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Perspective

Progress of research on dyslipidemia accompanied by nephrotic syndrome

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Abstract

Nephrotic syndrome is a relatively common clinical disease. Associated dyslipidemia is a risk factor for the occurrence and development of cardiovascular and renal diseases that might gradually develop into atherosclerosis, glomerulosclerosis or tubulointerstitial injury. It also confers an elevated risk of complications such as thromboembolism. If not properly controlled over the long term, dyslipidemia will become a key factor in a poor prognosis. Furthermore, dyslipidemia correlates with an increase in hepatic compensatory synthetic lipoprotein levels and a decrease in lipoprotein clearance, which can be sourced to the down-regulation of hepatic and lipoprotein lipase activities in endothelial cells, muscle, and adipose tissue, and clinically characterized as hypertriglyceridemia or hypercholesterolemia. However, further investigations into the mechanism(s) of dyslipidemia are needed, with the resultant detailed perspectives and analyses substantially aiding the further development of treatment guidelines. Currently, statins represent the most popular type of pharmaceutical intervention because they lower hepatic cholesterol production and promote the absorption of low-density lipoprotein-cholesterol from the bloodstream, followed by second-line and other potential therapies to regulate the expression of specific receptors.

Keywords: Nephrotic syndrome; Dyslipidemia; Atherosclerosis; Glomerulosclerosis; Statins

Introduction

The cause of primary nephrotic syndrome (NS) is renal disease, especially glomerular disease, and it is characterized by massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia. Nephrotic syndrome causes disordered lipid and lipoprotein metabolism, and manifests as abnormal levels of plasma triglycerides, cholesterol, and lipoproteins, including very low-density (VLDL), low-density (LDL), and high-density (HDL) lipoproteins that are risk factors for cardiovascular and renal diseases. Moreover, the degree of hyperlipidemia and the correlative transformation in lipoprotein metabolism are comparable to the severity of proteinuria. Specifically, glomerulus albuminuria

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of 3.5 g/day in adults, and a urinary albumin/creatinine ratio of 2 to >3 mg/mg creatinine in children facilitate NS.[1] The pathological types of NS include membrane nephropathy, minimal change NS (MCNS), IgA nephropathy, and focal segmental glomerulosclerosis.

Mechanism of abnormal lipid metabolism

High cholesterol and/or high triglyceridemia, as well as increased serum levels of lipoproteins mainly in the form of chylomicrons, VLDL, intermediate-density lipoprotein (IDL), LDL and HDL, always coexist with hypoalbuminemia in NS. This is because the liver increases protein secretion to compensate for the hypoproteinemia caused by the massive loss of serum proteins in urine.[2] Increased lipoprotein synthesis in the liver and reduced catabolism both play roles in dyslipidemia,[3] but the latter might be the more important cause of hyperlipidemia.

Lipoproteins are the main lipid carriers in the blood and they are involved in the exogenous, endogenous and the reverse cholesterol transport pathways that are responsible for lipid production and transportation.[4] Dietary fat digested in the exogenous pathway mainly consists of triglycerides, some phospholipids, free fatty acids and cholesterol, which are all wrapped into chylomicrons by intestinal mucosal cells. Chylomicrons (CM) enter the lymphatic system, and then the bloodstream. Triglycerides and phospholipids in CM are gradually hydrolyzed by lipoprotein lipase (LPL) on the surfaces of capillary endothelial cells and then released mainly as free fatty acids that are absorbed by muscle, adipose, and other tissues. In addition, remnant CM are recognized and bound by LDL receptor-associated protein (LRP) on the cell membrane and finally cleared by hepatocytes. The liver produces VLDL, which interacts with LPL in the blood to result in the formation of IDL and releases triglycerides and free fatty acids in the endogenous pathway. Hepatocyte-mediated IDL then removes LRP from the circulation.[4] The reverse cholesterol transport process essentially comprises HDL metabolism. The ATP-binding cassette (ABC) transporters ABCA1 and ABCG1 are responsible for most of the cholesterol efflux to HDL.[5] Under the guidance of these two transporters, cholesterol is removed from extrahepatic cells, including arterial smooth muscle cells (SMC) and macrophages, to HDL. Moreover, cholesterol carried by HDL that has been esterified by lecithin-cholesterol acyltransferase (LCAT) then appears to deliver cholesterol esters to hepatocytes through the blood circulation. Eventually, cholesterol in the liver is converted into bile acids or is directly excreted as free cholesterol by bile.

The metabolic disruption of serum lipids and lipoproteins in patients with NS primarily results from impaired clearance, which is due to decreased hepatic lipase activity and LPL in endothelial cells, and adipose and muscle tissues.[4] The activities of enzymes such as lecithin-cholesterol acyltransferase (LCAT) are decreased in NS, whereas enzymes such as plasma cholesteryl ester transfer protein (CETP) are activated, thus contributing to the generation of immature HDL[6] and reducing cholesterol efflux. The exchange of cholesterol esters and triglycerides between HDL and VLDL is facilitated by CETP, which rapidly transfers cholesterol esters from HDL to VLDL and triglycerides from VLDL to HDL.[7] The serine protease, proprotein convertase subtilisin kexin type 9 (PCSK9), is also closely involved in hyperlipidemia in NS through regulating hepatic LDL receptor expression. Normally, when LDL binds to the LDL receptor on the surface of hepatocytes, the entire complex is internalized into the hepatocyte. Thereafter, LDL and its constituent cholesterol become disaggregated, which allows the receptor to recirculate to the hepatocyte surface and continue to clear LDL from the circulation. However, PCSK9 inhibits this process.[8] The expression of PCSK9 is increased in NS, which leads to increased degradation of LDL receptors and decreased LDL uptake by the liver.[9] Hypercholesterolemia represents another major feature of dyslipidemia in NS. When teamed with elevated LDL levels caused by enhanced LDL production and impaired catabolism, hypercholesterolemia upregulates the expression and activity of liver acetyl-CoA acetyltransferase 2 (ACAT2), which is the main enzyme involved in intracellular cholesterol esterification. Consequently, this leads to increased cholesterol esterification and decreased intracellular free cholesterol.[4,6,10,11] In addition to hypercholesterolemia, hypertriglyceridemia, which is mostly associated with dysregulated fatty acid metabolism in the liver, often arises in NS, as it is involved in many steps of the fatty acid biosynthesis pathway, such as increasing the expression of key synthetic enzymes and downregulating fatty acid catabolism in the liver.[4,11] The defatting effect of triglyceride-rich lipoprotein mediated by defective LPL and hepatic lipase activity, ultimately induces the accumulation of VLDL and remnant lipoproteins such as IDL and decreases clearance rates. The impaired functioning of these enzymes might be due to the loss of their activating factors in urine.[12–14]

Consequences of dyslipidemia in NS

Atherosclerosis

The most prevalent and severe impact of abnormal lipid and lipoprotein metabolism in patients with NS is atherosclerosis. Elevated triglycerides (TG), total cholesterol (TC), and LDL, along with decreased high-density lipoprotein (HDL) all contribute to atherosclerosis even in the general population. Indeed, these imbalances lead to a higher risk of atherosclerosis among patients with NS, thus promoting the development of cardiovascular diseases. The mechanism of atherosclerosis has not yet been fully characterized. Oxidized low-density lipoprotein (ox-LDL) is currently considered the most important atherogenic factor and the key cause of damage to endothelial cells and SMC.

Several theories regarding the mechanism of atherosclerosis have been proposed. One is the lipid infiltration theory, in which excessive cholesterol, cholesterol esters and other fats circulating in the blood of patients with NS are gradually deposited in the arterial intima, thus promoting connective tissue hyperplasia. This would cause arterial walls to thicken and harden, eventually leading to connective tissue necrosis and atherosclerotic plaque formation. Another is the injury response or endothelial injury theory. Clinical evidence has shown that LDL-cholesterol (LDL-C) is an established major cardiovascular (CV) risk factor.[15] It enters the inner lining of the arterial wall, where it is oxidized to ox-LDL, which might impair endothelial cells and facilitate the entry of particles into the subcutaneous space. The pathological mechanism might be the eventual formation of foam cells, perhaps derived from monocytes. Injured endothelial cells release cytokines or growth factors that attract monocytes to gather and adhere to endotheliocytes and enter the subcutaneous space to become macrophages. Early studies identified binding sites called scavenger receptors, on macrophages that allowed cholesterol uptake and deposition.[16] These receptors recognize and ingest ox-LDL and thus the macrophages become monocyte-derived foam cells. Another mechanism is the formation of foam cells from SMC that enter the intima via the arterial media and proliferate due to endothelial damage or the activation of secreted growth factors. They are mediated by LPL receptors on the cell surface to engulf lipids, thus forming foam cells. However, foam cells then synthesize growth factors and proinflammatory mediators such as PDGF, FGF, TNF-γ and IL-1, that promote plaque growth and inflammation. Most importantly, ox-LDL causes foam cell disintegration that results in atheromatous necrosis, which is the formation of atherosclerotic plaques. Studies *in vitro* have found that macrophages treated with oxLDL become foam cells, whereas those treated with native LDL do not.[16] In addition, proliferating SMC also synthesize extracellular matrix components such as collagen protein and proteoglycan that thicken and harden lesion intima, expedite plaque generation and accelerate the development and progression of atherosclerosis. They also impose an elevated risk of myocardial infarction or cerebrovascular accidents (strokes). Whereas dyslipidemia is an established risk factor for both myocardial infarction and coronary death among adults with NS, little is known about these risks in children. However, evidence is accumulating about accelerated atherosclerosis in children with persistently high lipid levels, especially from the viewpoint of refractory NS.[17]

Glomerulosclerosis

The lipid nephrotoxicity hypothesis presented over 30 years ago[18] proposed that proteinuria, hypoalbuminemia and resultant hyperlipidemia lead to adverse effects in the kidneys and might cause glomerulosclerosis. Several findings support this hypothesis. For example, hyperlipidemia in NS gradually results in glomerulosclerosis, which further promotes kidney damage, and subsequently accelerates the progression of kidney disease that leads to renal failure and death. Glomerulosclerosis and arteriosclerosis have similar biochemical and pathological features. The pathological hallmarks of glomerulosclerosis comprise increased cellularity and a dilated mesangial matrix. High levels of LDL circulating in the bloodstream absorbed by mesangial cells can induce their proliferation and the production of macrophage chemotactic factors. Both mesangial cells and macrophages can oxidize LDL, thus contributing to the formation of foam cells. Various products released by macrophages and/or foam cells are cytotoxic to mesangial cells. Meanwhile, oxidized LDL also damages mesangial cells. Conversely, lipid-induced endothelial dysfunction might result in modifications to vascular tone and increased glomerular pressure, which could further alter mesangial cell biology.[4,19] In addition, other lipoproteins and filtered albumin resorption cause lipid accumulation and cytotoxicity in proximal tubular epithelial cells, which that could lead to nephron loss and progressive chronic kidney disease.[1]

Thus, hyperlipidemia is relevant to an increased risk of progressive kidney disease, and persistent NS is characterized by moderate to severe dyslipidemia. Long-term, uncontrolled hyperlipidemia thus becomes an important factor in a poor prognosis.

Thromboembolism

Atherosclerosis is generally accompanied by highly reactive platelets that increase thrombotic risk, which is further aggravated by dyslipidemia.[20] Thromboembolism is particularly prevalent in patients with membranous nephropathy, affecting as many as 37% of adults and 25% of children,[21] and it is a significant factor that directly affects the therapeutic effect and prognosis of NS. The mechanism is an increase in blood viscosity and the formation of blood hypercoagulability. Furthermore, the increased synthesis of prothrombotic factors, the administration of diuretics and glucocorticoids, and decreased levels of antithrombin III, protein C, and protein S further aggravate hypercoagulability, increasing risk for thromboembolic and cardiovascular complications.[22]

Treatments for dyslipidemia in NS

Dietary and drug interventions can reduce circulating lipid levels and prevent the progression of glomerulosclerosis and atherosclerosis. The amounts and structures of dietary protein and fat can be adjusted, whereas correcting disordered lipid and lipoprotein metabolism before alleviating of NS is difficult. Experts have suggested that a high-quality protein diet, such as animal protein rich in essential amino acids, should be given in normal amounts of 0.8−1.0 g/kg/d. Sufficient caloric intake in range of 126−147 kJ/kg (30−35 kcal/kg/d) should be ensured. A diet should be rich in polyunsaturated fatty acids (such as vegetable or fish oils) and soluble fiber (such as oats, rice bran or beans), whereas saturated fatty acids (such as animal fats) should be avoided.

Thus, lipid-lowering is the most direct therapy for hyperlipidemia, which might increase or at least maintain renal function and decrease proteinuria.[23] The most frequently administered medicines in clinical practice are statins, which are hydroxyglutarate monoacyl CoA reductase inhibitors that are mainly used to lower cholesterol. Decreasing hepatic cholesterol production, leads to an increased LDL-C uptake from the blood. Statins have inhibited renal injury progression in experimental models, mainly through pleiotropic effects. Possible pathways for the protective effect of statins on the kidneys, other than their hypocholesterolemic effects, include the cellular apoptosis/proliferation balance, inflammatory cytokine production, and signal transduction regulation.[23,24] One study assessed the clinical manifestations of IgA nephropathy in 24 patients before, and one year after starting statin therapy. The patients were not administered with either steroids or immunosuppressive agents during the study. The results indicated improved renal function in patients with IgA nephropathy, which helped to achieve stable renal function.[25] Lipid-lowering therapy with statins has decreased proteinuria and podocyturia in controlled clinical trials.[23,26] Whether other treatments that reduce protein excretion can also help to correct dyslipidemia in NS remains controversial. Only a few randomized controlled trials have found that therapies aiming to reduce urinary protein excretion such as angiotensin II-converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARB), and low-protein diets are associated with beneficial effects on the lipid profile.[12]

Fibrates, are generally well tolerated, but with some side effects.[27] They reduce serum triglyceride levels by 30%−50% by increasing LPL activity and decreasing triglyceride synthesis.[28] A reversible increase in serum creatinine has been identified in clinical trials of fibrates, but a decrease in creatinine clearance or glomerular filtration rates has not. Some investigators have proposed that fibrates might lead to an increase in creatinine production.[29] Therefore, clinicians are advised to measure creatinine levels in patients before administering fibrates. However, if a patient has a clinically significant creatinine elevation, with no other apparent relevant cause, or has NS associated with renal insufficiency, then therapy should be interrupted or the dose should be reduced.[27] The findings of clinical trials have suggested that the administration of both statins and fibrates, especially fenofibrate (which is not associated with the inhibition of statin metabolism), induces obvious decreases in LDL-C and TG.[28,30] However, this combination should be prescribed with caution as it increases the risk of myopathy.[31]

Potential future treatments might include inhibitors against PCSK9, because recommended LDL cholesterol concentrations are not achieved in many patients despite intensive statin treatment.[32,33] Increased PCSK9 expression is an important link in the pathogenesis of hyperlipidemia in NS, and is thus is an important factor in the regulation of plasma cholesterol levels and therapeutic targets. Therefore, PCSK9 inhibitors might benefit patients with hypercholesterolemia associated with NS.[34] A small interfering

RNA (siRNA) inhibitor of PCSK9 has been found safe and effective for reducing LDL cholesterol, without serious adverse events.[35] A placebo-controlled clinical trial of evolocumab (PCSK9 inhibitor) investigated the influence of PCSK9 inhibition on LDL-C in patients with desirable baseline LDL-C levels regardless of statin therapy. The study randomly selected 331 patients (age, 18−80 years), who had been on stable lipid-lowering therapy for at least four weeks, and had fasting LDL-C concentrations of ≥2.6 mmol/L. The results showed that evolocumab for 12 weeks lowered LDL-C by up to 61%.[8,36] Furthermore, evolocumab was well tolerated, with an incidence of adverse events that was similar to that of a placebo. The more common adverse events in patients given evolocumab compared with a placebo, comprised nasopharyngitis and muscle-related events.[36] Therefore, continuing studies on this topic should be worthwhile.

In general, hyperlipidemia can be relieved naturally after the remission of NS, so lipid-lowering drugs can be discontinued. However, different pathological types respond differently to treatment. For example, patients with minimal change NS (MCNS), can easily normalize serum cholesterol levels after steroids and/or other immunosuppressive therapies have achieved complete relief,[37] whereas those with focal segmental glomerulosclerosis (FSGS) respond poorly to treatment, and extreme hyperlipidemia persists over the long term.[37]

Conclusion

Most patients with clinical NS also show abnormal lipid metabolism. While the knowledge of the triggering factors responsible for the alterations in lipid metabolism has considerably improved, the underlying molecular mechanism(s) have not yet been fully elucidated. However, the consequences and complications of hyperlipidemia have been identified and clinically proven. Hyperlipidemia has been shown to affect prognoses and even develop into CKD or promote cardiovascular disease in the absence of timely intervention. Thus, targeted treatment is particularly important as dietary control alone is insufficient. Medication intervention should be undertaken to prevent glomerular sclerosis and atherosclerotic progression. Unlike pharmacotherapy with statins that has been widely applied in clinical practice, many other standardized therapies remain unconfirmed by experimental studies, or their adverse effects remain unknown. More detailed knowledge about their mechanisms will be available with additional investigations, in the near future, especially those from the field of molecular biology. It is only then that the available therapeutic methods could be validated and applied, and a gold standard could be determined for the patients suffering from NS.

Conflicts of interest

None.

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