation of peroxynitrite ($OONO^-$) and other oxidants, resulting in podocyte apoptosis. Ultimately, these processes confer predisposition to glomerulosclerosis.

Palmitate is the predominant circulating saturated free fatty acid in insulin-resistant states.

Palmitate induces ceramide overproduction in cultured podocytes, blocking insulin-stimulated glucose uptake (Lennon et al., 2009). Furthermore, palmitate induces podocyte apoptosis and cell death (Sieber et al., 2010). Podocyte apoptosis with podocytopenia may be an early pathomechanism of FSGS formation (Schiffer et al., 2001; Lee and Song, 2010). Fabry disease that results in cellular accumulation of globotriaosylceramide leads to proteinuria and renal failure with glomerular cell pathology (Najafian et al., 2011; Valbuena et al., 2011). Particularly, podocyte injury seems to play a pivotal role in the development and progression of Fabry nephropathy (Najafian et al., 2011). In cultured mesangial cells, palmitate also stimulates apoptosis (Mishra and Simonson, 2005), and ceramide is considered as a critical signaling molecule mediating the activation of NAD(P)H oxidase (Yi et al., 2004). Homocysteine-induced ceramide production may lead to glomerular endothelial cell dysfunction and injury by forming the redox signalling platforms (Yi et al., 2009).

Other potential mechanisms

An impairment of antioxidant defense mechanisms accompanying the disruption of fatty acid metabolism seems to be important in the pathogenesis of early podocyte lesions. VLDL lipolysis products induce lipid droplets in monocytes, which may contribute to the progression of CKD (Rutledge et al., 2010).

In summary, lipotoxicity caused by intracellular fatty acid overload in kidney may be more severe in the metabolic syndrome as compared with CKD. Cellular damage by fatty acid accumulation in kidney seems to be particularly severe in podocytes due to excessive ceramide formation, leading to cell dysfunction, apoptosis and cell death, resulting in insulin resistance and FSGS formation (Fig. 3).

Conclusions

Hypertriglyceridemia and intracellular lipid overload are commonly present in both CKD and metabolic syndrome. In metabolic syndrome, enhanced plasma levels of free fatty acids and TG, in association with increased lipoprotein synthesis, may lead to intracellular fatty acid accumulation in non-adipose tissues, including kidney. Excessive ceramide formation caused by increased free fatty acid uptake may lead to apoptosis in lipid-laden cells in kidney, which is particularly severe

in podocytes, resulting in FSGS formation. Hypertriglyceridemia in the CKD, however, is mainly caused by decreased catabolism. Binding/uptake of TG-rich VLDL via LDL receptors of glomerular cells seems to be increased in CKD, leading to endocytic accumulation of TG and foam cell formation. TG itself is not harmful to cells, yet degradation of TG to free fatty acids may induce lipotoxicity. In this regard, it is suggested that the direct toxic effects of excess free fatty acids on renal cells may initiate glomerular damage in metabolic syndrome, while cellular TG/fatty acid accumulation in diseased glomeruli may slowly aggravate the preexisting cellular injury, contributing to the progression of CKD. In summary, this review provides new mechanistic insights into intracellular lipid accumulation and lipotoxicity in CKD. Better understanding of lipotoxicity on glomerular cells may provide novel tools for the prevention of glomerulosclerosis.

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