

Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences

N. D. Vaziri

Division of Nephrology and Hypertension, University of California, Irvine, California

Vaziri, N. D. Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences. *Am J Physiol Renal Physiol* 290: F262–F272, 2006; doi:10.1152/ajprenal.00099.2005.—Chronic renal failure (CRF) results in profound lipid disorders, which stem largely from dysregulation of high-density lipoprotein (HDL) and triglyceride-rich lipoprotein metabolism. Specifically, maturation of HDL is impaired and its composition is altered in CRF. In addition, clearance of triglyceride-rich lipoproteins and their atherogenic remnants is impaired, their composition is altered, and their plasma concentrations are elevated in CRF. Impaired maturation of HDL in CRF is primarily due to downregulation of lecithin-cholesterol acyltransferase (LCAT) and, to a lesser extent, increased plasma cholesteryl ester transfer protein (CETP). Triglyceride enrichment of HDL in CRF is primarily due to hepatic lipase deficiency and elevated CETP activity. The CRF-induced hypertriglyceridemia, abnormal composition, and impaired clearance of triglyceride-rich lipoproteins and their remnants are primarily due to downregulation of lipoprotein lipase, hepatic lipase, and the very-low-density lipoprotein receptor, as well as, upregulation of hepatic acyl-CoA cholesterol acyltransferase (ACAT). In addition, impaired HDL metabolism contributes to the disturbances of triglyceride-rich lipoprotein metabolism. These abnormalities are compounded by downregulation of apolipoproteins apoA-I, apoA-II, and apoC-II in CRF. Together, these abnormalities may contribute to the risk of arteriosclerotic cardiovascular disease and may adversely affect progression of renal disease and energy metabolism in CRF.

chronic kidney disease; lipid disorders; cardiovascular disease; high-density lipoprotein metabolism; cholesterol metabolism; triglyceride

CHRONIC RENAL FAILURE (CRF) is associated with premature atherosclerosis and increased incidence of cardiovascular morbidity and mortality (2, 23, 38). Several factors contribute to atherogenesis and cardiovascular disease in patients with CRF. Notable among the CRF-induced risk factors are lipid disorders, oxidative stress, inflammation, physical inactivity, anemia, hypertension, vascular calcification, endothelial dysfunction, and depressed nitric oxide availability (32, 55, 69, 76, 78, 91).

In the past 30 years, numerous studies have been conducted to discern the features and the mechanisms of CRF-induced dyslipidemia. Most of the earlier studies were focused on the effect of CRF on the concentration, composition, and clearance of various plasma lipoproteins and their remnants. More recent studies were designed to elucidate the molecular mechanisms of CRF-induced alterations in lipid metabolism using experimental animals. The present paper is intended to provide an overview of the features, molecular mechanisms, and potential consequences of dysregulation of lipid metabolism in CRF.

PLASMA LIPID AND LIPOPROTEIN METABOLISM

In the plasma, lipids are carried by water-soluble particles known as lipoproteins, which consist of a nonpolar lipid core

(triglycerides, cholesterol esters) surrounded by an envelope composed of specific apolipoproteins (apo), phospholipids, and other polar lipids. The plasma lipoproteins are commonly classified as either high-density (HDL), low-density (LDL), intermediate-density (IDL), or very-low-density (VLDL) lipoproteins according to their ultracentrifugation characteristics. Chylomicrons and VLDL serve as vehicles to transport triglycerides and cholesterol from the sites of absorption (intestine) and endogenous production (liver) to the sites of consumption (myocytes, steroidogenic glands, etc.) or storage (adipocyte). In contrast, HDL serves as a vehicle to transport surplus cholesterol from peripheral tissues to the liver for disposal.

Chylomicrons

Chylomicrons (Fig. 1) serve as the vehicle for the transport of dietary lipids in the plasma. They are produced within the enterocytes from the packaging of fat droplets (containing triglycerides, cholesterol ester, and phospholipids) with a number of apolipoproteins including apoB-48, apoA-I, apoA-II, and apoA-IV. The nascent chylomicrons are then released into the circulation via the lymphatic system. In the circulation, the nascent chylomicrons acquire apoE, apoC, and additional cholesterol from HDL-2 in exchange for apoA-I, apoA-II, and phospholipids. This transaction with HDL is essential for subsequent lipolysis of chylomicrons by lipoprotein lipase (LPL) because apoE is necessary for chylomicron binding to

Address for reprint requests and other correspondence: N. D. Vaziri, Div. of Nephrology and Hypertension, UCI Medical Ctr., 101 The City Dr., Bldg. 53, Rm. 125, Rt. 81, Orange, CA 92668 (e-mail: ndvaziri@uci.edu).

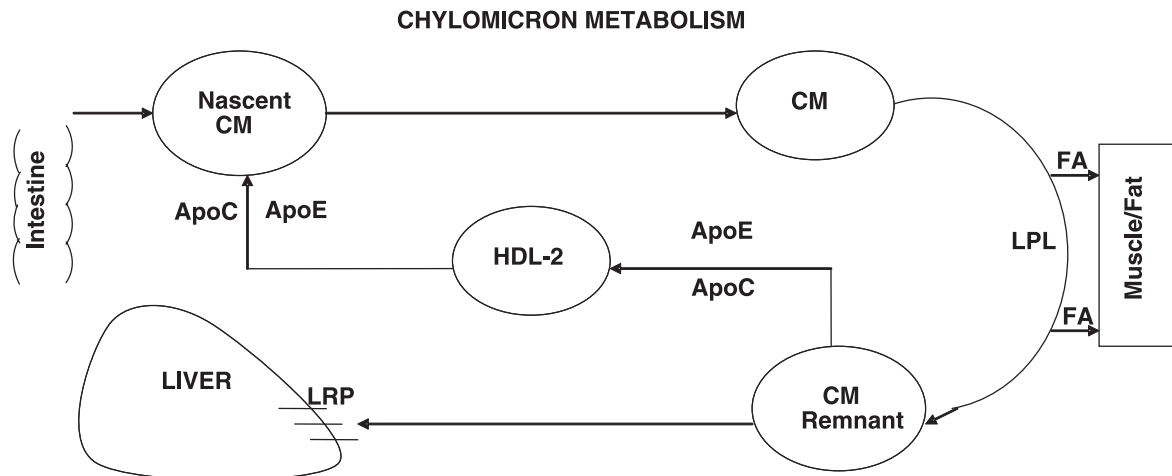


Fig. 1. Chylomicrons (CM) are packaged by the enterocytes and released in the circulation as nascent CM, which mature following acquisition of apolipoproteins apoE and apoC from high-density lipoprotein (HDL)-2. Mature CM undergo hydrolysis of their triglyceride content by lipoprotein lipase (LPL) in the capillaries perfusing muscles and adipose tissues. This leads to release of free fatty acids (FA) and their uptake by the surrounding adipocytes/myocytes and formation of CM remnants, which are subsequently cleared by the liver and other tissues via LDL receptor-related protein (LRP).

the endothelial surface and apoC-II is required for activation of LPL.

On reaching the capillary networks perfusing the muscle and adipose tissues, mature chylomicrons form a transient binding to the endothelial surface via their constituent apoE. The endothelium binding accommodates interaction of chylomicrons with the endothelium-bound LPL and its activation by apoC-II. This is followed by hydrolysis of the triglyceride content of chylomicrons and release of free fatty acids within the capillaries. The majority of fatty acids released diffuse into the adjacent myocytes for energy production or into adipocytes for energy storage. The remaining fatty acids are carried to distant sites by albumin and various lipoproteins. This results in formation and release of chylomicron remnants and return of the borrowed apoC and apoE to HDL before their eventual removal by the liver and other tissues via LDL receptor-related protein (LRP).

VLDL, IDL, and LDL

VLDL (Fig. 2) particles are produced by the liver and serve as the vehicle for delivery of endogenous lipids to the peripheral tissues. Nascent VLDL is formed within the hepatocyte from the fusion of partially lipidated, newly synthesized apoB-100 with a triglyceride-rich lipid droplet, followed by addition of apoE, apoA-I, and apoA-II. The triglycerides and cholesterol ester used by hepatocytes for incorporation into VLDL are generated by the enzymes acyl-CoA diglycerol acyltransferase (DGAT) and acyl-CoA cholesterol acyltransferase (ACAT), respectively. The fatty acids and cholesterol supplies used for these processes by the hepatocyte are derived from a combination of de novo synthesis and uptake from the circulating blood.

After being released into the circulation, nascent VLDL acquires apoC and apoE from HDL-2 in exchange for apoA-I,

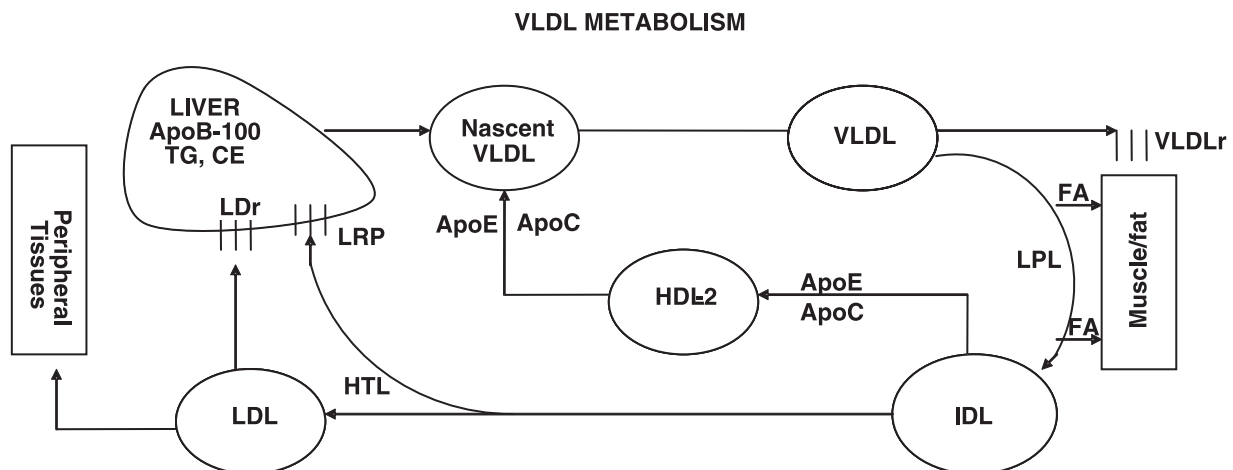


Fig. 2. Very low-density lipoproteins (VLDL) are produced by hepatocytes and released into the circulation as nascent VLDL, which mature following acquisition of apoE and apoC from HDL-2. Mature VLDL undergoes lipolysis of its triglyceride (TG) content by LPL in the capillaries perfusing muscles and adipose tissues. This leads to release and uptake of FA by the surrounding adipocytes/myocytes and formation of VLDL remnants, commonly known as intermediate-density lipoproteins (IDL). Most of the IDLs formed in this manner undergo further lipolysis by hepatic lipase (HTL) to become low-density lipoproteins (LDL). The remaining IDL are removed by the liver and other tissues via LRP. In addition to the lipolytic pathway, VLDL can be removed in their entirety by myocytes/adipocyte via the VLDL receptor (VLDLr). CE, cholesteryl ester.

apoA-II, and phospholipids. As with chylomicrons, this trans- action with HDL-2 is critical for subsequent metabolism of VLDL by LPL and the VLDL receptor. On reaching the capillary beds perfusing the muscle and adipose tissues, mature VLDL particles bind to the endothelial surface via their con- stituent apoE. This process facilitates interaction of VLDL with LPL and the VLDL receptor. LPL, which is attached to the endothelial surface through its heparin-binding domain, is enzymatically activated by the apoC-II content of the adjacent VLDL. This is followed by hydrolysis of VLDL triglycerides by the activated enzyme, leading to release of two fatty acids. Most of the fatty acids released in this manner diffuse into the adjacent myocytes or adipocytes for energy production or storage, respectively. The remaining fatty acids bind to albu- min and lipoproteins and are transported to the liver and other tissues. Lipolysis of VLDL by LPL results in a 70% reduction in their triglyceride content and detachment and release of a remnant particle, commonly known as IDL. In the circulation, IDL particles return the borrowed apoE and apoC to HDL and donate part of their remaining triglyceride cargo to HDL in return for cholesterol ester. The latter exchange is catalyzed by cholesteryl ester transfer protein (CETP). Most of the IDL particles undergo further lipolysis via hepatic triglyceride lipase. This leads to extraction of nearly all remaining triglyc- erides from IDL by the liver and formation of cholesterol-rich LDL, which are normally devoid of triglycerides. LDL parti- cles are then removed via the LDL receptor by the liver, as well as extrahepatic tissues. The remaining IDL particles are re- moved by the liver (and other tissues) via LRP. The latter pathway is commonly referred to as the shunt pathway.

An alternative pathway for clearance of VLDL has been recently identified, in which VLDL is removed in its entirety by myocytes and adipocytes via binding to the novel VLDL receptor (71).

HDL

The primary function of HDL (Fig. 3) is retrieval and transport of surplus cholesterol from the extrahepatic tissues for disposal in the liver (24). This process, which is commonly known as reverse cholesterol transport, is critical for cellular cholesterol homeostasis and protection against atherosclerosis, renal disease, and other complications.

In addition, HDL plays a major role in metabolism of triglyceride-rich lipoproteins by serving as a donor and accep- tor of apoC and apoE for the nascent and remnant chylomi- crons and VLDL, a process which is vital in triglyceride metabolism. Moreover, HDL serves as a potent endogenous inhibitor of inflammation, platelet adhesion, and LDL oxida- tion (58).

The principal apolipoprotein constituents of HDL are apoA-I and apoA-II, which are produced by the liver and intestine and secreted with VLDL and chylomicrons, respec- tively. On reaching the extracellular space, apoA-I and apoA-II dissociate from VLDL and chylomicrons (as phos- pholipid complexes) and coalesce to form nascent HDL. apoA-I constitutes 70% of HDL protein content. In addition to serving as the main structural constituent of HDL, apoA-I serves as the activator of LCAT, which is essential for the HDL-mediated cholesterol retrieval from extrahepatic tis- sues. The second most abundant apolipoprotein constituent of HDL is apoA-II, which represents 20% of HDL protein content. In addition to its role as a major structural consti- tuent of HDL, apoA-II serves as an activator of hepatic lipase, which plays a central role in the removal of HDL- borne triglycerides by the liver. Once formed, nascent HDL acquires apoE-phospholipid and apoC-phospholipid com- plexes from either the available pool in the plasma or from chylomicron and VLDL remnants. The assembly of these

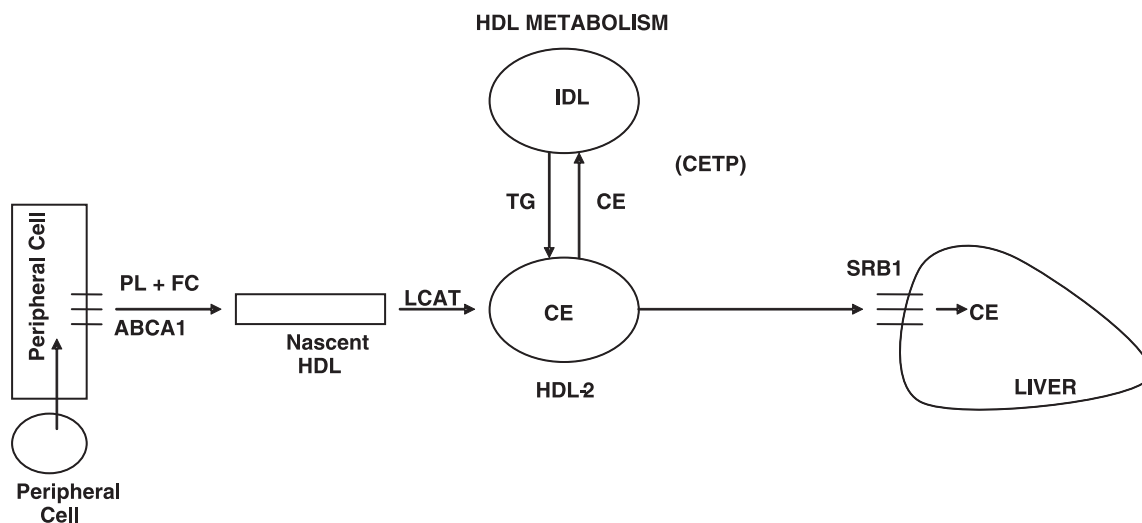


Fig. 3. Retrieval of surplus cholesterol from peripheral tissues by HDL requires binding of the lipid-poor, discoid-shaped nascent HDL to ATP binding cassette transporter type I (ABCA1). This leads to active transport of phospholipids (PL) and free cholesterol (FC) from the cell to the HDL surface. Free cholesterol is then esterified to CE by lecithin: cholesterol acyltransferase (LCAT). This is followed by sequestration of CE in the core of HDL, which helps to maintain a favorable concentration gradient for maximal FC uptake. CE-loaded HDL (HDL-2) is then released in the circulation, wherein it receives TG from IDL in exchange for CE, a process catalyzed by cholesterol ester transfer protein (CETP). Finally, HDL-2 forms a reversible binding to hepatic HDL receptor (SRB-1), which accommodates unloading of its CE content and lipolysis of its TG and PL content by HL. Delipidated HDL (HDL-3) is then released into the circulation to repeat the cycle.

components leads to formation of a small cholesterol-poor discoid particle known as HDL-3.

HDL-mediated removal of surplus cholesterol from extrahepatic tissues requires attachment of nascent HDL to the ATP binding cassette transporter type I (ABCA1) (22, 44, 59). 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 (22). Free cholesterol reaching the surface of HDL is promptly esterified by LCAT. Due to its intense hydrophobicity, cholesterol ester formed on the surface of HDL immediately moves to the core of HDL, thus sustaining the favorable gradient for maximal cholesterol uptake by the maturing HDL. These observations illustrate the critical role of LCAT in the maturation of cholesterol-poor HDL-3 to spherical, cholesterol ester-rich HDL-2 and, hence, HDL-mediated reverse cholesterol transport. Once fully loaded, HDL-2 dissociates from the binding site and returns to the bloodstream. While in transit, HDL-2 participates in a series of elaborate exchanges of apoproteins and lipids with the apoB-containing lipoproteins (described above) before reaching the liver. In the liver, HDL-2 forms a reversible binding with the HDL receptor (SRB-1), which facilitates simultaneous unloading of its cholesterol ester content, as well as hydrolysis and extraction of its fatty acid cargo by hepatic lipase. These events lead to transformation of HDL-2 to HDL-3, its detachment from SRB-1, and its return to the blood stream for recycling (1). These observations highlight the critical role of SRB-1 in HDL-mediated reverse cholesterol transport and hepatic lipase-dependent disposal of HDL-borne triglycerides in the liver.

Another significant pathway of cellular cholesterol efflux is the facilitated and passive diffusion of free cholesterol followed by its binding to albumin and subsequent transfer to HDL in the circulation. This phenomenon highlights the important role of albumin in reverse cholesterol transport (22, 97).

PLASMA LIPIDS AND LIPOPROTEIN PROFILE IN CRF

Plasma triglyceride concentration is frequently elevated in patients and experimental animals with CRF. However, plasma cholesterol concentration is usually normal, even reduced, and only occasionally elevated in patients with end-stage renal disease (ESRD). Elevation of plasma triglycerides in ESRD patients is accompanied by increased plasma concentration and impaired clearance of VLDL. This is associated with the

accumulation of atherogenic VLDL remnants, commonly known as IDL. Similarly, clearance of chylomicrons is impaired and plasma concentration of chylomicron remnants is elevated in CRF patients. In contrast, plasma concentration of LDL is usually normal and only occasionally elevated in ESRD patients. Plasma HDL concentration is consistently reduced, and maturation of cholesterol ester-poor HDL-3 to cholesterol ester-rich cardioprotective HDL-2 is impaired in CRF (5, 7, 8, 13, 31, 53, 68).

In addition to the quantitative abnormalities cited above, the composition of plasma lipoproteins is altered in CRF (5, 31, 53, 68). For instance, the cholesterol content of VLDL is relatively increased and its triglyceride content is relatively reduced in CRF. In contrast, CRF results in a relative reduction in cholesterol and relative increase in the triglyceride content of LDL. Similarly, cholesterol ester and free cholesterol content of HDL are consistently reduced, whereas its triglyceride content is elevated, in CRF. The above compositional abnormalities are present in nearly all patients with mild to severe renal insufficiency (even those with normal plasma total cholesterol and triglyceride levels) and point to redistribution of cholesterol from HDL to VLDL and IDL and defective removal of triglycerides from LDL and HDL particles. It should be noted that in many instances development and progression of renal insufficiency are accompanied by heavy proteinuria, leading to superimposition of nephrotic dyslipidemia (77) on CRF-induced lipid disorders. In these circumstances, plasma total cholesterol and LDL cholesterol concentrations are frequently elevated. However, with progression to ESRD and the consequent decline in proteinuria (reduced filtered protein), a lipid profile typical of CRF emerges. It is of note that losses of proteins through the peritoneum in ESRD patients treated with chronic peritoneal dialysis simulate nephrotic syndrome and lead to a lipid profile that frequently includes hypercholesterolemia and an elevated LDL level. The effects of peritoneal losses of protein on lipid metabolism in peritoneal dialysis patients are compounded by peritoneal absorption of large quantities of glucose, which tends to accentuate the hypertriglyceridemia. The common features of dyslipidemia of CRF and their modifications by heavy proteinuria and dialytic modalities are summarized in Table 1 and described in detail in elegant articles by Attman et al. (6) and Deighan et al. (20). Finally, in transplant recipients and patients with autoimmune disorders, administration of drugs known to cause hyperlipidemia (corticosteroids, calcineurin inhibitors, or rapamycin)

Table 1. Common features of serum lipid/lipoprotein profile in predialysis CKD patients with or without nephrotic proteinuria and in ESRD patients treated with chronic hemodialysis or peritoneal dialysis

Serum Lipid	CKD Patients		Hemodialysis Patients	Peritoneal Dialysis Patients
	Heavy proteinuria	Minimal proteinuria		
Triglycerides	↑	↑	↑	↑
Total cholesterol	↑	↔, ↓	↔, ↓ Rarely ↑	Frequently ↑
LDL cholesterol	↑	↔, ↓ or ↑	↔, ↓ Rarely ↑	Frequently ↑
Small dense LDL	↑			
IDL cholesterol	↑	↑	↑	↑
HDL cholesterol	↓	↓	↓	↓
apoA-I, apoA-II	↓	↓	↓	↓
apoC-III	↑	↑	↑	↑

CKD, chronic kidney disease; ESRD, end-stage renal disease; LDL, IDL, HDL: low-density, intermediate-density, and high-density lipoproteins, respectively; apo, apolipoprotein.

(88) further complicates the associated dyslipidemia. In addition, patients with hereditary dyslipidemias exhibit a profile similar to that of the genetic disorder.

Besides affecting plasma lipid levels and their distribution within lipoproteins, CRF affects plasma concentration of various apolipoproteins (5). For instance, plasma concentrations of apoA-I, apoA-II, and apoE are reduced, whereas that of apoC-III is elevated and the apoC-II-to-apoC-III concentration ratio is diminished. In addition to serving as lipid carriers, apolipoproteins serve as ligands for lipoprotein binding to specific receptors and as regulators of the key enzymes in lipid metabolism. Thus the CRF-induced changes in plasma apolipoprotein concentrations are responsible, in part, for the associated lipid disorders. It is of interest that significant changes in plasma apolipoprotein concentrations usually precede discernible alterations in plasma lipid levels in early stages of chronic renal insufficiency (5).

MECHANISMS OF UREMIC DYSLIPIDEMIA

The features of dyslipidemia and the alterations in plasma lipoprotein metabolism in humans with CRF have been well characterized. However, the inherent limitations of clinical studies have precluded in-depth investigation of the underlying molecular mechanisms in humans. Such investigations involve probing for mRNA and protein expression in such key organs/tissues as the liver, skeletal muscle, adipose tissue, and myocardium, which cannot be obtained in humans. Moreover, the variabilities in genetic and dietary factors, underlying systemic diseases, and therapeutic regimens among patients with CRF further complicate the task. For these reasons, studies aimed at unraveling the molecular basis of uremic dyslipidemia have employed animals with experimental CRF. Most of these studies have been facilitated by the recent identification of the genes and the corresponding proteins for various enzymes and receptors involved in lipid metabolism. The available data pertaining to the molecular mechanisms of various CRF-induced lipid/lipoprotein abnormalities are reviewed below and summarized in Table 2.

Table 2. Major changes in the key enzyme and receptors in chronic renal failure and their impact on plasma lipid/lipoprotein levels

Protein	Change	Effect on Plasma Lipids/LPs
apoA-I	↓	↓ HDL
LCAT	↓	↓ HDL-Chol, ↓ HDL-2/HDL-3
CETP	↑	↓ HDL-Chol, ↑ HDL-TG
ACAT	↑	↑ VLDL-Chol, ↓ HDL-Chol
LPL	↓	↑ TG, (↓ delipidation of VLDL and CM)
VLDL receptor	↓	↑ VLDL, ↑ TG
Hepatic lipase	↓	↑ IDL, ↑ CM remnants, ↑ HDL-TG, ↑ TG, ↑ LDL-TG
LRP	↓	↑ IDL, ↑ CM remnants
apoCII/CIII (ratio)	↓	↑ TG (↓ LPL activity)
Pre-β-HDL	↑	↑ TG (↓ LPL activity)
Hepatic DGAT	↓	↓ VLDL-TG

LP, lipoprotein; LCAT, lecithin cholesterol acyltransferase; CETP, cholesterol ester transfer protein; ACAT, acyl-CoA cholesterol acyltransferase; DGAT, acyl-CoA diacylglycerol acyltransferase; TG, triglyceride; Chol, cholesterol; LPL, lipoprotein lipase; LRP, LDL receptor-related protein; CM, chylomicron.

Abnormalities in HDL Metabolism

As noted earlier, CRF is consistently associated with reduced plasma HDL cholesterol concentration, impaired maturation of cholesterol ester-poor HDL-3 to cholesterol ester-rich HDL-2, increased HDL triglycerides, and depressed plasma apoA-I. These abnormalities are primarily due to CRF-induced dysregulation of several important proteins, which are briefly described below.

LCAT. LCAT 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. Thus LCAT deficiency can potentially account for diminished plasma HDL cholesterol and impaired HDL maturation in CRF. In fact, plasma LCAT activity is consistently diminished in patients with ESRD (27, 56, 68). This is accompanied by a significant elevation of plasma-free cholesterol and a marked reduction in plasma esterified cholesterol concentration, providing functional evidence for diminished LCAT-dependent cholesterol esterification. 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. This issue was addressed by a series of studies which demonstrated that the reduction in plasma LCAT activity in uremic rats is associated with a parallel reduction in plasma concentration of immunodetectable LCAT and downregulation of hepatic LCAT gene expression (46, 90, 92).

CETP. CETP mediates transfer of cholesterol ester from HDL to IDL in exchange for triglycerides. Thus a potential increase in plasma CETP can contribute to the CRF-associated reduction in HDL cholesterol ester and elevation of HDL triglycerides. In fact, according to a recent study, more than 34% of hemodialysis-dependent patients were found to have high plasma CETP levels (40). The mechanism responsible for the reported elevation of CETP in ESRD patients is unknown and requires future investigation. The effect of CRF is amplified by proteinuria, which has been shown to increase synthesis and markedly raise plasma concentration of CETP (21). Thus plasma CETP is expectedly elevated in patients with heavy proteinuria and mild to severe renal insufficiency.

Hepatic lipase. Hepatic lipase catalyzes hydrolysis and removal of the triglyceride content of HDL. Thus hepatic lipase deficiency can potentially contribute to increased HDL triglyceride content. In fact, as described later (abnormalities of lipoprotein remnants), CRF results in pronounced hepatic lipase deficiency in humans and experimental animals (41).

apoA-I and apoA-II. apoA-I and apoA-II constitute the main structural constituents of HDL. In addition, apoA-I serves as the LCAT activator as well as ligand for the SRB-1 and HDL binding protein (ABCA1 transporter), whereas apoA-II serves as the hepatic lipase activator. Plasma concentrations of apoA-I and apoA-II are significantly reduced in patients with ESRD (5). Studies in animals with experimental CRF have demonstrated that the CRF-induced reduction in plasma apoA-I is due to downregulation of hepatic apoA-I gene expression (80). The reduction in plasma concentration of these important constituents can, therefore, contribute to both diminished plasma HDL concentration and impaired HDL function in CRF.

SRB-1. Hepatic SRB-1 is the primary pathway for disposal of HDL-borne cholesterol ester and triglycerides (1). Therefore, potential dysregulation of this protein can impact HDL metabolism. Heavy glomerular proteinuria has been shown to significantly reduce hepatic SRB-1 protein expression in experimental animals (48). In contrast, CRF per se, without heavy proteinuria, induced by 5/6 nephrectomy, does not significantly change SRB-1 mRNA or protein abundance in the liver (80). However, concomitant heavy proteinuria and renal insufficiency may affect SRB-1 expression and hence, HDL-mediated reverse cholesterol transport.

ACAT. HDL-mediated cholesterol uptake from the extrahepatic tissues depends on deesterification of cholesterol esters contained in the intracellular vesicles and the resultant release of free cholesterol. This process is opposed by ACAT, which is the main enzyme for intracellular esterification of cholesterol. Therefore, a relative increase in ACAT activity can potentially limit HDL-mediated cholesterol uptake and, hence, contribute to the reduction in plasma HDL cholesterol and impaired maturation of HDL. Although the effect of CRF on ACAT expression and activity in the extrahepatic tissues is not known, CRF has been recently shown to markedly raise hepatic ACAT-2 mRNA and protein abundance, as well as total ACAT activity (50). The potential contribution of ACAT to the CRF-induced dysregulation of HDL metabolism was illustrated by a recent study which revealed that pharmacological inhibition of ACAT results in a dramatic shift in plasma cholesterol from apoB-containing lipoproteins to HDL with virtually no change in plasma total cholesterol in CRF animals (83). Interestingly, the improvement in the lipid profile with an ACAT inhibitor was accompanied by a significantly higher creatinine clearance in the treated than the untreated animals. This phenomenon may be due to amelioration of dyslipidemia and enhanced HDL-mediated reverse cholesterol transport, leading to attenuation of glomerulosclerosis.

Triglyceride Synthesis

Hypertriglyceridemia is a common feature of CRF (5, 8, 9). Potential causes include increased synthesis and/or diminished clearance from the circulation. As described later in this review, CRF results in several abnormalities that work in concert to severely impair clearance of triglyceride-rich lipoproteins, and thereby cause hypertriglyceridemia. However, the contribution, if any, of altered triglyceride synthesis to uremic hypertriglyceridemia is uncertain. In this regard, a number of factors were initially thought to increase lipogenesis in CRF. For instance, because renal insufficiency causes insulin resistance (8, 54), which can, in turn, promote hepatic VLDL production, it has been suggested that increased production may be responsible, in part, for CRF-associated elevations in plasma VLDL and triglycerides (9). In addition, influx of acetate from acetate-based dialysates (no longer used) was thought to contribute to hypertriglyceridemia by providing an abundant supply of substrate for fatty acid synthesis. However, despite abandonment of acetate-based dialysates and conversion to bicarbonate-based dialysates, hypertriglyceridemia remains unabated in this population.

It is of note that earlier studies of triglyceride and VLDL production in humans and experimental animals have yielded contradictory results. While some studies have shown increased triglyceride production (15, 18, 94), others have found

no such increases (10, 26). Interestingly, fatty acid production and expression of enzymes involved in fatty acid synthesis are reportedly increased in the adipose tissues of CRF rats (42, 65, 70). This phenomenon appears to represent a compensatory response to diminished fatty acid entry into the adipose tissue occasioned by LPL and VLDL receptor deficiencies, as exemplified in LPL-deficient mice (96).

Hepatic DGAT. DGAT is the final step in triglyceride biosynthesis. In a recent study, we found downregulation of hepatic DGAT expression and activity in rats with CRF and minimal proteinuria induced by 5/6 nephrectomy, suggesting decreased hepatic triglyceride biosynthetic capacity in this model (79). This observation tends to argue against increased production as a contributing factor to uremic hypertriglyceridemia and provides an explanation for the reduction in VLDL triglyceride content in uremia. It should be noted that heavy proteinuria results in significant upregulation of hepatic DGAT and, hence, triglyceride synthetic capacity (81). Thus concomitant renal insufficiency and heavy proteinuria can exert opposing influences in the affected animals and, presumably, humans.

Abnormalities in Triglyceride-Rich Lipoprotein Metabolism

As noted earlier, CRF is associated with impaired clearance of VLDL and chylomicrons and accumulation of their atherogenic remnants. This is coupled with elevated VLDL cholesterol, reduced VLDL triglycerides, increased LDL triglycerides, and diminished LDL cholesterol. These abnormalities are primarily caused by dysregulation of LPL, hepatic lipase, the VLDL receptor, hepatic ACAT and LRP expressions/activities, as well as impaired HDL metabolism.

LPL. This glycoprotein enzyme is a member of the lipase gene family that includes pancreatic and hepatic lipases. 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 enzyme is stored in the Golgi vesicles, from which it is directed for either intracellular degradation or secretion. The secreted enzyme binds to the heparan sulfate proteoglycans on the surface of the original cell and, eventually, the adjacent capillary endothelium. The endothelium-bound pool of LPL is relevant to lipolysis of VLDL and chylomicrons. It should be noted that soluble heparin can displace and release LPL from binding sites on endothelial cells. Accordingly, measurement of lipolytic activity in plasma obtained after intravenous injection of soluble heparin can be used to assess LPL activity in humans and animals.

Several studies have demonstrated a marked reduction in plasma postheparin lipolytic activity in ESRD patients (3, 14, 66). In addition, adipose tissues obtained from ESRD patients contain subnormal triglyceride content and diminished LPL activity (25). The reduction in postheparin lipolytic activity in hemodialysis-dependent patients was initially attributed to chronic intermittent heparin administration (as an anticoagulant during dialysis treatments), leading to depletion of the endothelial pool of LPL. Also considered was accumulation of some unidentified nondialyzable LPL inhibitors. One such inhibitor was subsequently identified as being the pre- β -HDL, whose concentration is elevated in uremic plasma (16). Another contributing factor is insulin resistance, which is a feature

of CRF (63). In addition, a number of studies have suggested that reduced LPL activity in ESRD patients is due, in part, to secondary parathyroidism and could be ameliorated by parathyroidectomy (3). The other major factors contributing to diminished LPL activity in CRF include reductions in the apoC-II (LPL cofactor) and apoE (ligand for endothelial binding) content of VLDL and chylomicrons (5). The latter abnormalities are primarily caused by the defective maturation of HDL-3 to HDL-2, which serves as an apoC and apoE donor to the nascent VLDL and chylomicrons. Subsequent animal studies demonstrated that the reduction in LPL activity is coupled with marked downregulation of both LPL gene expression and protein abundance in adipose tissue, skeletal muscle, as well as myocardium (85). These observations clearly demonstrated that in addition to limiting LPL activity, CRF causes a true LPL deficiency. The animal studies further showed the contribution of secondary hyperparathyroidism to downregulation of LPL expression in CRF animals, thus confirming earlier observations in ESRD patients (93).

Hepatic lipase. Hepatic lipase, another member of the lipase gene family, bears considerable structural homology with LPL. It is exclusively produced and released by hepatocytes for binding to heparan sulfate proteoglycans on the hepatocyte surface and hepatic endothelial cells. Unlike LPL, hepatic lipase activity is independent of apoC-II and as such can catalyze hydrolysis of triglycerides in IDL particles (which are normally devoid of apoC-II) and their conversion to LDL. In addition, hepatic lipase is responsible for hydrolysis of triglycerides and phospholipids in HDL and chylomicron remnants. Accordingly, hepatic lipase plays a central role in the metabolism of lipoprotein remnants and HDL.

As noted earlier, CRF is associated with impaired clearance and elevated plasma concentration of IDL as well as the triglyceride-enrichment of IDL, LDL, chylomicron remnants, and HDL, events that are indicative of hepatic lipase deficiency. In fact, CRF results in marked downregulation of hepatic lipase expression and activity in experimental animals (41). The CRF-associated hepatic lipase deficiency appears to be caused, in part, by secondary hyperparathyroidism and dysregulation of cytosolic Ca^{2+} (41).

LRP. LRP is a member of the LDL receptor gene family, which is larger than, but structurally similar to, the LDL receptor. It is abundantly expressed in the liver (30) and recognizes >30 different ligands including IDL and chylomicron remnants. apoB-48 and apoE serve as ligands for LRP-mediated removal of chylomicron remnants and IDL by the liver, respectively. CRF is associated with impaired clearance and elevated plasma concentration of IDL and chylomicron remnants. Given the critical role of LRP in the removal of these lipoprotein remnants, their impaired clearance and increased plasma concentrations in CRF could be due, in part, to LRP deficiency. In fact, hepatic LRP gene expression and protein abundance are diminished in rats with CRF (39). Thus hepatic lipase deficiency (which limits IDL conversion to LDL) and downregulation of hepatic LRP, which limits hepatic removal of IDL and chylomicron remnants, work in concert to raise plasma concentration of these atherogenic remnants in CRF.

The VLDL receptor. The VLDL receptor is another member of the LDL receptor gene family, which is expressed in skeletal muscle, myocardium, brain, and adipose tissue. The VLDL receptor has substantial structural homology with the LDL

receptor; however, unlike the LDL receptor, it has a specific affinity for VLDL and none for LDL. The ligand-binding domain of the VLDL receptor consists of 8 tandem copies of 40 cysteine-rich amino acid repeats compared with 7 repeats in the LDL receptor. The VLDL receptor binds (via apoE) and internalizes VLDL particles and, as such, participates in the clearance of VLDL from the circulation (71). As mentioned earlier, plasma VLDL concentration is elevated and VLDL clearance is impaired in CRF. Given the role of the VLDL receptor in VLDL clearance, its deficiency can potentially contribute to an elevated plasma level and impaired clearance of VLDL in CRF. In fact, VLDL receptor mRNA and protein abundance in adipose tissue, skeletal muscle, and myocardium are severely reduced in CRF animals (47, 86). Thus downregulation of the VLDL receptor pathway can, in part, account for the associated hypertriglyceridemia, elevated plasma concentration, and depressed clearance of VLDL in CRF.

Cholesterol Synthesis and Catabolism

Plasma total cholesterol is usually normal or reduced and only occasionally elevated in patients with ESRD. However, plasma cholesterol is consistently, albeit mildly, elevated in the CRF rats. Plasma cholesterol concentration is primarily a function of its biosynthesis, catabolism (cholesterol conversion to bile acids), and tissue uptake. The effects of CRF on regulation of these pathways have been investigated in a very limited number of studies. The findings of these studies are summarized here.

Hydroxy-3-methylglutaryl-CoA reductase and cholesterol 7 α -hydroxylase. Hydroxy-3-methylglutaryl (HMG)-CoA reductase is the rate-limiting enzyme for cholesterol biosynthesis. In a study of rats examined 3 wk after 5% nephrectomy and fed a high-protein diet, Pandak and associates (61) found elevated hepatic HMG-CoA reductase activity in the face of normal HMG-CoA reductase mRNA abundance. This was coupled with a significant increase in cholesterol 7 α -hydroxylase activity, the rate-limiting enzyme for cholesterol catabolism and conversion to bile acids (61). However, surprisingly, the rate of biliary bile acid excretion was unchanged in these animals. The authors concluded that CRF results in posttranscriptional upregulation of these hepatic enzymes. Because a high-protein diet is neither clinically desirable nor appealing to the uremic individual, in a subsequent study we tested CRF animals fed a regular diet at 6 wk after 5% nephrectomy. The study revealed no discernible difference in hepatic HMG-CoA reductase gene expression or activity between the CRF and sham-operated control animals. Similarly, the abundance of hepatic cholesterol 7 α -hydroxylase mRNA and protein was unchanged in the CRF animals (49).

It should be noted that heavy proteinuria leads to upregulation of HMG-CoA reductase (87). Therefore, heavy proteinuria, when present, can modify HMG-CoA reductase expression and activity in humans and animals with chronic renal insufficiency. This is best exemplified by rats with advanced spontaneous focal, segmental glomerulosclerosis exhibiting heavy proteinuria and moderate renal insufficiency. Severe hypercholesterolemia in these animals is accompanied by a marked increase in hepatic HMG-CoA reductase protein abundance (92). It is tempting to speculate that a similar phenomenon may be operative in the pathogenesis of hypercholesterolemia in ESRD patients maintained on peritoneal dialysis in

whom CRF is compounded by substantial obligatory losses of proteins through the peritoneum.

The LDL receptor. LDL receptor-mediated cholesterol uptake plays an important role in cholesterol homeostasis. Chronic renal insufficiency in the absence of heavy proteinuria does not alter hepatic LDL receptor gene expression or protein abundance (49, 61). However, heavy proteinuria alone or in combination with chronic renal insufficiency results in acquired LDL receptor deficiency, which plays a central role in the genesis of the associated hypercholesterolemia (84, 92).

CONSEQUENCES OF DYSLIPIDEMIA

Progression of Renal Disease

Hyperlipidemia can potentially accelerate progression of renal disease by several mechanisms. First, reabsorption of fatty acids, phospholipids, and cholesterol contained in the filtered proteins (albumin and lipoproteins) by tubular epithelial cells can stimulate tubulointerstitial inflammation, foam cell formation, and tissue injury (12, 52). Second, accumulation of lipoproteins in glomerular mesangium can promote matrix production and glomerulosclerosis (45, 57, 95). In this context, native and oxidized lipoproteins, particularly LDL, stimulate production of matrix proteins by cultured mesangial cells and promote generation of proinflammatory cytokines, which can lead to recruitment and activation of circulating and resident macrophages (17, 28, 52, 64). In addition, impaired HDL-mediated reverse cholesterol transport can further contribute to tissue injury by limiting the unloading of the excess cellular cholesterol and phospholipid burden. In fact, low plasma HDL has been identified as an independent risk factor for progression of renal disease (33, 67). Moreover, hereditary LCAT deficiency, which is associated with a marked reduction in HDL cholesterol and impaired HDL-mediated reverse cholesterol transport, results in progressive renal disease (43). It is of note that both chronic renal insufficiency and nephrotic syndrome lead to acquired LCAT deficiency and impaired HDL metabolism (89, 90). Correction of these abnormalities by ACAT inhibitor administration has been shown to reduce proteinuria and retard progression of renal disease in experimental animals (82, 83).

In the past two decades, several studies have attempted to explore the effects of dyslipidemia and lipid-lowering therapies on the progression of renal disease and proteinuria in animals and humans. A number of animal studies have provided evidence for the role of hyperlipidemia in the progression of renal disease. For instance, consumption of a high-fat diet exacerbates, whereas correction of hyperlipidemia attenuates the severity of glomerulosclerosis and tubulointerstitial fibrosis in animal models of experimental renal disease (36, 37, 52, 57, 75). Moreover, pharmacological intervention aimed at normalization of HDL metabolism per se, with no change in serum total cholesterol, has been shown to retard the progression of renal disease in 5% nephrectomized rats (83).

In addition to the animal studies, a number of clinical studies have provided evidence for the potential contribution of dyslipidemia in progression to renal disease. For instance, the Physicians Health Study demonstrated a significant increase in the risk of deterioration of renal function among individuals with mildly elevated baseline serum creatinine who had elevated serum cholesterol and/or reduced HDL cholesterol con-

centrations (67). Similarly, the Modification of Diet in Renal Disease (MDRD) study identified low plasma HDL cholesterol as an independent risk factor for progression of renal disease (33). Together, these observations have prompted a limited number of clinical trials exploring the effect of lipid-lowering agents in humans with chronic kidney disease (CKD). For instance, a limited number of prospective studies have revealed significant reductions in proteinuria (11, 74) and the rate of decline in renal function (11) with statin administration in diabetic and nondiabetic patients with CKD. In addition, meta-analysis of 13 small prospective studies revealed a significant reduction in the rate of decline in the glomerular filtration rate (GFR) and marginal reductions in proteinuria and progression toward ESRD with lipid-lowering therapy primarily with various statins (22). Similarly, the Heart Protection Study showed a significantly lower rate of rise in serum creatinine concentration in the statin-treated group compared with the placebo-treated group (29). Also, in a large study of patients with coronary heart disease and dyslipidemia, statin administration for 3 yr resulted in a significant improvement in creatinine clearance compared with a placebo group (4). In contrast, post hoc analysis of data from the Cholesterol and Recurrent Event Study (73) showed no significant difference in the rate of decline in estimated GFR between the statin- and placebo-treated CKD patients. However, among patients with a baseline GFR below 40 ml/min, statin administration was associated with a significantly lower rate of decline in estimated GFR (73). The beneficial effects of statins have been attributed to both the lipid-lowering and lipid-independent anti-inflammatory (via interference with isoprenylation processes) (19, 62) action of these drugs.

Trials of the other lipid-lowering agents in patients with CKD have been very limited. For instance, administration of a nicotinic acid derivative for 12 mo was reported to lower proteinuria and the rate of decline in creatinine clearance in a small group of CKD patients with hyperlipidemia (60). In contrast, a large trial conducted at Veterans Affairs facilities revealed no significant difference in the rate of decline in renal function among patients with moderate renal insufficiency treated for 5 yr with gemfibrozil vs. those treated with a placebo (72). Thus the value of lipid-lowering therapies on the progression of renal disease in humans remains uncertain and requires further investigation.

Cardiovascular Disease

The risk of cardiovascular morbidity and mortality is profoundly increased in patients with CKD. For instance, the majority of patients with CKD die of cardiovascular events before reaching ESRD (2, 38). Moreover, cardiovascular mortality among dialysis-dependent ESRD patients is 10- to 30-fold greater than in the general population despite stratification for gender, age, race, and the presence of diabetes (23). Numerous factors contribute to atherogenic diathesis and the high risk of cardiovascular disease in CKD. These include oxidative stress, inflammation, hypertension, and altered metabolism of lipids, carbohydrates, nitric oxide, calcium, and phosphate, among others.

While plasma cholesterol concentration is frequently elevated in patients with nephrotic proteinuria and mild to moderate renal insufficiency, it is frequently normal or reduced and

only occasionally elevated in those with ESRD. Accordingly, the high risk of cardiovascular disease in ESRD populations cannot be attributed to hypercholesterolemia. On the contrary, a reduction in plasma cholesterol (which denotes intense inflammation) predicts cardiovascular events (34, 35, 51), in contrast to the pattern in the general population. However, the paradox of plasma total cholesterol by no means diminishes the participation of lipid disorders as a culprit in this process. Instead, accumulation of oxidation-prone atherogenic lipoprotein remnants and impaired HDL-mediated reverse cholesterol transport, which are the defining features of uremic dyslipidemia, may play a major part in the pathogenesis of atherosclerosis in this population.

Impact on Energy Metabolism

Impaired clearance of triglyceride-rich lipoproteins, i.e., VLDL and chylomicrons in CRF, is generally viewed in the context of associated dyslipidemia and cardiovascular disease. However, the author believes that those abnormalities may also adversely affect energy metabolism in CRF. VLDL and chylomicrons are the principal vehicles for the delivery of fatty acids to the skeletal muscles and myocardium for energy production and to the adipose tissue for energy storage. Fatty acids and glucose are the principal sources of energy that fuel all mechanical, biochemical, and biophysical functions of the body. Thus impaired LPL-mediated lipolysis of VLDL and chylomicrons, as well as, diminished VLDL receptor-mediated uptake of VLDL by skeletal muscle and myocardium, can necessarily limit the availability of fatty acid fuel in these tissues. Therefore, I believe that this phenomenon can contribute to the reduction in exercise capacity in ESRD patients. Similarly, insulin resistance, which is a common consequence of renal failure, can compound the problem by limiting the availability of glucose for energy production in the muscle tissue. Together, these events can account for the profound reduction in exercise capacity in ESRD patients despite adequate anemia control.

In addition to affecting muscle tissue, CRF results in downregulation of LPL and the VLDL receptor in adipose tissues. This phenomenon can limit the long-term storage of energy and can contribute, in part, to wasting and weight loss in the uremic state.

CONCLUSIONS

CRF results in profound dysregulation of several key enzymes and receptors involved in the metabolism of lipoproteins, particularly those of HDL and triglyceride-rich lipoproteins. Downregulation of LCAT, apoA-1, and hepatic lipase together with upregulation of CETP are largely responsible for the reduction in HDL cholesterol and elevation of HDL triglyceride in CRF. Downregulation of skeletal muscle and adipose tissue LPL, hepatic lipase, and the VLDL receptor and of hepatic LRP is collectively responsible for hypertriglyceridemia, impaired clearance, and elevated plasma levels of VLDL, IDL, and chylomicron remnants despite downregulation of hepatic triglyceride synthetic capacity (DGAT). Dysregulation of lipid metabolism can contribute to atherogenic diathesis and possibly to progression of renal disease and impaired energy metabolism in CRF.

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