Mechanisms of Altered Lipid Metabolism in Nephrotic Syndrome

N.D. Vaziri, M.D., MACP

Professor of Medicine, Physiology and Biophysics,
Chief, Division of Nephrology and Hypertension, University of California, Irvine, USA

Heavy glomerular proteinuria (nephrotic syndrome) leads to severe hyperlipidemia and profound derangement of lipid metabolism[1-5]. The associated hyperlipidemia has been shown to increase the risk of cardiovascular complications and accelerate the progression of renal disease[6, 7]. Nephrotic hyperlipidemia is marked by elevations of plasma total cholesterol, triglycerides, LDL, VLDL, total chol-to-HDL-chol ratio and lipoprotein (a), impaired clearance of HDL, LDL, VLDL and chylomicrons (CM), as well as, accumulation of VLDL remnants (IDL) and CM remnants[1-4]. This communication is intended to describe the molecular basis of these lipid abnormalities.

1. Cholesterol synthesis and catabolism

Plasma cholesterol dramatically rises from normal levels prior to the onset of nephrotic syndrome to very high levels after the onset of nephrotic syndrome. This phenomenon must be due either to an increased cholesterol biosynthesis, a reduction in cholesterol catabolism or a combination thereof. In order to explore these possibilities, we carried out a series of studies which showed upregulation of hepatic HMG-CoA reductase (the key enzyme in cholesterol biosynthesis) during the induction of hypercholesterolemia in rats with puromycin-induced nephrotic syndrome[8] and in chronic nephrotic syndrome in Imai rats with spontaneous focal glomerulosclerosis[9].

The upregulation of HMG-CoA reductase in these animals was accompanied by no change in hepatic cholesterol 7α-hydroxylase (the key enzyme for cholesterol catabolism to bile acids)[9, 10]. Thus, induction of hypercholesterolemia in nephrotic syndrome is associated with and, in part, due to increased hepatic cholesterol biosynthetic capacity without a concomitant increase in cholesterol catabolism.

In an attempt to discern whether hypoalbuminemia or proteinuria is responsible for dysregulation of the above enzymes, we studied male Nagase rats with hereditary analbuminemia (NAR)[11]. The study showed a significant upregulation of hepatic HMG-CoA reductase in NAR, suggesting that the reduction of plasma albumin alone can augment HMG-CoA reductase and, hence, cholesterol biosynthetic capacity. However, in contrast to the nephrotic animals, the NAR exhibited a significant upregulation of hepatic cholesterol 7α-hydroxylase[11]. This appropriate rise in cholesterol catabolic capacity can, in part, account for the mild nature of hypercholesterolemia, despite virtual absence of albumin in the male NAR.

In the course of the above studies, we noted that despite severe hypercholesterolemia liver tissue cholesterol concentration is normal and microsomal free cholesterol is actually reduced in the nephrotic animals[8, 10]. We hypothesized that the observed disparity may be due to impaired hepatic uptake of lipoproteins from the blood in nephrotic syndrome. This supposition was vali-

dated by our subsequent studies.

2. LDL Metabolism

Plasma LDL is elevated and LDL clearance is impaired in nephrotic syndrome[1-4]. The primary pathway for LDL catabolism is its removal by LDL receptor. Therefore, we hypothesized that abnormal LDL metabolism in nephrotic syndrome may be due to LDL receptor deficiency. This hypothesis was validated by our subsequent studies which revealed marked downregulation of hepatic LDL receptor in rats with puromycin-induced nephrotic syndrome[12] and Imai rats with spontaneous focal glomerulosclerosis[9] despite normal receptor mRNA abundance.

3. HDL Metabolism

HDL particles play a major role in protection against renal and cardiovascular disease by transporting the surplus cholesterol from extrahepatic tissues for disposal in the liver, a process commonly know as reverse cholesterol transport. This process involves binding of cholesterol-poor HDL-3 particles to the surface of the target cells in the peripheral tissues leading to extraction of free cholesterol and its sequestration in the core of HDL as cholesterol ester by LCAT. This is followed by detachment of cholesterol-rich HDL particle (HDL-2) from the peripheral site and the disposal of its lipid cargo in liver via HDL receptor (SRB-1).

Maturation of HDL-3 to HDL-2 is impaired and HDL clearance is depressed in nephrotic syndrome[1-5]. We hypothesized that impaired maturation of HDL must be due to LCAT deficiency and its depressed clearance may be due HDL receptor deficiency in nephrotic syndrome. These suppositions were substantiated by our earlier studies which revealed marked reduction in plasma LCAT[9, 13] and hepatic HDL receptor[14] in nephrotic rats. The LCAT deficiency in nephrotic syndrome was found to be due to its heavy losses in urine[13]. These studies helped to elucidate the molecular basis of altered HDL metabolism in nephrotic syndrome.

Triglyceride-Rich Lipoprotein Metabolism

Plasma triglycerides arise from either endogenous or dietary (exogenous) sources.

Endogenous triglycerides are packaged as VLDL and released in the circulation by the liver. VLDL particles undergo lipolysis by lipoprotein lipase which is produced by myocytes and adipocytes, and bound to heparan sulfate proteoglycans on the surface of capillary endothelial cells. This leads to an approximately 75% removal of VLDL triglyceride and generation of VLDL remnant known as IDL. IDL, in turn, undergoes further lipolysis by hepatic triglyceride lipase to become LDL. Alternatively, IDL is removed by the liver via the LDL receptor-related protein (LRP). In addition to lipolytic pathway, VLDL can be removed in its entirety by the myocytes and adipocytes via the novel VLDL receptor.

Dietary lipids are packaged as chylomicrons (CM) and released into the lymphatic system by enterocytes. CM undergo lipolysis by lipoprotein lipase to become CM remnants which are removed via LRP-mediated endocytosis by the liver and other cell types.

Plasma triglyceride and VLDL concentrations are elevated and VLDL and CM clearance is impaired in nephrotic syndrome[1-4]. These abnormalities are largely due to downregulations of lipoprotein lipase and VLDL receptor in the skeletal muscles and adipose tissues in nephrotic syndrome[15-18]. In addition, hepatic tissue expression and activity of DGAT, an enzyme which catalyzes the final step in triglyceride biosynthesis is elevated in animals with nephrotic syndrome[19]. Thus, hypertriglyceridemia in nephrotic syndrome appears to be due to a combination of

impaired clearance and to a lesser extent increased synthesis of triglycerides.

Nephrotic hyperlipidemia is marked by elevated plasma concentrations of the highly atherogenic IDL and CM remnants. This is largely due to downregulation of hepatic triglyceride lipase[17, 20] which is critical for lipolysis of these lipoprotein remnants. In addition, impaired HDL-3 to HDL-2 maturation contributes to the defective lipolysis of VLDL and CM since HDL-2 serves as an efficient vehicle for transfer of ApoC-II (lipoprotein lipase cofactor) and ApoE (lipoprotein lipase and VLDL receptor ligand) between the nascent and remnant VLDL and CM.

Another potential mechanism for IDL and CM remnant accumulation in nephrotic syndrome could be their impaired LRP-mediated uptake by the liver. However, LRP expression was recently shown to be upregulated in nephrotic syndrome[21], thus, excluding a quantitative deficiency of this receptor as a possible culprit.

Upregulation of ACAT

ACAT is a microsomal enzyme that catalyzes intracellular esterification of cholesterol. This process is essential for packaging and secretion of Apo-B containing lipoproteins by the liver and intestine, production of milk and intracellular storage of cholesterol.

In addition, via esterification of cholesterol ACAT can modulate expression of various lipid-regulatory enzymes and receptors. Moreover, ACAT plays a central role in foam cell formation and atherogenesis. Nephrotic syndrome has been recently shown to cause marked upregulation of liver-specific ACAT-2 in experimental animals [9, 22].

The important contribution of the upregulation of ACAT in the pathogenesis of nephrotic hyperlipidemia was recently substantiated by a recent study which revealed dramatic improvement of hyperlipidemia and proteinuria and reversal of the associated LCAT, LDL receptor and HDL receptor deficiencies with the use of an ACAT inhibitor in rats with nephrotic syndrome[23].

Conclusions

Nephrotic dyslipidemia is due to profound alterations of key enzymes and receptors involved in lipid metabolism. Proteinuria as opposed to hypoalbuminemia is responsible for the majority of these abnormalities.

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