Molecular mechanisms of lipid disorders in nephrotic syndrome

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A 37-year-old executive was referred by her internist to the nephrology service at the University of California at Irvine for evaluation of proteinuria and lower extremity edema. She had been healthy until 2 months prior to referral when she first noticed mild swelling of her ankles in the late afternoon. During the ensuing weeks, the edema steadily increased, extending to her legs and subsequently to the lower portion of her thighs.

A review of systems was unremarkable except for the recent onset of diminished exercise capacity and lower extremity edema. The past medical history was negative except for an appendectomy 17 years ago. Because the patient was adopted when she was 2 years old, her family history was unknown. She is married and has no children. She does not smoke and denies use of illicit drugs or exposure to solvents, heavy metals, or industrial or occupational toxins. A thorough annual medical evaluation 6 months ago had been normal. Results from laboratory tests at that time all were within normal limits, including the hemogram, lipid profile, urinalysis, blood urea nitrogen, creatinine and albumin concentrations, and liver function tests. A test for occult blood in the stool was negative. A mammogram and Pap smear were normal.

The current physical examination was notable for mild hypertension (140/90 mm Hg) and marked bilateral, lower extremity pitting edema extending to the mid-thigh. No other abnormalities were found. Urinalysis revealed 4+ proteinuria, numerous hyaline casts, and no hematuria or leukocyturia. A 24-hour urine collection contained 10 g of protein. A fasting serum chemistry panel showed severe hypoalbuminemia, 2.1 g/dL; hypercholesterolemia, 387 mg/dL; hypertriglyceridemia, 420 mg/dL; mild hyponatremia, 132 mEq/L; and a normal glucose level. Tests for antinuclear antibody, antidouble-stranded DNA antibody, hepatitis, and HIV serologies, as well as a rapid plasma reagin (RPR) test were negative. Complement levels were within the normal range. Light, immunofluorescent, and electron microscopy of a percutaneous renal biopsy specimen revealed unequivocal evidence of membranous nephropathy.

DISCUSSION

DR. NOSRATOLA D. VAZIRI (Chief, Division of Nephrology and Hypertension; and Professor of Medicine, Physiology, and Biophysics, University of California, Irvine, California, USA): This patient represents a typical case of nephrotic syndrome (NS) exhibiting heavy proteinuria, hypoalbuminemia, sodium retention, and hyperlipidemia. Hyperlipidemia is one of the cardinal manifestations of NS. Nephrotic hyperlipidemia is marked by elevations of plasma low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and lipoprotein(a) [LP(a)] [1–5]. Nephrotic hyperlipidemia also is frequently accompanied by a reduced [6] or unchanged [1] HDL concentration and an increased LDL/HDL cholesterol ratio. These abnormalities denote a high risk for cardiovascular disease in patients with chronic NS. In addition, NS significantly alters the composition of lipoproteins. For instance, the ratios of cholesterol to triglycerides, free cholesterol to cholesterol esters, and phospholipids to proteins are significantly increased in all lipoprotein fractions in NS [6]. These alterations are accompanied by impaired clearance of VLDL and chylomicrons, and accumulation of their atherogenic remnants in the plasma [1, 7–11].

In the course of this presentation, I will review the effect of NS on the metabolism of different classes of plasma lipoproteins and the relevant lipid regulatory enzymes and receptors.
LDL and cholesterol metabolism

Plasma LDL and total cholesterol are markedly elevated in NS. Elevation of plasma LDL in NS is thought to be due to increased LDL synthesis [7] and depressed LDL catabolism [1]. In fact, Warwick et al [10, 12] have demonstrated a significant reduction in the rate of catabolism of apolipoprotein B (Apo B), the principal apoprotein constituent of LDL. Most of the earlier studies of lipid metabolism in NS had focused on characterization of the plasma lipid profile, determination of the rate of clearance of labeled lipoprotein fractions, indirect measurements of lipid biosynthesis, and apoprotein expressions. However, until recently, the molecular bases of altered cholesterol biosynthesis and catabolism were not known, and the mechanism of impaired LDL clearance had not been elucidated. To explore the molecular mechanisms of nephrotic hypercholesterolemia, we carried out a series of studies testing the hypothesis that the marked rise in serum cholesterol characteristic of NS must be due either to increased biosynthesis and/or to decreased cholesterol catabolism. To this end, we first examined the effect of NS on hepatic tissue expression of 3-hydroxysterol-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis. We then studied expression of hepatic cholesterol 7α-hydroxylase (Ch 7α-hydroxylase), the rate-limiting step in cholesterol catabolism to bile acids. We subsequently examined the hepatic LDL receptor to further explore the mechanism of hypercholesterolemia and impaired LDL clearance in NS. Finally, we investigated the expression of the liver-specific enzyme, acylcoenzyme A:cholesterol acyltransferase-2 (ACAT-2), which plays a critical role in cholesterol signaling as well as in assembly and secretion of Apo B-containing lipoproteins. I will briefly describe the functions of these proteins and their alterations in NS.

HMG-CoA reductase is the rate-limiting enzyme in the biosynthesis of cholesterol. Hepatic HMG-CoA reductase activity closely correlates with cholesterol biosynthesis under a broad range of cholesterol biosynthetic rates [13]. Although it is expressed in virtually all tissues, it is most abundant in the liver, which plays a central role in the regulation of plasma cholesterol. Hepatic HMG-CoA reductase expression and activity are tightly regulated by intracellular free cholesterol (or oxycholesterols), which can suppress the transcription, translation, and catalytic activity of the enzyme [14]. Similarly, bile acids, the main products of cholesterol catabolism, exert a negative feedback on hepatic HMG-CoA reductase at the levels of transcription, translation, and enzymatic activity. Finally, hepatic expression and activity of this enzyme are influenced by diurnal variation and numerous hormones. For instance, thyroid hormone, insulin, and estrogen up-regulate, whereas glucocorticoids down-regulate, HMG-CoA reductase, and glucagon counteracts insulin’s action [14].

In our initial study of rats with puromycin-induced NS (a popular model of minimal-change disease), we found a marked up-regulation of HMG-CoA reductase mRNA and enzymatic activity during the induction phase of proteinuria and hypercholesterolemia [15]. These changes were followed by a gradual decline in HMG-CoA reductase mRNA and activity toward baseline values despite persistent hypercholesterolemia during the chronic phase of NS. Interestingly, withdrawal of food for 20 hours resulted in a pronounced but transient up-regulation of HMG-CoA reductase in rats with chronic nephrosis but had no effect in the control rats. These observations suggest that up-regulation of HMG-CoA reductase during the induction phase, and with food restriction during the chronic phase, contributes to generation and maintenance of hypercholesterolemia in NS [15]. In contrast to the nephrotic animals, rats fed a high-cholesterol, high-saturated fat diet to produce an equally severe hypercholesterolemia showed an appropriate down-regulation of hepatic HMG-CoA reductase expression and activity [15]. These observations point to a defective HMG-CoA reductase regulatory response to hypercholesterolemia in NS.

In a recent study, we found a marked increase in immunodetectable HMG-CoA reductase protein abundance in the livers of Imai rats with spontaneous focal glomerulosclerosis and severe nephrotic proteinuria [16]. This observation proved that up-regulation of HMG-CoA reductase in nephritic syndrome is independent of the cause of the underlying glomerulopathy. In an attempt to dissect the effect of proteinuria from that of the resultant hypoalbuminemia, we examined hepatic tissue expression of immunodetectable HMG-CoA reductase in Nagase rats with hereditary analbuminemia. We found a significant up-regulation of hepatic HMG-CoA reductase in male Nagase rats that exhibited profound hypoalbuminemia and mild hypercholesterolemia (unpublished data). Up-regulation of HMG-CoA reductase expression in both NS and hereditary analbuminemia, which share hypoalbuminemia but not proteinuria, indicates the role of hypoalbuminemia per se in mediating this change.

The principal pathway of cholesterol catabolism is its conversion to bile acids for secretion into the small intestine and eventual fecal excretion. Ch 7α-hydroxylase is the first and the rate-limiting step in cholesterol conversion to bile acids and, as such, plays a critical role in cholesterol catabolism. Expression of this unique cytochrome P450 enzyme is up-regulated by increased intracellular free cholesterol concentration, thyroid hormone, high cholesterol intake, and bile acid depletion. In contrast, bile acids, glucocorticoids, and starvation down-regulate Ch 7α-hydroxylase [17]. Given the critical role of Ch 7α-hydroxylase in cholesterol metabolism, we explored expression of hepatic Ch 7α-hydroxylase in rats with
NS, rats with diet-induced hyperlipidemia, and normal control rats. The study revealed a marked up-regulation of Ch 7α-hydroxylase mRNA and immunodetectable protein in rats with diet-induced hypercholesterolemia. However, despite equally severe hypercholesterolemia, nephrotic rats showed no rise in either Ch 7α-hydroxylase mRNA or protein abundance [16, 18]. In a subsequent study, we found that bile secretion rate was markedly elevated in rats with diet-induced hypercholesterolemia but was virtually unchanged in the nephrotic rats, thus demonstrating the inability of nephrotic animals to increase bile secretion rate in response to severe hypercholesterolemia [19].

To discern the reason for the disparity in hepatic HMG-CoA reductase and Ch 7α-hydroxylase expression between the nephrotic and diet-induced hypercholesterolemias, we measured intracellular cholesterol concentration, which plays a major role in the regulation of these enzymes. The study showed a 16-fold increase in hepatic tissue cholesterol content in rats with diet-induced hypercholesterolemia, but no increase in the nephrotic animals despite equally severe hypercholesterolemia [15, 18]. These observations point to the lack of rise in hepatocellular cholesterol content as an underlying mechanism for the observed dysregulation of HMG-CoA reductase and Ch 7α-hydroxylase in NS. To elucidate the mechanism of the observed discordance in plasma and hepatocyte cholesterol levels, we next explored the effect of NS on LDL receptor expression.

Hepatic cholesterol uptake represents the primary pathway of cholesterol clearance from the circulation. We therefore considered that discordance between plasma and hepatocyte cholesterol concentrations and the resultant dysregulations of HMG-CoA reductase [15, 16] and Ch 7α-hydroxylase [16, 18] in NS might be partly due to impaired hepatic cholesterol uptake. As the LDL receptor provides the predominant pathway for plasma cholesterol clearance, we hypothesized that NS results in acquired LDL receptor deficiency. To test this hypothesis, we determined LDL receptor mRNA and protein abundance and gene transcription rate in the livers of nephrotic and control rats [16, 20]. The results showed severe reduction of hepatic LDL receptor protein abundance in the nephrotic animals despite normal LDL receptor mRNA abundance and gene transcription rate. The latter findings point to inefficient translation and/or increased LDL receptor protein turnover as a cause of LDL receptor deficiency in NS. Given the critical role of LDL receptor, acquired LDL receptor deficiency must contribute to hypercholesterolemia, elevation of plasma LDL, impaired LDL clearance [10], and inappropriately low hepatocellular cholesterol in NS. The reduction in hepatocellular cholesterol concentration can, in part, account for dysregulation of HMG-CoA reductase and Ch 7α-hydroxylase expressions in nephrotic animals [15, 18].

Regulation of HMG-CoA reductase, Ch 7α-hydroxylase, and other cholesterol-responsive factors by cholesterol depends on intracellular free cholesterol as opposed to cholesterol esters, which constitute the bulk of the cellular cholesterol pool. Given the importance of cellular free-cholesterol concentration and the cholesterol esterification system in cholesterol metabolism, we examined gene expression, protein abundance, and enzymatic activity of the liver-specific enzyme ACAT-2, which is responsible for esterification of cholesterol in the liver [16, 21].

Primarily localized in the endoplasmic reticulum, ACAT catalyzes intracellular esterification of cholesterol and formation of cholesterol esters in nearly all mammalian cells. Recently, two distinct isoforms of ACAT, ACAT-1 and ACAT-2, have been identified in the hepatocytes of humans and animals [22–24]. ACAT-1 is ubiquitously expressed in all tissues, whereas ACAT-2 is primarily expressed in the liver and intestine. Esterification of cholesterol by ACAT limits its solubility in the cell membrane lipid bilayer and promotes accumulation of cholesterol esters in the fat droplets. By modulating intracellular free cholesterol concentration, ACAT regulates cholesterol signaling pathways [25]. In addition, ACAT-mediated esterification of cholesterol contributes to production, packaging, and release of VLDL by the liver [26]. Finally, ACAT contributes to cholesterol ester accumulation in macrophages and vascular tissue, hence, foam cell formation and atherosclerosis [27].

Free cholesterol regulates HMG-CoA reductase and Ch 7α-hydroxylase, and ACAT modulates cellular free cholesterol level, so we hypothesized that dysregulation of lipid metabolism in NS in part reflects a possible up-regulation of hepatic ACAT activity. Therefore we determined the mRNA abundance, immunodetectable protein, and enzymatic activity of the liver-specific ACAT-2 in rats with chronic NS caused by either puromycin or spontaneous focal glomerulosclerosis and compared the results with those obtained in normal control rats [16, 21]. To dissect the effect of proteinuria from that of hypoalbuminemia, we included a group of Nagase rats with hereditary analbuminemia in the study. The nephrotic animals exhibited a 3- to 4-fold increase in liver tissue ACAT-2 mRNA and protein abundance as well as enzymatic activity. The increase was accompanied by a significant reduction of hepatic tissue free-cholesterol concentration, which provided functional evidence for excess ACAT-2 activity in the nephrotic liver. In contrast, despite extreme hypoalbuminemia, rats with hereditary analbuminemia showed only a mild elevation of hepatic ACAT-2 mRNA, protein, and enzymatic activity. Hepatic ACAT-2 protein and activity strongly correlated with plasma lipid concentrations and urinary protein.
excretion. The study therefore demonstrated a marked up-regulation of hepatic ACAT-2 and its possible contribution to the associated dyslipidemia in NS. The study further showed that elevation of hepatic ACAT-2 in NS is primarily due to proteinuria as opposed to hypoalbuminemia [21]. The observed overexpression of hepatic ACAT-2 can, in part, contribute to dysregulation of HMG-CoA reductase and Ch 7a-hydroxylase [28] by lowering intracellular free-cholesterol concentration while simultaneously generating abundant supplies of cholesterol esters for incorporation into Apo B-containing lipoproteins.

To determine the effect of NS on the intestinal transport of cholesterol, we measured the rate of absorption of micellar preparations of cholesterol in nephrotic, diet-induced hypercholesterolemic, and in control rats. The results showed no significant difference in the rates of cholesterol absorption among the study groups. Thus, neither nephrotic hyperlipidemia nor diet-induced hyperlipidemia affects intestinal absorption of cholesterol [19].

In sum, NS is associated with a relative elevation of hepatic HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis, and with a relative reduction of Ch 7a-hydroxylase, the rate-limiting enzyme in cholesterol catabolism. These alterations are accompanied by, and are at least in part due to, LDL receptor deficiency, which limits hepatic cholesterol uptake, and up-regulation of hepatic ACAT-2, which lowers hepatocyte free-cholesterol concentration. These molecular events can account for the induction and maintenance of nephrotic hypercholesterolemia, impaired LDL clearance, and cholesterol enrichment of VLDL and newly synthesized LDL particles.

**HDL metabolism**

The primary function of HDL is retrieval of surplus cholesterol from extrahepatic tissues for disposal in the liver. Cholesterol ester delivery by HDL to the liver can occur either directly via receptor-mediated processes or indirectly via transfer of cholesterol esters to Apo B[100] containing particles and their uptake by LDL receptor or by LDL-receptor-related protein (LRP). HDL-mediated cholesterol retrieval, commonly known as reverse cholesterol transport, is essential for cellular cholesterol homeostasis and protection against atherosclerotic cardiovascular disease. Other functions of HDL include participation in the shuttling of Apo C and Apo E proteins between nascent triglyceride-rich lipoproteins and their remnants, transport of clusterin and paraoxonase, delivery of cholesterol to steroidogenic glands (for example, adrenal and gonads), adsorption of bacterial endotoxins, inhibition of platelet aggregation (via regulation of Cox-2), and modulation of cytokine-mediated endothelial adhesion molecule expression [29]. The main apoprotein constituents of HDL are Apo A-I (70% of HDL protein) and Apo A-II (20% of HDL protein), which are produced by the liver and intestine. (The remaining 10% consist of Apo A-IV, Apo C, and Apo E.) These apoproteins are secreted with VLDL and chylomicrons. After reaching the extracellular space, Apo A-I and Apo A-II dissociate from the original particles as phospholipid complexes and coalesce to form the nascent HDL. Subsequently, nascent HDL particles incorporate Apo C-phospholipid and Apo E-phospholipid complexes, which are either derived from lipolysis of VLDL and chylomicrons by lipoprotein lipase or are directly secreted by the liver. These events lead to formation of small cholesterol-poor HDL-3 particles. As reviewed by Genest et al [29], retrieval of surplus cholesterol by the small cholesterol-poor discoid HDL particle begins with its attachment to the cell surface via HDL-binding protein, which has been shown to be identical to vigilin. The binding of HDL to its binding protein leads to mobilization of intracellular cholesterol pools and translocation of free cholesterol via the Golgi apparatus to the caveolae and ultimately to the plasma membrane. Accumulation of free cholesterol in the plasma membrane generates a concentration gradient favoring its diffusion to the surface of the HDL particle. Free cholesterol reaching the surface of HDL is immediately esterified by the enzyme lecithin:cholesterol acyltransferase (LCAT) in the presence of its cofactor Apo A-I to form cholesterol ester. Because of its intense hydrophobicity, cholesterol ester formed on the surface sinks into the core of the HDL particle, thus sustaining the favorable gradient for maximal cholesterol uptake by the maturing HDL. Once fully loaded, the cholesterol ester–rich HDL particle dissociates from the HDL binding protein and returns to the circulation for transport to the liver. In the circulation, the cholesterol ester–rich HDL-2 particle donates part of its cholesterol ester cargo to VLDL remnants (IDL) in exchange for triglycerides. This process is facilitated by plasma cholesterol ester transfer protein (CETP), which is present in humans but absent in rats. In addition, HDL acquires Apo C and Apo E from VLDL and chylomicron remnants for subsequent donation to the nascent VLDL and chylomicrons. These events lead to further reduction of triglyceride content of the VLDL remnants, thus contributing to their eventual conversion to LDL or hepatic removal by either LDL receptors or LRP-mediated endocytosis. Extraction of Apo C proteins from the remnant particles by HDL is necessary for the uptake of remnants by the liver, as the receptor binding is inhibited by Apo C proteins. Moreover, donation of Apo C and Apo E to the nascent VLDL and chylomicrons by HDL is critical for their subsequent lipolysis by lipoprotein lipase (LPL). This is because Apo E is necessary for their binding to the endothelial surface and Apo C-II is necessary for activation of LPL. Finally, the lipid-loaded HDL particle binds to the newly discovered HDL receptor, which serves as
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by urinary losses of proteins of intermediate molecular weight; the molecular mass of LCAT (63 kD) is very close to that of albumin. In contrast to the nephrotic animals, the Nagase rats with hereditary analbuminemia showed normal LCAT mRNA abundance in the liver and normal plasma and urine LCAT activity. These observations suggested that LCAT deficiency in NS is due to proteinuria, not hypoalbuminemia.

In the presence of LCAT deficiency, accumulation of unprocessed free cholesterol on the surface of HDL limits the gradient-driven cholesterol uptake by HDL. This limitation leads to a rise in cellular cholesterol and impaired maturation of cholesterol-poor HDL-3 to cholesterol ester–rich HDL-2 [33, 34]. In addition to transporting the surplus cholesterol to the liver, HDL shuttles Apo C-II and Apo E between nascent VLDL and chylomicrons and their remnants [35]. Among HDL species, HDL-2 is the most efficient donor of Apo C-II and Apo E. Therefore, an LCAT deficiency–induced reduction of HDL-2 reduces Apo C-II (cofactor of lipoprotein lipase) and Apo E (ligand for endothelial heparan sulfate) in VLDL and chylomicrons, which, in turn, can depress lipolysis of VLDL and chylomicrons and promote hypertriglyceridemia. Unlike rats, humans possess CETP, which catalyzes the exchange of triglycerides in VLDL remnants for cholesterol ester in HDL. Therefore, reduction in the cholesterol ester content of HDL, occasioned by LCAT deficiency in humans, can limit maturation of VLDL remnants and lead to generation of abnormal particles with a high-triglyceride content. Thus, the severe LCAT deficiency shown in our study [32] can contribute to the reported abnormalities of HDL maturation and metabolism [31], as well as to impaired clearance and abnormal composition of VLDL and chylomicrons and their remnants in NS [1, 7–9, 36], compounding the effects of lipoprotein lipase, hepatic triglyceride lipase, and VLDL receptor deficiencies [37–39].

Apo A-I (molecular mass, 28 kD) is the main structural component of HDL, the obligate cofactor for LCAT, and the likely ligand for the HDL binding protein (viginin) and HDL receptor (SR-B1). Synthesized by the liver and intestine, it is primarily catabolized by liver, kidney, skin, and other tissues. Hepatic Apo A-I mRNA is increased, its fractional catabolic rate is reduced, and despite its urinary losses, plasma Apo A-I concentration is elevated in nephrotic rats [40, 41]. In contrast to rats, fractional catabolism of Apo A-I is often elevated in nephrotic humans [42]. The observed disparity appears to be due to the absence in the rat [43] and upregulation in nephrotic humans [44] of CETP, which catalyzes transfer of cholesterol esters from HDL-2 to VLDL remnants. This process favors formation of HDL-3; HDL-3’s affinity for Apo A-I is less than that of HDL-2 [45]. Therefore, an increased level of cholesterol-ester-poor HDL-3 occasioned by elevated CETP [44], and reduced LCAT [32]...
can contribute to elevation of unincorporated Apo A-I, which, owing to its small size, is susceptible to urinary excretion and catabolism in the kidney [41].

As I said earlier, HDL plays an important role in the reverse transport of cholesterol from the extrahepatic tissues to the liver, as well as delivery of cholesterol esters to nonplacental steroidogenic tissues (gonads and adrenal glands). Prior to discovery of the HDL receptor, the mechanism of cholesterol uptake from HDL by liver and the steroidogenic glands was unknown. The HDL receptor, originally identified by Acton and colleagues as an SR-B1 molecule, is a cell membrane-associated protein, which is expressed in the liver, adrenal glands, testes, and ovaries and which has a high affinity for HDL. Cells transfected with the HDL receptor gene exhibit a strong saturable binding affinity for HDL. Binding of HDL to its receptors on the transfected cells removes its lipid contents without uptake or degradation of the HDL apoprotein constituents [30]. Reversible binding of HDL to the HDL receptor on the surface of the hepatocyte unloads cholesterol esters from the core of HDL into the hepatocyte. In addition, binding to the receptor facilitates lipolysis of triglycerides in the HDL by hepatic triglyceride lipase and removal of fatty acids by the liver. Thus, unlike the LDL receptor, the HDL receptor serves as a docking receptor that allows HDL to operate as a recycling shuttle for cholesterol transport from the extrahepatic tissues to the liver and steroidogenic glands. Notably, hepatic removal and catabolism of Apo A-I involve a different and as-yet- unidentified pathway with niacin-responsive and niacin-unresponsive components [46].

To discern the possible effect of NS on hepatic HDL receptor expression, we studied HDL receptor mRNA and immunodetectable HDL receptor protein abundance in rats with chronic NS [47]. The nephrotic animals showed marked down-regulation of hepatic HDL receptor protein expression that was accompanied by a normal HDL receptor mRNA abundance. Thus, NS appears to affect the hepatic HDL receptor at the level of protein in a manner virtually identical to that seen with LDL receptor expression [20]. Combined down-regulation of the hepatic HDL receptor and LDL receptor, which represent the two major pathways of plasma cholesterol clearance, can play a central role in the pathogenesis of nephrotic hypercholesterolemia and the associated dysregulation of HMG-CoA reductase and Ch 7a-hydroxylase expressions [15, 18]. As I noted earlier, in addition to accommodating the removal of cholesterol esters, HDL binding to HDL receptor facilitates hydrolysis of HDL triglycerides by hepatic triglyceride lipase, which is also severely depressed in NS [38]. Thus, combined HDL receptor and hepatic triglyceride lipase deficiencies can severely affect HDL-dependent lipid transport in NS.

In short, proteinuria produces urinary losses of LCAT and severe LCAT deficiency, which limit the HDL-mediated uptake of surplus cholesterol from extrahepatic tissues. This limitation can contribute to the reported abnormalities of HDL, VLDL, chylomicrons, and their remnants in NS. Impaired HDL-mediated cholesterol uptake from the extrahepatic tissues is compounded by marked reduction of the hepatic HDL receptor, which can limit HDL-mediated cholesterol (and triglyceride) disposal in the liver. These events work in concert to limit reverse cholesterol transport and hence cardiovascular, and perhaps renoprotective, actions of HDL. Indeed, they probably contribute to cardiovascular complications in chronic nephrosis.

**Triglyceride-rich lipoprotein metabolism**

The critical role of lipids in energy metabolism is evidenced by the fact that as much as 80% of energy produced in the body passes through some lipid intermediary. Triglyceride-rich lipoproteins, which consist of chylomicrons, VLDL, and their remnants, are the primary vehicles for transport of fatty acids (as triglycerides) among the sites of absorption, production, storage, and consumption. In addition, albumin binds and transports free fatty acids and lyssolecithins.

Chylomicrons serve as the vehicle for transport of dietary lipids. Nascent chylomicrons are produced in the enterocytes from fatty droplets containing triglycerides, phospholipids, and cholesterol esters supplemented with an array of apoproteins including Apo B-48, Apo A-I, Apo A-II, and Apo A-IV. After being released in the circulation via the lymphatic system, nascent chylomicrons acquire free cholesterol, Apo C, and Apo E from HDL in exchange for Apo A-I, Apo A-II, and phospholipid. Acquisition of Apo C and Apo E from HDL is essential for the subsequent lipolysis of chylomicrons by lipoprotein lipase, which requires Apo C-II for enzymatic activity and Apo E for particle binding to the endothelial surface (Fig. 2).

Very-low-density lipoprotein is the vehicle for transport of endogenous lipids. Nascent VLDL is produced in the hepatocyte from fusion of partially lipidated, newly synthesized Apo B-100 with a triglyceride-rich particle and subsequent addition of Apo E, Apo A-I, and Apo A-II. After release into the circulation, nascent VLDL acquires Apo C and Apo E from HDL in exchange for Apo A-I, Apo A-II, and additional phospholipid. Again, acquisition of additional Apo E is needed for proper binding, while acquisition of Apo C-II is necessary for optimal lipolysis of VLDL by lipoprotein lipase. Fatty acids used for incorporation into VLDL in the liver are derived from de novo synthesis from surplus carbohydrates, plasma albumin-bound fatty acid pool and hepatic lipase-mediated lipolysis or receptor-mediated uptake of IDL, and chylomicron remnants and HDL.

Triglyceride-rich lipoproteins deliver fatty acids as triglycerides to various tissues for energy production
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Fig. 2. Formation and metabolism of chylomicrons (CM). Abbreviations are: LPL, lipoprotein lipase; LRP, low-density lipoprotein (LDL)-receptor-related protein, also known as remnant receptor; HDL, high-density lipoprotein; Apo C & E, apolipoprotein C and E.

(skeletal muscle and myocardium) or energy storage (adipose tissue). Delivery of fatty acids to these tissues involves hydrolysis of triglyceride by lipoprotein lipase leading to release of two fatty acids, followed by removal of the third fatty acid, which involves a separate monoglyceride system. Two thirds of the fatty acids released from VLDL and chylomicrons diffuse into the adjacent myocytes or adipocytes for energy production or storage, respectively. However, the remaining free fatty acids enter the plasma pool bound to albumin or lipoproteins for transport to distant sites, mainly the liver. Lipoprotein lipase-mediated lipolysis causes an approximately 70% reduction in triglyceride contents of chylomicrons and VLDL under normal conditions. This reduction significantly decreases the particle diameter coupled with partial transfer of phospholipid/free cholesterol monolayer, substantial transfer of Apo E, and total transfer of Apo C and Apo A from the shrinking chylomicrons or VLDL to the adjacent HDL. The chylomicron remnants formed in this manner are endocytosed by hepatocytes via LRP. In the hepatocyte, part of the triglycerides released from chylomicron remnants is returned to the circulation via newly synthesized VLDL. In the circulation, the VLDL remnants (IDL) donate part of their remaining triglycerides to the nearby HDL in exchange for cholesterol esters with the aid of CETP. Thereafter, most of the IDL undergoes further lipolysis by hepatic triglyceride lipase and becomes LDL, which normally consists exclusively of Apo B-100 with a core of cholesterol ester and negligible amounts of triglycerides (major pathway). The remaining IDLs are removed by the liver via either LDL receptor or LRP (minor pathway) (Fig. 3).

Plasma concentrations of triglycerides, VLDL, and IDL remnants are markedly elevated, triglyceride content of Apo B–containing lipoproteins is increased, and clearance of VLDL and chylomicrons is significantly impaired in NS [1, 7, 9–11]. Although increased production of lipids and lipoproteins can contribute to the nephrotic hyperlipidemia [48], impaired clearance of chylomicrons [49, 50] and VLDL [9, 49] has emerged as the dominant factor. Impaired VLDL and chylomicron clearance in NS was originally attributed to proteinuria, not hypoalbuminemia [49]. Recently, however, Shearer et al [50] have demonstrated that both proteinuria and hypoalbuminemia can separately contribute to impaired lipoprotein catabolism.

Lipoprotein lipase (LPL) is the rate-limiting step in lipolysis of VLDL and chylomicrons [51]. This glycoprotein enzyme is a member of the lipase family, which also includes hepatic triglyceride lipase and pancreatic lipase. Heavily expressed in adipose tissue, skeletal muscle, myocardium, and several other tissues, LPL is produced as an inactive enzyme that requires sequential glycation, glucose trimming, and cleavage of a 27 amino acid peptide to become active. The LPL is then stored in the Golgi vesicles and directed for either intracellular degradation or secretion to the cell surface [52]. The secreted LPL binds to heparan sulfate proteoglycans on the cell surface and eventually translocates to the lumen of the adjacent capillaries, where it attaches to the heparan sulfate on the endothelial cells. Only the endothelial-bound pool of LPL is relevant to lipolysis of VLDL and chylomicrons. Since soluble heparin can displace and release LPL from the binding sites, measurement of plasma post heparin lipolytic activity or heparin releasable LPL can be used to investigate LPL activity in humans and animals. Several in vivo studies had demonstrated marked reduction of heparin-releasable LPL in nephrotic animals and humans [8, 9, 11, 36, 49, 53, 54]. However, the effect of NS on gene expression and protein abundance of LPL in the relevant tissues such as skeletal muscle, myocardium, and adipose tissue was not known. Our studies showed significant reductions of heparin-releasable, nonreleasable (intracellular), and total
LPL activities in the myocardium and adipose tissues and of total LPL activity in the skeletal muscle of nephrotic rats [37]. These reductions were accompanied by marked reductions of LPL protein abundance in all tested tissues and of LPL mRNA in the myocardium. However, despite significant reductions in LPL activity and protein abundance, LPL mRNA abundance in skeletal muscle and adipose tissue of the nephrotic rats was unchanged, reflecting post-translational regulation. In earlier studies, we had shown that by increasing the left ventricular workload, hypertension leads to marked up-regulation of LPL expression in the myocardium [55]. Because NS is frequently accompanied by hypertension, coexistent hypertension can modify the effect of NS on cardiac LPL expression. The down-regulation of LPL protein abundance and enzymatic activity found in puromycin-induced NS was recently confirmed by our group in nephrotic rats with spontaneous focal glomerulosclerosis [56].

Our studies thus demonstrated marked down-regulation of LPL in skeletal muscle, myocardium, and adipose tissue, the principal sites of consumption and storage of fatty acids. The obvious implication of LPL deficiency relates to its role in the pathogenesis of hyperlipidemia and the associated risk of cardiovascular disease. The less obvious consequence of severe LPL deficiency is its impact on energy metabolism in skeletal and cardiac muscles, which draw much of their energy requirements from fatty acids derived from circulating VLDL via LPL and possibly VLDL receptor. This phenomenon can potentially contribute to diminished exercise capacity and easy fatigability, frequently seen in nephrotic patients. Hepatic lipase is another member of the lipase family that has considerable structural homology with LPL [57]. However, hepatic lipase is distinct from LPL in its tissue distribution, substrate specificity (IDL and HDL), and independence from Apo C-II. Hepatic lipase plays a critical role in maturation of IDL to LDL and in triglyceride unloading of HDL-2 in the liver. Plasma IDL is markedly elevated, and composition of HDL is abnormal in NS [1, 5, 6, 8, 9, 11, 58, 59]; both of these alterations point to depressed hepatic lipase activity. In fact, in vitro perfusion of livers from rats with puromycin-induced NS yields 50% lower heparin-releasable lipase activity as compared with control rats [9]. We demonstrated that the reduction in hepatic lipase activity in NS is due to severe down-regulation of hepatic lipase gene expression [38]. In addition to its role in metabolism of IDL, hepatic lipase plays a major role in the lipolysis of triglycerides in HDL-2, which depends on its binding to hepatic HDL receptor. Therefore, the combination of HDL receptor deficiency [47] and hepatic lipase deficiency [38] can severely affect HDL metabolism in NS.

The VLDL receptor is a newly recognized member of the LDL receptor family, which binds and internalizes VLDL but not LDL. Tissue distribution of VLDL receptor (skeletal muscle, myocardium, and adipose tissue) is similar to that of LPL [60–62]. In addition to their shared tissue distribution, VLDL receptor and LPL appear to be functionally interdependent [63]. For instance, LPL facilitates binding of VLDL particles to VLDL receptor by forming a bridge between heparan sulfate proteoglycan and VLDL. Nephrotic syndrome is associated with impaired clearance and elevated plasma concentration of VLDL, which might reflect possible VLDL receptor deficiency. Therefore, we studied VLDL receptor mRNA and protein abundance in skeletal muscle and myocardium of nephrotic and control rats and found a marked reduction of VLDL receptor protein in both tissues in the nephrotic animals. This decrease was coupled with a parallel reduction in VLDL receptor mRNA in the cardiac but not skeletal muscle [39]. In a more recent study, we found a severe progressive reduction of VLDL...
receptor in the skeletal muscle and adipose tissue of nephrotic rats with spontaneous focal glomerulosclerosis and severe hyperlipidemia [56]. Given the functional interdependence of VLDL receptor and LPL, their severe combined deficiency might play a role in the pathogenesis of the associated hypertriglyceridemia and impaired catabolism of triglyceride-rich lipoproteins.

Does defective VLDL binding play a role in NS? In an in vitro study, Furukawa et al [64] found that LPL-mediated lipolysis is significantly lower with VLDL preparations from nephrotic rats as compared to the VLDL obtained from normal rats. They further showed that the defective LPL-mediated lipolysis of the nephrotic VLDL can be corrected by the addition of normal rat HDL. More recently, Shearer et al [50] demonstrated that binding of VLDL from nephrotic rats to cultured rat aorta endothelial cells is markedly reduced, while binding of VLDL from Nagase rats with hereditary albuminemia is increased. They further showed that defective binding of nephrotic VLDL can be reversed by pre-incubation of nephrotic VLDL with HDL from either normal or Nagase rats but not with the nephrotic HDL. Likewise, infusion of normal HDL improved chylomicron clearance in nephrotic rats. These observations pointed to an intrinsic defect of triglyceride-rich lipoproteins in nephrotic animals, which was linked to an abnormality in nephrotic HDL. Analysis of apoprotein-lipid ratios of VLDL and HDL revealed a significant reduction in the Apo B-to-triglyceride ratio in nephrotic VLDL and a marked reduction in the Apo E-to-Apo A-I ratio in the nephrotic HDL. A similar reduction in the Apo E-to-Apo A-I ratio was reported in HDL from salt-sensitive Dahl rats with NS [54]. Because HDL is a source of Apo E and Apo C for the nascent VLDL, and these apoproteins are required for activation and binding to LPL, Shearer et al suggested that Apo E depletion of nephrotic HDL can contribute to impaired lipolysis of triglyceride-rich lipoproteins by LPL [50]. Similarly, a relative reduction of Apo E, which is a ligand for the VLDL receptor, can interfere with its efficient binding and clearance by VLDL receptor [50]. Lipoprotein lipase deficiency appears to be partly responsible for diminished Apo E content of HDL because LPL-mediated lipolysis of VLDL is required for the transfer of Apo C and Apo E from VLDL remnants to HDL. It is therefore intuitive that insufficient lipolysis of VLDL due to LPL deficiency can limit the ability of HDL to maintain adequate supplies of Apo E. This viewpoint is supported by studies by Garber et al [9], who showed a marked increase in Apo E content of HDL following incubation of nephrotic serum with purified LPL in vitro.

**Lipoprotein(a)**

Lipoprotein(a) [LP(a)] is formed from the covalent binding of a protein known as apolipoprotein(a) [Apo(a)] to an LDL-like particle via a disulfide bond. Elevation of plasma LP(a) constitutes an independent risk factor for atherosclerotic cardiovascular disease and vascular thrombosis [65]. Structural analysis of Apo(a) has revealed a high degree of homology with plasminogen [66]. The Apo(a) molecule consists of variable numbers (12 to 51) of kringle IV-like repeats, a single kringle V copy, and an inactive protease-like segment. The wide variation in the number of kringle IV repeats is responsible for the extreme size polymorphism of this protein and the wide range of plasma LP(a) concentration (more than 1000-fold) among the general population [67]. For this reason, plasma LP(a) levels are often genetically determined in the general population. Apo(a) is synthesized by the liver and is partially removed by the kidney. Plasma LP(a) increases independently of the genetically determined Apo(a) isoform in patients with NS [68–70]. De Sain-van der Velden et al [71] determined fractional catabolic and synthesis rates of LP(a) in a group of 5 nephrotic and 5 normal control individuals. The mean plasma LP(a) concentration in the nephrotic group was approximately threefold greater than that of the control group. This was accompanied by an increased absolute rate of synthesis but a normal fractional catabolic rate of LP(a), and suggested increased synthesis as the cause of elevated plasma LP(a) in NS.

Owing to its homology with plasminogen, Apo(a) interferes with plasminogen-mediated fibrinolysis. Consequently, a high plasma LP(a) concentration produces a procoagulant diathesis by promoting an imbalance between coagulation and fibrinolytic systems. This consequence is of particular interest because NS results in urinary losses and deficiency of antithrombin III [72]; marked elevations of plasma factor VIII, von Willebrand factor, factor XIII, fibrinogen, and fibronectin; and increased platelet reactivity [73, 74]. The constellation of these abnormalities creates a profound hypercoagulable state marked by a high incidence of thromboembolic events [74, 75].

**CONCLUSION**

The induction of hypercholesterolemia during the early phase of NS is accompanied by, and primarily related to, up-regulation of HMG-CoA reductase. Maintenance of hypercholesterolemia in the chronic phase of NS is supported by the up-regulation of hepatic ACAT and down-regulations of LDL receptor and HDL receptor. Urinary losses of LCAT result in severe LCAT deficiency, which impairs HDL-mediated cholesterol uptake from the extrahepatic tissues in NS. This impairment is accompanied by down-regulation of hepatic HDL receptor (SR-B1), which limits HDL-mediated cholesterol and triglyceride disposal in the liver. These events lead to profound dysregulation of HDL metabolism and undoubtedly limit the cardiovascular, and perhaps renoprotective, functions of...
HDL. Nephrotic syndrome results in severe down-regulations of LPL, VLDL receptor, and hepatic triglyceride lipase as well as impairment of HDL-mediated shuttling of Apo E and Apo C-II between the nascent and remnant VLDL and chylomicrons. These events are largely responsible for profound abnormalities in the metabolism of triglyceride-rich lipoproteins in NS. Finally, increased Apo(a) biosynthesis elevates the plasma LP(a) concentration and can compound numerous other risk factors for cardiovascular disease and thromboembolism in NS.

Dr. Madias: For a number of other enzymes involved in the metabolism of cholesterol or lipoproteins, you suggested that the changes in their activity observed in the NS are triggered by proteinuria rather than by hypoalbuminemia. Could you speculate on which consequences of proteinuria might be responsible for such changes?

Dr. Vaziri: Thank you for this intriguing question. Once again, the precise mechanisms by which proteinuria leads to dysregulation of various lipid-regulatory enzymes and receptors is not clear, but we can examine several possibilities. The most popular assumption is the potential loss in the urine (hence, deficiency) of an undefined lipid regulatory protein that leads to a cascade of events culminating in dysregulation of the given enzymes, receptors, and apoproteins. In this regard, our recent demonstration of heavy urinary losses of LCAT and the resultant LCAT deficiency in nephrotic rats [32] lends support to this supposition. For instance, depressed HDL-mediated, reverse cholesterol transport caused by LCAT-deficiency can potentially contribute to altered hepatic cholesterol biosynthesis and catabolism by limiting cholesterol uptake from extrahepatic tissues. Moreover, as I said earlier, by impairing HDL maturation, LCAT deficiency can compromise VLDL and chylomicron metabolism by limiting HDL-mediated shuttling of Apo C and Apo E between their nascent and remnant forms.

Dr. Nicolaos E. Madias (Executive Academic Dean, Tufts University School of Medicine, Boston, Massachusetts): You indicated that the HMG-CoA reductase message and abundance increase in the NS as a consequence of hypoalbuminemia. How much do we know about the transcriptional regulation of the HMG-CoA reductase gene? Are there plausible mechanisms for hypoalbuminemia or its consequences to affect such transcription?

Dr. Vaziri: A number of factors regulate hepatic HMG-CoA reductase, not only at the level of transcription, but also at the level of translation and enzymatic activity. These factors include intracellular free cholesterol and bile acid concentrations, as well as several hormones such as thyroid hormone, glucocorticoids, and gonadal hormones. Reduction of intracellular free cholesterol in the liver tissue, occasioned by marked up-regulation of ACAT-2 [16, 21] and down-regulation of LDL receptor and HDL receptor, plays a major role in up-regulation of HMG-CoA reductase in NS. In addition, urinary losses of thyroid hormone and gonadal hormones along with their binding proteins can contribute to dysregulation of hepatic HMG-CoA reductase expression and activity in NS [76]. Finally, hypoalbuminemia per se contributes to up-regulation of HMG-CoA reductase in NS. This supposition is based on our recent study demonstrating a marked up-regulation of hepatic HMG-CoA reductase protein abundance in rats with hereditary analbuminemia, in which proteinuria is absent (unpublished data). The mechanism by which hypoalbuminemia alters expression of HMG-CoA reductase and other proteins is uncertain. However, it is commonly thought to be mediated by an undefined signal evoked by depressed plasma oncotic pressure in the hepatic sinusoids, in which plasma is in direct contact with the hepatocyte. Alternatively, the effect of hypoalbuminemia might be due to diminished delivery (or increased free forms) of one or more compounds, such as free fatty acids, hormones, minerals, and other materials normally bound to and carried by albumin.

Dr. Harrington: Second, you mentioned that there was a new inhibitor of ACAT that might have some potential benefit. Can you tell us more about that?

Dr. Vaziri: A number of ACAT inhibitors are currently under investigation as potential lipid-lowering and anti-atherogenic agents. We are currently investigating the effect of an ACAT inhibitor on lipid metabolism in...
animal models of NS and chronic renal failure, both of which are associated with marked up-regulation of hepatic ACAT-2 expression. We anxiously await the completion of these studies.

Dr. Ronald Perrone (Division of Nephrology, New England Medical Center, Boston): Would you care to speculate on the clinical therapies of hyperlipidemia in NS based on the pathophysiologic abnormalities that you have identified?

Dr. Vaziri: The most effective step in managing nephrotic dyslipidemia is treating the underlying proteinuria. For instance, administration of an angiotensin-converting-enzyme (ACE) inhibitor, angiotensin II type-1 (AT-1) receptor blocker, or immunomodulatory agents as well as dietary protein restriction can help ameliorate nephrotic dyslipidemia by lowering or reversing proteinuria. However, in many instances, nephrotic-range proteinuria and hence hyperlipidemia persist and necessitate lipid-lowering therapies, including dietary modifications, increased physical activity, and lipid-lowering drugs such as HMG-CoA reductase inhibitors, bile acid sequestrants, and other agents. I should note that because of the associated hypoalbuminemia, the biologically active free fraction of HMG-CoA reductase inhibitors can be greater. As such, risk of rhabdomyolysis and hepatic toxicity can be higher in nephrotic patients as compared to the general population. Accordingly, liver function tests and muscle enzyme levels should be closely monitored, and caution should be exercised in determining appropriate drug dosages in nephrotic patients.

Dr. Madias: Is the nephrotic syndrome associated with any changes in cholesterol-ester transfer protein?

Dr. Vaziri: Yes. Plasma cholesterol-ester transfer protein (CETP) is markedly elevated in patients with NS. Elevation of CETP, which mediates transfer of cholesterol ester from HDL to IDL in exchange for triglycerides, is partly responsible for depressed plasma HDL cholesterol and elevated HDL triglycerides in NS. Because CETP is absent in rats, we could not study it in our rat models. Absence of CETP in rodents is largely responsible for a higher plasma HDL cholesterol concentration in these animals and for their natural resistance against atherogenesis.

Dr. Madias: How much do the lipoprotein profile and the activities of the relevant enzymes change in response to the superimposition of renal insufficiency on the nephrotic state?

Dr. Vaziri: Nephrotic syndrome and chronic renal insufficiency each depress lipoprotein lipase, hepatic triglyceride lipase, and VLDL receptor. This dysregulation accounts for impaired clearance of triglyceride-rich lipoproteins and their remnants in each of these conditions. Thus, superimposed renal insufficiency can aggravate the lipoprotein lipase, hepatic lipase, and VLDL receptor deficiencies in patients and animals with concomitant heavy proteinuria. In addition, concomitant chronic renal insufficiency, which down-regulates hepatic LCAT expression, and NS, which results in urinary losses of LCAT, can lead to severe LCAT deficiency and hence to impaired HDL metabolism. With few exceptions, the advent of severe renal insufficiency is accompanied by a parallel reduction of proteinuria, and the plasma lipid profile gradually changes from nephrotic dyslipidemia to that characteristic of chronic renal failure.

Dr. Bertrand Jaber (Division of Nephrology, New England Medical Center): You mentioned the possible role of negative nitrogen balance occasioned by proteinuria in modifying the liver’s biosynthetic properties. Could you comment on that and on the role of cytokines in driving the acute-phase reaction in the liver? Finally, are you aware of any published work identifying the role of inflammatory cytokines in modulating hepatic LCAT and HMG-CoA reductase activity?

Dr. Vaziri: Thank you for raising this important issue. Heavy proteinuria indeed represents a biologic stress that is frequently accompanied by inflammation and which leads to increased production of positive-phase reactants and a relative reduction of negative-phase reactants. To my knowledge, however, this classification has been primarily applied to plasma proteins, not to the cell-associated proteins, such as HMG-CoA reductase, which is an intracellular enzyme. In fact, as I indicated in my presentation, up-regulation of HMG-CoA reductase in NS appears to be a response to diminished intracellular free cholesterol, which is occasioned by marked up-regulation of ACAT-2 and down-regulation of LDL receptor and HDL receptor. Accordingly, increased abundance of this enzyme in NS reflects a predictable regulatory response as opposed to a nonspecific characteristic of acute-phase reactants. On the other hand, LCAT, a liver-derived plasma protein, can potentially behave as a negative-phase reactant. As I noted earlier, LCAT deficiency in NS is largely a consequence of its loss in the urine.

Dr. Jaber: What is the effect of HMG-CoA reductase inhibitors on ACAT activity?

Dr. Vaziri: I do not have a precise answer to this important question at this time, but we are currently conducting a series of studies that will provide a definitive answer in the near future. I speculate that the reduction in cholesterol synthesis caused by HMG-CoA reductase inhibition down-regulates ACAT by diminishing the need for esterification.

Dr. Harrington: Could you comment on the gender differences, if any, in your experimental model of spontaneous NS?

Dr. Vaziri: Renal disease and hyperlipidemia occur much later in life, are far less severe, and progress much more slowly in female Imai rats. The protective advantage of female gender is lost by oophorectomy in this model pointing to a role for hormonal influences. In
contrast, female Nagase rats with hereditary analbuminemia exhibit a far more severe hyperlipidemia than do their male counterparts. Severity of hyperlipidemia in female Nagase rats is attenuated by oophorectomy and is aggravated by estrogen therapy. It thus appears that gender and gonadal hormones affect lipid metabolism and renal involvement differently in different models and disease states.

Dr. Harrington: Given that information, and other information that dyslipidemia has an important effect on progression of renal disease, would you argue that all patients with progressive renal insufficiency should be treated with lipid-lowering agents no matter what the serum cholesterol level is?

Dr. Vaziri: HMG-CoA reductase inhibitors appear to confer cardiovascular and renal protection not only by their lipid-lowering action, but also by their lipid-independent action. The latter phenomenon might form the theoretical basis for their potential utility in the management of progressive renal disease, regardless of plasma lipid levels. However, in view of the potential risk of rhabdomyolysis and hepatotoxicity associated with the use of these agents, and the lack of sufficient clinical studies, I find it difficult to recommend their use in the absence of hyperlipidemia.

Dr. Madias: Are other clinical circumstances associated with acquired down-regulation of the LDL and VLDL receptors?

Dr. Vaziri: Hypothyroidism in experimental animals, and presumably in humans, causes down-regulation of LDL receptor, which can at least partly account for hypercholesterolemia in hypothyroidism. Similarly, experimental hypothyroidism down-regulates lipoprotein lipase and VLDL receptor, and this down-regulation could contribute to the associated hypertriglyceridemia.

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