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Pathophysiological mechanisms of dyslipidemia in patients with nephrotic syndrome: A fresh look

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Abstract

Qualitative and quantitative lipoprotein abnormalities are commonly found in patients with nephrotic syndrome irrespective of the underlying renal disease, including elevated triglycerides, LDL cholesterol, and Lp(a) levels, increased postprandial lipemia, as well as increased concentrations of TRG-rich lipoproteins containing ApoB, while various disturbances of the metabolism of HDL particles are also noticed. These lipid derangements play a prominent role in the pathogenesis of the cardiovascular disease as well as in the evolution of the underlying renal disease. In this review a detailed analysis of the pathogenetic mechanisms of dyslipidemia in this population is attempted.

Key words: nephrotic syndrome; dyslipidemia; PCSK9; increased LDL CHOL levels

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The nephrotic syndrome is characterized by proteinuria (greater than 3g/24h/1.73m^2, hypoproteinemia, edema, hyperlipidemia and lipiduria and is due to both primary kidney diseases (mainly minimal change disease, focal segmental glomerulosclerosis and membranous glomerulopathy) as well as to secondary forms of kidney disease (mainly diabetic glomerulosclerosis and amyloidosis).

Quantitative and qualitative lipoprotein abnormalities are commonly encountered in patients with nephrotic syndrome (**Table 1**). These parallel the severity of proteinuria and contribute to the pathogenesis of cardiovascular disease but also to the evolution of the underlying renal disease.[1-3] The two most important mechanisms of lipid derangements in patients with nephrotic syndrome are the decreased li-

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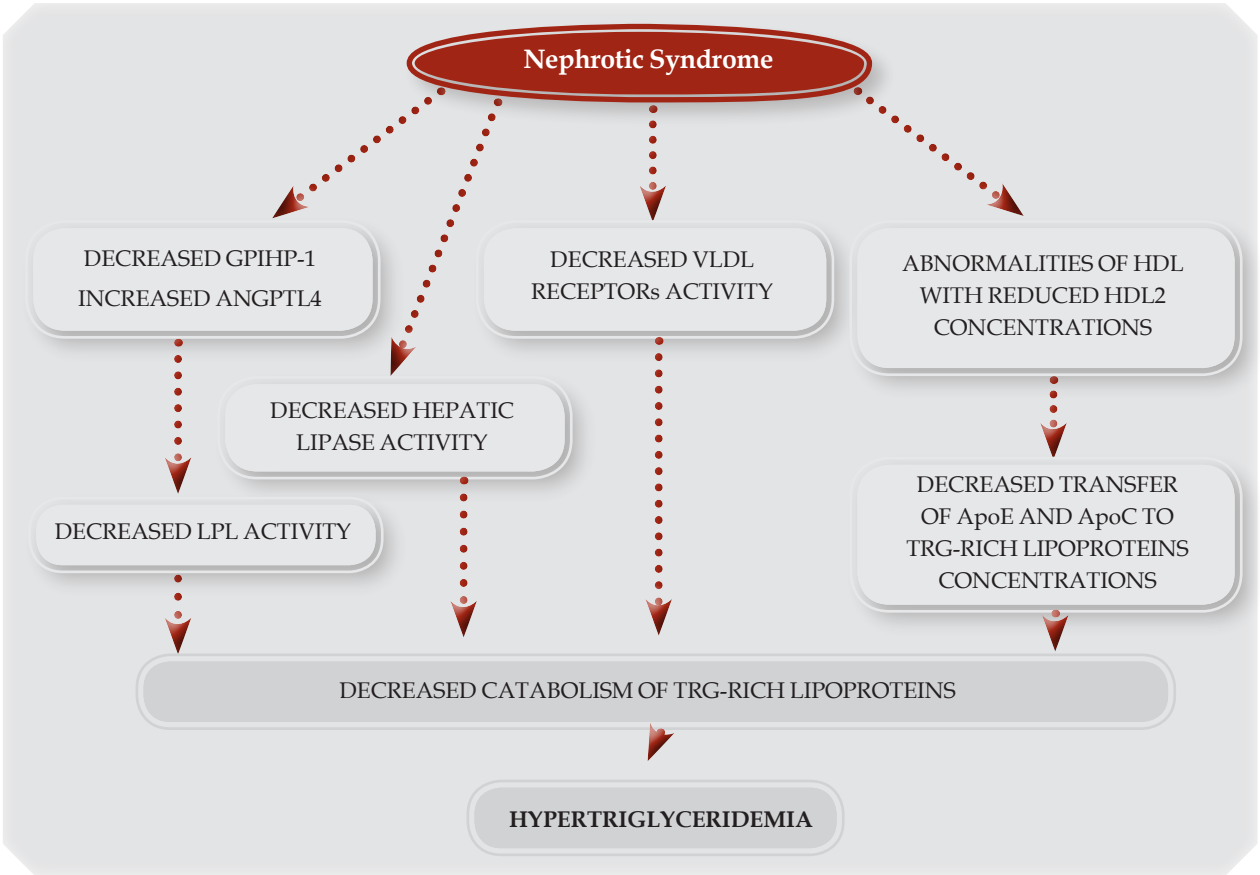

Figure 1. Abnormalities of TRG-rich lipoproteins metabolism in individuals with nephrotic syndrome
LPL= Lipoprotein lipase, ANGPTL4= Angiopoietin-like protein 4, GPIHP-1= Glucosylphosphatidylinositol-anchored binding proteins

Table 1. Lipoprotein abnormalities in patients with nephrotic syndrome

Increased VLDL, IDL and TRGs
Increased TRG-content of ApoB containing lipoproteins
Increased postprandial lipemia
Increased ApoB concentrations
Increased LDL CHOL concentrations
Increased Lp(a) concentrations
HDL CHOL levels: normal, reduced, or even increased

poprotein clearance and the increased lipoprotein biosynthesis.

1. Abnormalities of TRG-rich lipoproteins metabolism (Figure 1)

As shown in **table 1** patients with nephrotic syndrome commonly exhibit hypertriglyceridemia associated with increased concentrations of VLDL, IDL as well as increased TRG content of lipoproteins containing ApoB. Furthermore, increased postprandial lipemia is evident.[3-7] The impaired catabolism of TRG-rich lipoproteins is due to:

a) decreased lipoprotein lipase activity (LPL), which is critical for the lipolysis of both VLDL and chylomicrons. This LPL deficiency is possibly related to downregulation of endothelial-derived glucosylphosphatidylinositol-anchored binding proteins (GPIHBP1), which affects LPL function by

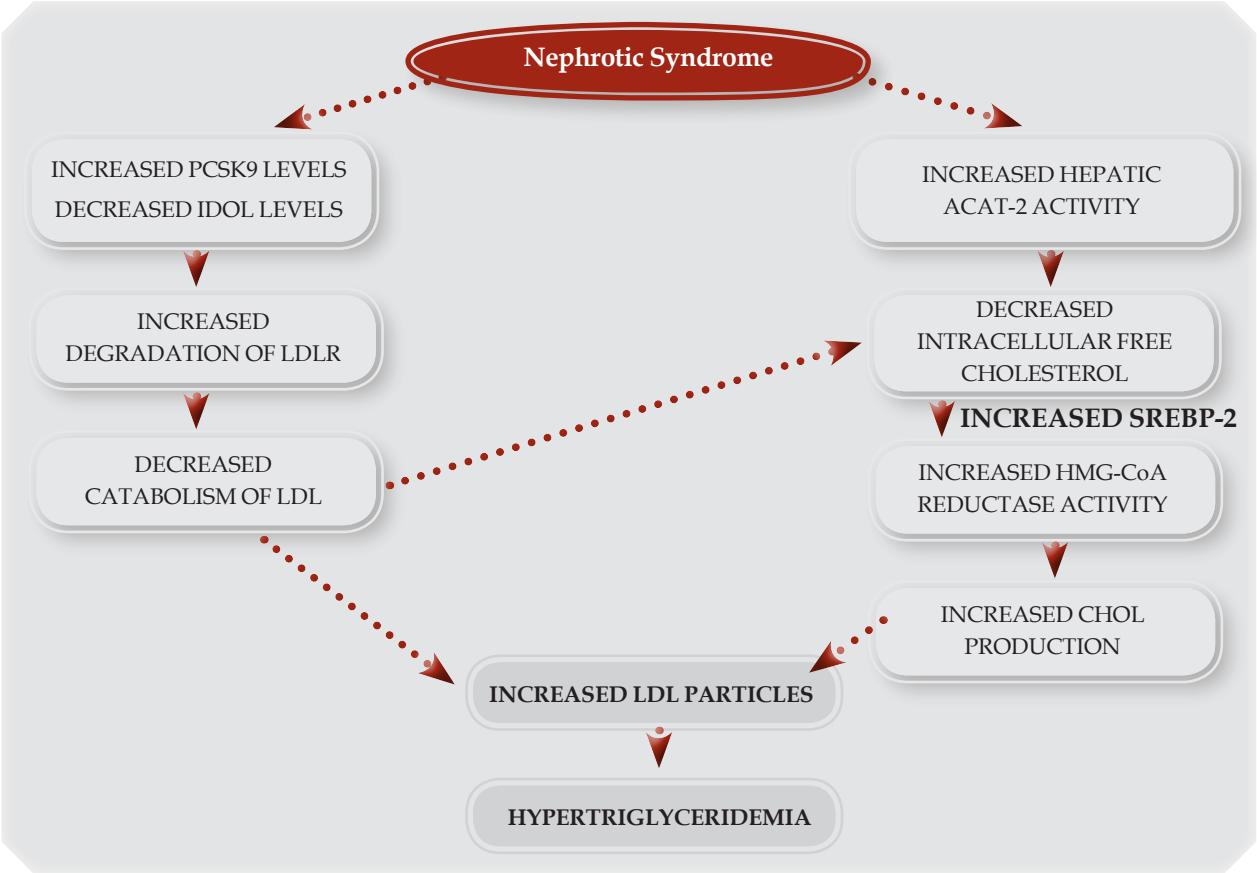

Figure 2. Abnormalities of LDL in patients with nephrotic syndrome
PCSK9= Proprotein convertase subtilisin kexin 9, IDOL= Inducible degrader of the LDLR, SREBP-2= Sterol regulatory element-binding protein, ACAT= Acyl –CoA: cholesterol acyltransferase-2

anchoring LPL on the endothelium and serving as a ligand for chylomicrons[8],

b) the reduction of ApoE (the principal ligand for VLDL and chylomicron binding to endothelium) as well as to the reduction of the ratio of ApoC II / ApoC III [since ApoC II is an LPL activator and ApoC III in an LPL inhibitor].[9,10] These apolipoprotein changes may be due to abnormalities of HDL metabolism, namely the decrease of large rich in cholesterol HDL2, commonly found in this population, which provide ApoE and ApoC to nascent VLDL and chylomicrons (in exchange for ApoA)[2]

c) decreased hepatic lipase activity, which leads to decreased catabolism of the atherogenic IDL, resulting in hypertriglyceridemia, increased atherogenic IDL, increased TRG content of LDL but also to abnormalities of HDL metabolism (increased TRG content of HDL)[4,5,11],

d) increased angiopoietin-like protein 4 (ANGPTL4, a glycoprotein molecular weight 45-65KDa), which can also decrease the activity of both LPL and hepatic lipase (but increases the expression of intracellular hormone-sensitive lipase leading to increased production of fatty acids in the adipose tissue).[12,13] The increased ANGPTL4 activity in nephrotic syndrome patients is related to an increased free fatty acid to albumin ratio since free fatty acids increase its production *via* PPARs.[14] Interestingly, the inhibitory effect of ANGPTL4 is mitigated by GP1HBP1, which is markedly reduced in this population[15], and

e) to decreased VLDL receptors activity, which play a significant role in the catabolism of VLDL.[16]

2. Abnormalities of LDL metabolism (Figure 2)

Increased LDL CHOL levels are commonly encountered in patients with nephrotic syndrome.

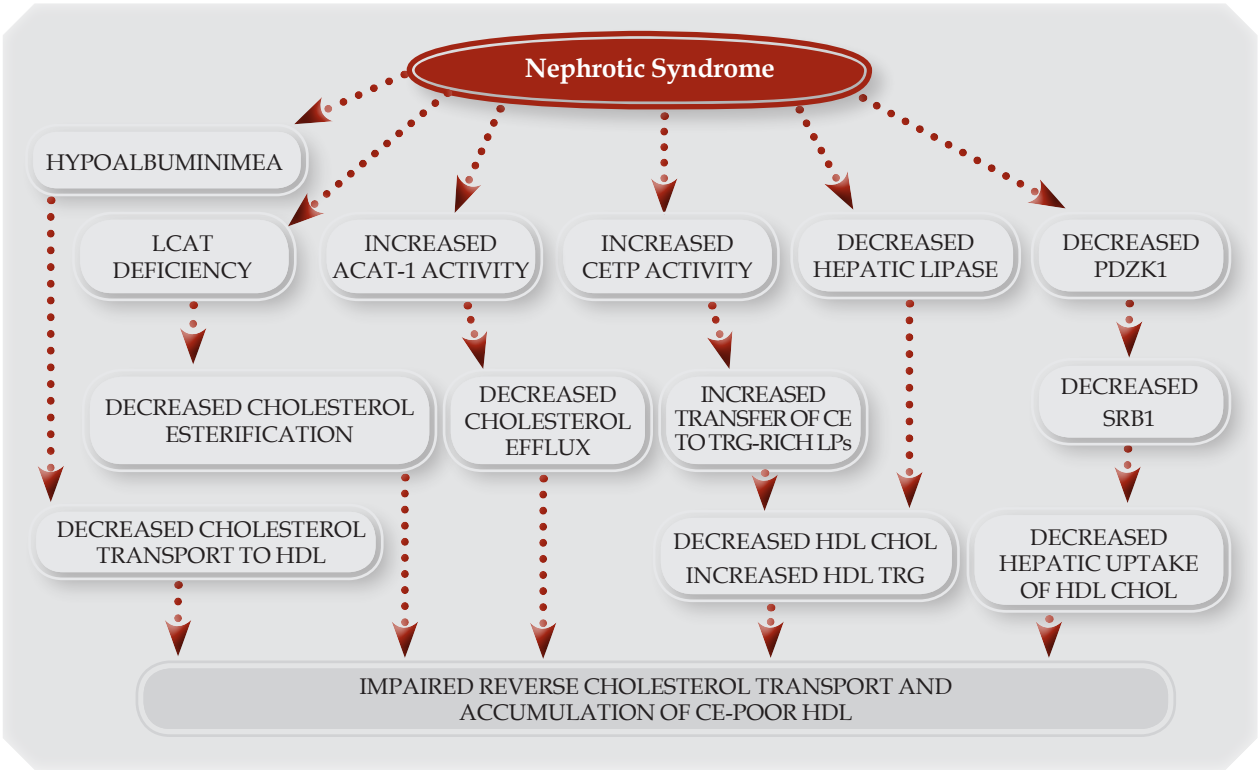

Figure 3. Abnormalities of HDL particles in patients with nephrotic syndrome
LCAT= Lecithin cholesterol ester acyltransferase, ACAT-1= Acyl –CoA: cholesterol acyltransferase-1, CETP= Cholesterol ester transfer protein, PDZK1= PDZ-containing kidney protein-1, SRB1= Scavenger receptor class B type (SR-B1), CE= cholesterol esters LPs= lipoproteins

This increase is due to increased production but mainly to reduced LDL particles catabolism due to decreased LDL receptors activity.[1,6,17] Recent data have delineated the underlying mechanisms of the decreased LDL receptors activity is this population. In fact, an upregulation of hepatic protein convertase subtilism kexin type 9 (PCSK9) is observed leading to accelerated degradation of LDLR.[18,19]

A recently published carefully conducted experimental study showed that podocyte damage can trigger marked inductions of plasma PCSK9, due to both increased secretion and also decreased clearance. This increased production of PCSK9 may be due to both sterol regulatory element-binding protein (SREBP2) and hepatocyte nuclear factor (HNF1a). It has been suggested that podocyte injury results in protein loss in the urine, which indirectly may affect PCSK9 metabolism or alternatively this injury is associated with increased tumor necrosis factor-a levels, which is known to induced cellular inhibitor of apoptosis-1 (CIAP1), known to promote PCSK9 secretion. The same study showed that knockout of PCSK9 can ameriorate dyslipidemia in a mouse model of nephrotic syndrome. These data suggest that PCSK9 inhibitors may be particularly useful for the management of dyslipidemia in patients with nephrotic syndrome.[20]

Furthermore, an increased liver tissue inducible degrader of the LDLR (IDOL) is also found.[18] Furthermore, alterations in LDL composition may also affect the LPL receptors-mediated clearance of LDL particles.[1] Additionally, increased cholesterol production due to upregulation of cholesterol biosynthesis owing to the previously mentioned decreased LDL catabolism through the LDLR but also to upregulation of hepatic acyl-CoA: Cholesterol acyltranferase-2 (ACAT-2), the enzyme which esterifies free cholesterol and also plays an important role in packaging cholesterol in ApoB100 in the liver for release in the circulation. This increased

Table 2. The main antiatherogenic effects of HDL

Participation in the reverse cholesterol transport
Antioxidant effects (through paraoxonase-1 and glutathione peroxidase)
Antiinflammatory effects
Enhancement of endothelial function and prevention of endothelial-cell apoptosis
Antithrombotic effects

cholesterol production is the result of a decrease in free cholesterol content in hepatocytes which through activation of sterol regulatory element-binding protein 2 (SREBP-2) increase HMG-CoA reductase activity and cholesterol biosynthesis.[1,21]

It should be mentioned that the activation of SREBP-1 can increase the production of fatty acids, which can also contribute to the dyslipidemia observed in this population.[1] Moreover, the increase in PCSK9 levels in patients with nephrotic syndrome can also affect lipid metabolism through promotion of CD36 degradation, which results in increased serum fatty acid and TRG levels and decreased adipose tissue mass. In fact, CD36 plays a paramount role for the adipocyte uptake of fatty acids and for the growth and function of adipose tissue.[22,23]

3. Increased Lp(a) levels

Increased Lp(a) levels are also commonly noticed in patients with nephrotic syndrome mainly due to increased liver production. These increased Lp(a) levels may contribute to the atherothrombic complications encountered in these patients.[1,24,25]

4. Abnormalities of HDL metabolism (Figure 3)

Various abnormalities of HDL metabolism have been reported in patients with nephrotic syndrome.[2] Thus, serum HDL CHOL levels are normal or somewhat low in this population. However, disturbances in the structure and function of HDL have been reported leading to impaired maturation of HDL particles and subsequently to impaired reverse cholesterol transport suggested as the main antiatherogenic mechanism of HDL (**Table 2**). Thus, these abnormalities may play a prominent role in the development and progression of atherosclerosis.[2] The main abnormalities of HDL in patients with proteinuria include:

a) decreased lecithin cholesterol ester acyltranferase (LCAT) activity due to its urinary losses resulting in reduced esterification of free cholesterol and maturation of HDL particles (from nascent HDL to cholesterol-rich HDL-particles[26],

b) decreased transfer of free cholesterol to HDL particles due to coexistent hypoalbuminemia, since albumin serves as a carrier of free cholesterol from tissues to HDL[27],

c) increased CETP activity leading to increased cholesterol transfer from HDL to IDL and LDL, thus resulting in a reduced formation of cholesterol-rich HDL (HDL2) and decreased HDL CHOL levels[28-30],

d) decreased scavenger receptor class B type 1 (SR-B1) activity, which limits the transfer of cholesterol to the hepatocytes, that is the final step in the reverse cholesterol transport [RCT][31]. A recently published study showed that the decreased expression of the adapter molecule PDZ-containing kidney protein-1 (PDZK1) (which stabilizes SR-BI in the hepatocytes) is responsible for the degradation of SR-B1 and subsequently for the lower SR-B1 activity observed in these patients[32] but also to impaired effects of HDL of proteinuric patients on endothelial cells[33],

e) an up-regulation of the β-chain ATP synthase, which serves as a ApoA1 receptor and mediates the endocytosis of ApoA1 and lipid poor HDL (hepatic HDL endocytic receptors)[34],

f) the previously mentioned decreased hepatic lipase activity resulting in a decrease of the catabolism of TRGs of HDL particles leading to triglyceride enrichment of these particles.[11]

5. Consequences of hyperlipidemia

Qualitative and quantitative lipoprotein changes play a prominent role in the development and evolution of atherosclerosis and subsequently in the increased risk of cardiovascular events observed in this population.[1,2] Additionally, the decreased LPL

expression and activity could result in reduced delivery of fatty acids to fat and muscles leading to reduced body mass and exercise capacity.[34] Interestingly, dyslipidemia may contribute to the progression of the underlying renal disease through increased uptake of abnormal lipoproteins by mesangial cells and also reabsorption of albumin and other lipid containing proteins which results in accumulation and cytotoxicity of the proximal tubular cells.[12,35-37]

6. Treatment of dyslipidemia of nephrotic syndrome

Statins are the cornerstone of treatment of dyslipidemia in patients with nephrotic syndrome. A recently published review and meta-analysis has shown that statins do not decrease the risk of renal failure events but they may modestly decrease proteinuria and the rate of estimated glomerular filtration rate (eGFR) decline.[38] However it has been suggested that rosuvastatin should be avoided, since studies have shown that it may increase proteinuria and/or decrease renal function.[39,40] Since the upregulation of PCSK9 plays a central role in the dyslipidemia of nephrotic syndrome, PCSK9 inhibitors may be particularly useful drugs for the management of nephrotic dyslipidemia. However, no available data on the effects of PCSK9 inhibitors in this population are available.[1,20] Finally, taking into account the multiple effects of ACAT in lipid metabolism and the up-regulation of this enzyme in liver, kidney and arterial wall in nephrotic syndrome, ACAT inhibitors theoretically are especially useful drugs for the management of dyslipidemia and the decrease of the risk of cardiovascular and renal disease. However, more data are needed concerning the long-term effects of this class of drugs in this population.[1]

Conflict of interest: All authors declare no conflict of interest.

Περίληψη

Παθοφυσιολογικοί μηχανισμοί της δυσλιπιδαιμίας σε ασθενείς με νεφρωσικό σύνδρομο

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Οι ασθενείς με νεφρωσικό σύνδρομο εμφανίζουν συχνά ποσοτικές και ποιοτικές διαταραχές του μεταβολισμού των λιποπρωτεϊνών και συγκεκριμένα υπερτριγλυκεριδαιμία, αύξηση της LDL χοληστερόλης και της Lp(a), αυξημένη μεταγευματική λιπαιμία, καθώς και αύξηση της συγκέντρωσης των πλούσιων σε τριγλυκερίδια λιποπρωτεϊνών που περιέχουν Apo B, ενώ επίσης παρατηρούνται ποικίλες διαταραχές του μεταβολισμού των HDL σωματιδίων. Οι διαταραχές του μεταβολισμού των λιπιδίων δεν συσχετίζονται με την υποκείμενη νεφρική νόσο και διαδραματίζουν σημαντικό ρόλο στην παθογένεση της καρδιαγγειακής νόσου που παρατηρείται συχνά σε αυτούς τους ασθενείς, καθώς και στην εξέλιξη της νεφρικής νόσου. Στην παρούσα ανασκόπηση αναλύονται οι παθοφυσιολογικοί μηχανισμοί της δυσλιπιδαιμίας σε ασθενείς με νεφρωσικό σύνδρομο.

Λέξεις ευρετηρίου: νεφρωσικό σύνδρομο, δυσλιπιδαιμία, PCSK9, αύξηση της LDL χοληστερόλης

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