Disorders of lipid metabolism in nephrotic syndrome: mechanisms and consequences

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Nephrotic syndrome results in hyperlipidemia and profound alterations in lipid and lipoprotein metabolism. Serum cholesterol, triglycerides, apolipoprotein B (apoB)–containing lipoproteins (very low-density lipoprotein [VLDL], immediate-density lipoprotein [IDL], and low-density lipoprotein [LDL]), lipoprotein(a) (Lp[a]), and the total cholesterol/high-density lipoprotein (HDL) cholesterol ratio are increased in nephrotic syndrome. This is accompanied by significant changes in the composition of various lipoproteins including their cholesterol-to-triglyceride, free cholesterol–to-cholesterol ester, and phospholipid-to-protein ratios. These abnormalities are mediated by changes in the expression and activities of the key proteins involved in the biosynthesis, transport, remodeling, and catabolism of lipids and lipoproteins including apoproteins A, B, C, and E; 3-hydroxy-3-methylglutaryl-coenzyme A reductase; fatty acid synthase; LDL receptor; lecithin cholesteryl ester acyltransferase; acyl coenzyme A cholesterol acyltransferase; HDL docking receptor (scavenger receptor class B, type 1 [SR-B1]); HDL endocytic receptor; lipoprotein lipase; and hepatic lipase, among others. The disorders of lipid and lipoprotein metabolism in nephrotic syndrome contribute to the development and progression of cardiovascular and kidney disease. In addition, by limiting delivery of lipid fuel to the muscles for generation of energy and to the adipose tissues for storage of energy, changes in lipid metabolism contribute to the reduction of body mass and impaired exercise capacity. This article provides an overview of the mechanisms, consequences, and treatment of lipid disorders in nephrotic syndrome.

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Glomerular proteinuria ≥3.5 g/day in adults or a urine protein/creatinine ratio of 2 to 3 mg/mg creatinine or greater in children results in nephrotic syndrome, which is characterized by the tetrad of proteinuria, hypoalbuminemia, edema, and hyperlipidemia. The magnitude of hyperlipidemia and the associated alteration in lipoprotein metabolism in nephrotic syndrome parallels the severity of proteinuria. Plasma concentrations of cholesterol, triglycerides, apolipoprotein B (apoB)–containing lipoproteins (very low-density lipoprotein [VLDL], immediate-density lipoprotein [IDL], and low-density lipoprotein [LDL]), and lipoprotein(a) (Lp[a]) are elevated in nephrotic syndrome. However, high-density lipoprotein (HDL) cholesterol concentration is usually unchanged or reduced and occasionally elevated and the total cholesterol to HDL cholesterol ratio is generally increased in nephrotic animals and humans.[1,2] In addition to the quantitative changes, nephrotic syndrome markedly alters the composition and function of the lipoproteins. In this context, the cholesterol to triglyceride, free cholesterol to cholesterol ester, and phospholipid to protein ratios in the lipoproteins are altered in nephrotic syndrome. This is accompanied by a significant increase in apoA-I, apoA-IV, apoB, apoC, and apoE levels and the apoC-III to apoC-II ratio. These abnormalities are mediated by profound changes in the pathways involved in the biosynthesis, transport, remodeling, and catabolism of lipids and lipoproteins. The disorders of lipid metabolism in nephrotic syndrome contribute to the development and progression of cardiovascular and kidney disease and impaired delivery of lipid fuel to the muscles for generation of energy and to the adipose tissues for the storage of energy. The abnormalities of serum lipids and lipoproteins in nephrotic syndrome are largely due to their impaired clearance and, to a lesser extent, their altered biosynthesis.[2–8] The underlying mechanisms by which nephrotic syndrome alters lipid and lipoprotein metabolism are summarized in the following.

Triglyceride-rich lipoproteins and their abnormalities in nephrotic syndrome

The triglyceride-rich lipoproteins, that is, VLDL and chylomicrons, serve as vehicles for delivery of fatty acids to various cells/tissues in the body for generation and storage of energy. Nascent VLDL is produced by encasing triglycerides, cholesterol ester, and phospholipids in apoB-100 within the hepatocytes and released in the circulation, where it obtains apoE and apoC from cholesterol ester–rich HDL-2. In the

capillaries perfusing the target tissues, VLDL binds to the endothelial surface via its apoE content and activates lipoprotein lipase (LPL) via its apoCII content. This results in LPL-mediated hydrolysis of 70% of the VLDL triglyceride content, release of free fatty acids and phospholipids, and transformation of VLDL to intermediate density lipoprotein (IDL). Nascent chylomicrons are generated by incorporation of triglycerides in apoB-40 within the enterocytes and released in the lymphatic circulation and eventually the systemic circulation where it acquires apoE and apoC from HDL-2. Like VLDL, LPL mediates hydrolysis of 70% of a chylomicron's triglyceride contents and formation of a chylomicron remnant. Nearly two-thirds of the fatty acids released from VLDL and chylomicrons are taken up by the adjacent myocytes or adipocytes, whereas the remaining free fatty acids bind to albumin and lipoproteins and are carried to distant tissues, mainly the liver. Once formed, IDL and chylomicron remnants, which contain 30% of their original triglyceride cargos, are released in the circulation. The triglyceride and phospholipid contents of IDL are removed by cholesterol ester transfer protein (CETP)–mediated exchange of triglycerides for cholesterol ester from HDL-2 and hydrolysis of the triglyceride and phospholipid contents of IDL by hepatic lipase and their uptake by the liver. These events lead to the formation of low-density lipoprotein (LDL), which is normally cleared by LDL receptor. The chylomicron remnants are cleared by LDL receptor–related protein (LRP), a large multifunctional receptor that is expressed on hepatocytes. In addition to the lipolytic pathway, a small fraction of VLDL is cleared by the VLDL receptor, which is expressed in skeletal muscle, adipose tissue, and myocardium, and as such, its tissue distribution is similar to that of LPL.[9–11]

Nephrotic syndrome results in elevated serum triglyceride, VLDL, and IDL levels; increased triglyceride contents of apoB-containing lipoproteins; and prolonged postprandial lipemia.[2–6] These abnormalities are due to impaired VLDL and chylomicron clearance.[4,7,8] LPL, hepatic lipase, LRP, VLDL receptor, and proper shuttling of lipids and apoproteins between HDL and apoB-containing lipoproteins are essential steps in maturation and clearance of VLDL and chylomicrons and generation of normal LDL. As described in the following, nephrotic syndrome results in deficiencies of LPL, hepatic lipase, and VLDL receptor and upregulation of CETP and LRP. In addition, changes in the structure of these lipoproteins limit their effective binding to the key receptors, their ability to activate lipolytic enzymes, and their proper lipid and apoprotein exchange with HDL. The impact of nephrotic syndrome on the key steps in triglyceride-rich lipoprotein metabolism (Figure 1) is described here.

LPL deficiency and dysfunction. LPL is the rate-limiting step in lipolysis of chylomicrons and VLDL. LPL is produced in myocytes, adipocytes, and several other cell types and stored in the Golgi apparatus for either intracellular degradation or release to the cell surface. Once released, LPL binds to the endothelium in the adjacent capillaries where it catalyzes hydrolysis of triglycerides in VLDL and chylomicrons. In the capillaries, LPL binds to the endothelial surface via interaction of its positively charged heparin-binding domains with the negatively charged heparan sulfate proteoglycans.[12] The endothelium-derived glycosylphosphatidylinositol-anchored binding protein 1 (GPIHBP1), plays a central part in the fate and function of LPL by anchoring LPL on the endothelium and serving as the ligand for chylomicrons.[13,14] Because heparin can displace and release LPL from the endothelium, measurement

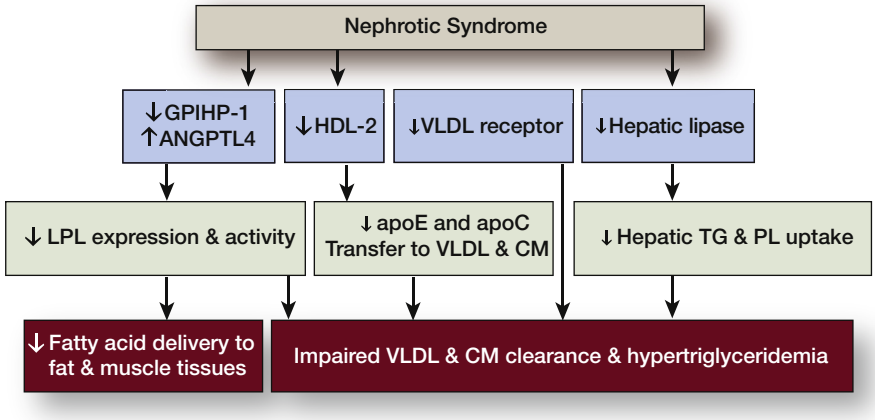

Figure 1 | Via downregulation of the lipoprotein lipase (LPL) adapter molecule GPIHP-1 and upregulation of the LPL inhibitor molecule ANGPTL4, nephrotic syndrome results in a marked decrease in abundance and activity in muscle and adipose tissue. The impact of LPL deficiency is compounded by the scarcity of cholesterol ester–rich high-density lipoprotein (HDL), which is the apoE and apoC donor to the nascent very low-density lipoprotein (VLDL) and chylomicrons (CM) enabling their ability to bind to the endothelial lining and activate LPL. The resulting LPL deficiency and dysfunction limits delivery of lipid fuel to the muscles for generation of energy and to the adipose tissue for storage of energy. In addition, nephrotic syndrome causes hepatic lipase deficiency, which impairs the ability of the liver to extract the triglyceride (TG) and phospholipid (PL) contents of immediate-density lipoprotein (IDL) and HDL. Together, these abnormalities contribute to the development of hypertriglyceridemia, elevation of serum VLDL, and accumulation of atherogenic IDL, CM remnants, and triglyceride (TG)-rich LDL in patients with nephrotic syndrome.