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Secondary dyslipidemia: its treatments and association with atherosclerosis

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Abstract: Dyslipidemia is classified into primary and secondary types. Primary dyslipidemia is basically inherited and caused by single or multiple gene mutations that result in either overproduction or defective clearance of triglycerides and cholesterol. Secondary dyslipidemia is caused by unhealthy lifestyle factors and acquired medical conditions, including underlying diseases and applied drugs. Secondary dyslipidemia accounts for approximately 30-40% of all dyslipidemia. Secondary dyslipidemia should be treated by finding and addressing its causative diseases or drugs. For example, treatment of secondary dyslipidemia, such as hyperlipidemia due to hypothyroidism, by using statin without controlling hypothyroidism, may lead to myopathy and serious adverse events such as rhabdomyolysis. Differential diagnosis of secondary dyslipidemia is very important for safe and effective treatment. Here, we describe an overview about diseases and drugs that interfere with lipid metabolism leading to secondary dyslipidemia. Further, we show the association of each secondary dyslipidemia with atherosclerosis and the treatments for such dyslipidemia.

***Keywords*:** hypothyroidism, low-density lipoprotein, nephrotic syndrome, triglyceride

Introduction

Dyslipidemia is classified into primary and secondary dyslipidemia. Primary causes are single or multiple gene mutations that result in either overproduction or defective clearance of triglycerides (TG) and low-density lipoprotein (LDL), or in underproduction or excessive clearance of high-density lipoprotein (HDL). Secondary dyslipidemia is induced by other underlying diseases and drugs. Almost 30-40% of dyslipidemia is categorized into secondary dyslipidemia (*1*). Secondary dyslipidemia should be treated by finding and addressing its causative diseases or drugs. For example, treatment of secondary dyslipidemia due to hypothyroidism by using statin, without controlling hypothyroidism, may lead to myopathy and serious adverse events such as rhabdomyolysis. This indicates the importance of differential diagnosis of secondary dyslipidemia.

Causes of secondary dyslipidemia are shown in Table 1. Among secondary dyslipidemia, there are types which show elevation of cholesterol such as hypothyroidism, types which show elevation of TG such as alcohol intake, and types which show elevation of both cholesterol and TG such as nephrotic syndrome.

Hypothyroidism

When addressing dyslipidemia due to hypothyroidism, we should separately consider overt hypothyroidism, in which thyroid hormone levels are low, and subclinical hypothyroidism in which thyroid stimulating hormone (TSH) levels are high despite normal thyroid hormone levels. In overt hypothyroidism, elevations of total cholesterol (TC), LDL-cholesterol (LDL-C), apolipoprotein (Apo) B and lipoprotein (a) [Lp(a)] are observed (*2*). LDL-C is remarkably elevated by about 30% (*2*). Thyroid hormone stimulates LDL-C degradation and the conversion of cholesterol to bile acids by inducing LDL-receptor and 7 alpha-hydroxylase expression, respectively (*3*); which explains elevated LDL-C levels in hypothyroidism.

Subclinical hypothyroidism is observed in 4-10% of patients with dyslipidemia. In the meta-analysis which studied the effect of dyslipidemia due to subclinical hypothyroidism on carotid artery intima-media thickness (cIMT), subclinical hypothyroidism with TSH ≥ 10 μU/mL was associated with elevations of TC, LDL-C, TG and cIMT (*4*). In the meta-analysis which studied thyroid hormone replacement therapy on dyslipidemia, those with a duration of over 6 months were associated with reductions of TC and LDL-C regardless of TSH values (*5*). Furthermore, the thyroid hormone replacement therapy reduced IMT in patients with subclinical hypothyroidism (*6,7*). However, there is presently no evidence which shows thyroid hormone replacement therapy reduces cardiovascular events (*8*).

Table 1. Causes of secondary dyslipidemia

Items	Cholesterol	Triglyceride
1. Hypothyroidism	↑	
2. Nephrotic syndrome	↑	↑
3. Chronic kidney disease (CKD)		↑
4. Primary biliary cholangitis (PBC)	↑	
5. Obstructive jaundice	↑	
6. Diabetes	↑	↑
7. Obesity		↑
8. Cushing's syndrome	↑	↑
9. Pheochromocytoma	↑	↑
10. Drugs	Drug dependent	
11. Alcohol intake		↑
12. Smoking		↑

Hypothyroidism is a risk factor for statin-induced myopathy (*9*). A reported case of a patient developing acute renal failure due to rhabdomyolysis after statin use (*10*) shows the importance of differential diagnosis of secondary dyslipidemia due to hypothyroidism.

Hypothyroidism can be the cause of secondary dyslipidemia, and thyroid hormone replacement therapy may improve dyslipidemia and prevent progression of atherosclerosis.

Nephrotic syndrome

An excess urinary protein loss-induced hepatic overproduction of lipoproteins, including LDL and very low-density lipoprotein (VLDL), a reduced clearance of TG-rich lipoproteins due to decreased activities of hepatic lipase (HL) and lipoprotein lipase (LPL), and an impaired maturation of HDL were associated with the development of dyslipidemia in patients with nephrotic syndrome (*11,12*). Recently, the association of proprotein convertase subtilisin/kexin type 9 (PCSK9) which determines LDL-receptor turnover with dyslipidemia due to nephrotic syndrome was proposed (*13*). Plasma PCSK9 levels were significantly higher in patients with nephrotic syndrome as compared with healthy individuals, and plasma PCSK9 levels were significantly and positively correlated with TC and LDL-C levels (*13*).

Regarding the relationship between nephrotic syndrome and arteriosclerosis, cIMT values in children with nephrotic syndrome were higher than controls (*14*). cIMT values were not correlated with dyslipidemia, but, were significantly and positively correlated with age, relapse frequency, and disease duration of nephrotic syndrome. Augmentation index (AI) which reflects systemic arteriosclerosis was significantly higher in patients with nephrotic syndrome than healthy individuals, and univariate linear correlation analysis showed that AI was significantly and positively correlated with TG, TC, LDL-C, non-HDL-C (*15*).

In the cohort study, the unmatched analysis adjusted by hypertension and smoking at diagnosis of nephrotic syndrome showed that relative risks of myocardial infarction and coronary death were 5.5 [95% confidence interval (95% CI): 1.6-18.3] and 2.8 (95% CI: 0.7-11.3), respectively (*16*). The development of thromboembolism was observed in 2.8% of children and 26.7% of adults with nephrotic syndrome (*17*). Thromboembolism is induced by loss of anti-thrombotic factors into urine, and hepatic overproduction of prothrombotic factors (*17,18*). Various observational studies showed that patients with nephrotic syndrome frequently develop arterial and venous thromboembolism, however, neither of them showed the association of dyslipidemia with development of thromboembolism (*19-22*).

In the dietary intervention for nephrotic syndrome, a soy diet (low fat; protein, 0.71g/kg/day; cholesterol-free; mono- and poly-unsaturated fatty acids (PUFA)-rich; the ratio of PUFA to saturated fatty acids, 2.5; dietary fiber, 40g/day) was tried (*23,24*) (Table 2). The soy diet significantly reduced TC, LDL-C, HDL-C, Apo A, Apo B and urinary protein in patients with nephrotic syndrome. An intake of omega-3 fatty acids significantly reduced TG, VLDL-C, small dense LDL, remnant-like lipoprotein particles (RLP)-C and RLP-TG in patients with nephrotic syndrome (*25*). Various studies, including randomized controlled trials (RCTs), showed that statin reduced TC, LDL-C and TG safely and effectively (*26-32*). However, evidence showing beneficial effects of statin for renal outcomes was very limited, and one study showed that statin significantly improved urinary protein, serum albumin, creatinine, renal interstitial fibrosis and renal fat deposits (*27*). In the interventional studies using fibrates, gemfibrozil significantly reduced TG, TC, LDL-C and Apo B and significantly increased HDL-C (*33,34*). However, beneficial effects of fibrates for renal outcomes was not reported. In patients with treatment-resistant focal segmental glomerulosclerosis or nephrotic syndrome, the combination therapy of LDL-apheresis with steroid significantly reduced LDL-C and induced remission in 47.7-71.0% of such patients (*35-38*). In the meta-analysis which studied lipid-lowering agents on cardiovascular events in patients with nephrotic syndrome, the beneficial effects of these agents on mortality, cardiovascular death and non-fatal myocardial infarction were not obtained (*39*). For patients with minimal change nephrotic syndrome, which is steroid-responsive, the lipid-lowering therapy may not be needed. However, for patients with treatment-resistant nephrotic syndrome such as membranous nephropathy, the lipid-lowering therapy may be needed because such patients are middle-aged, prone to develop thromboembolism, and have prolonged steroid treatment.

Although they were no studies with patients who met the diagnostic criteria for nephrotic syndrome, several studies have shown beneficial effects of hypolipidemic agents on suppression of progression of proteinuria, and cardiovascular events, in patients with renal diseases.

Table 2. Effects of hypolipidemic interventions on serum lipids and renal outcomes in patients with nephrotic syndrome

Interventions	Effects on serum lipids	Effects on renal outcomes
Soy diet (*n* = 2)	● Reduction of TC, LDL-C, HDL-C ● Reduction of apolipoprotein A, B ● No change of TG	● Reduction of urinary protein
Omega-3 fatty acids (*n* = 1)	● Reduction of TG, VLDL-C, small dense LDL ● Reduction of RLP-C and RLP-TG ● No change of HDL-C	● No available data
Statin (*n* = 7)	● Reduction of TC, LDL-C, TG (*n* = 5) ● Reduction of TG (*n* = 4) ● Reduction in apolipoprotein B (*n* = 3) ● Increase of apolipoprotein A (*n* = 1)	● Reduction of proteinuria (*n* = 1) ● Increase of serum albumin (*n* = 2) ● Reduction of renal fat deposits (*n* = 1) ● No change of proteinuria or serum albumin (*n* = 2)
Fibrates (*n* = 2)	● Reduction in TC, LDL-C, TG, apolipoprotein B (*n* = 2) ● Increase of HDL-C (*n* = 1) ● No change of HDL-C (*n* = 1)	● No change of renal outcomes (*n* = 1) ● No available data (*n* = 1)
LDL-apheresis (*n* = 4)	● Reduction in TC, LDL-C (*n* = 4) ● No change of TG and HDL-C (*n* = 2) ● Decrease of TG (*n* = 1)	● Complete or partial remission rate, 47.7-71.0%

HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density-cholesterol; RLP, remnant-like particles; TC, total cholesterol; TG, triglyceride.

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, type 2 diabetic patients (*n* = 9,795) aged 50 to 75 years were randomly assigned to fenofibrate (*n* = 4,895) or placebo (*n* = 4,900) for 5 years (*40*). Fenofibrate reduced urine albumin concentrations by 14% ($p < 0.001$), with 14% less progression and 18% more albuminuria regression ($p < 0.001$) than placebo. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial randomized 5,518 participants to either fenofibrate and simvastatin, or placebo and simvastatin (*41*). A post hoc analysis in the ACCORD Lipid Trial showed that fenofibrate was associated with lower rates of incident albuminuria and a slower estimated glomerular filtration rate (eGFR) decline as compared with placebo (*42*). In both FIELD study and ACCORD Lipid Trial, fenofibrate did not show a significant suppression of atherosclerotic cardiovascular disease (ASCVD) in the overall analysis, however, it did show a significant suppression of ASCVD in the sub-analysis using patients with high TG and low HDL-C (*43*). However, the fibrate use should be cautioned for patients with impaired renal function.

Chronic kidney disease (CKD)

Recently, an innovative established analysis method for lipoprotein profiles using high-performance anion-exchange liquid chromatography (AEX-HPLC) is accelerating the understanding of secondary dyslipidemia such as CKD and diabetes (*44*). In patients with CKD and proteinuria, a loss of Apo C-II, an activator of LPL, into urine impairs catabolism of VLDL (*45*). In patients with CKD and reduced GFR, hepatic VLDL production is not elevated, and the catabolism of VLDL is impaired. Further, serum Apo C-III, an inhibitor of LPL, is increased and HL activity is reduced (*46,47*). Therefore, serum intermediate-density lipoprotein (IDL) levels increase in patients with CKD. We examined the lipoprotein profiles measured by AEX-HPLC in patients undergoing hemodialysis (HD), and found decreased HDL-C levels and increased levels of IDL-C and VLDL-C in HD patients as compared with healthy individuals (*48*).

CVD is the most common cause of mortality in patients with CKD. Dyslipidemia may be highly associated with the development of CVD in patients with CKD.

Primary biliary cholangitis (PBC)

PBC is an autoimmune liver disease characterized by positive anti-mitochondrial antibody. In PBC, the impaired secretion of cholesterol and bile acid into bile juice increases serum cholesterol. LDL-C is elevated regardless of disease stage of PBC, and HDL-C is relatively high even at the end stage of disease (*49*). In the systematic review which studied the association between PBC and coronary artery disease (CAD), PBC was not associated with the development of CAD (*49*). An observational study showed that 12% of PBC patients died of CVD (*50*), suggesting the existence of a population which needs the management of serum lipids.

Obstructive jaundice

Obstructive jaundice is induced by cholestasis due to obstruction of the extra-hepatic bile duct by gallstone or tumor. Intestinal cholesterol production is increased due to the impaired secretion of bile juice into the intestine

resulting in a disturbed absorption of fat. Hepatic and intestinal HDL productions are decreased by liver dysfunction and insufficient fat supply to the intestine. Therefore, LDL-C is elevated and HDL-C is reduced. Phospholipids-rich and free cholesterol-rich lipoprotein, lipoprotein X, increases in the blood of patients with obstructive jaundice (*51*).

Diabetes

When patients with type 1 (insulin-dependent) diabetes develop diabetic ketoacidosis, a remarkable elevation of chylomicron (CM) with TG > 1,000 mg/dL and a resulting acute pancreatitis are sometimes observed. However, such hyperchylomicronemia or hypertriglyceridemia is transient and is not associated with the development of atherosclerosis. In type 2 diabetes and obesity, insulin resistance induces dyslipidemia (*52*). Insulin resistance activates hormone-sensitive lipase (HSL) which hydrolyzes TG to free fatty acids (FFAs), and then serum FFAs increase. Increased FFAs enter the liver and increase hepatic VLDL production. Insulin resistance decreases LPL activity, which impairs VLDL metabolism and results in increased VLDL and decreased HDL. Our previous study using the AEX-HPLC showed lower values of HDL-C and higher values of IDL-C and VLDL-C in the order of type 2 diabetic patients with obesity, type 2 diabetic patients without obesity, low Framingham risk score subjects, young lean men (*53*).

In addition, large VLDL (VLDL1) and small dense LDL are increased, and apolipoproteins are glycated in the serum of patients with diabetes (*54*). Obesity and overweightness induce an abnormal fat accumulation which induces metabolic disorders such as type 2 diabetes. Adiponectin is released by adipose tissue, and plasma adiponectin levels are inversely correlated with body mass index (BMI) (*55*). High levels of circulating adiponectin can protect against atherosclerosis by the improving lipid and glucose metabolism (*56*). We estimated correlations between lipoprotein profiles and serum adiponectin levels in patients with type 2 diabetes and found an inverse correlation between adiponectin levels and VLDL-C levels (*57*).

Elevations of RLP which include CM remnant and VLDL remnant are associated with the progression of atherosclerosis and CAD (*58*). A high RLP-C (> 0.12 mmol/L) is a significant risk factor for CAD in Japanese patients with type 2 diabetes (*59*). We found that RLP-C is significantly correlated with IDL-C and VLDL-C measured by AEX-HPLC (*60*), suggesting that IDL-C and VLDL-C are also crucial risk factors for CAD in Japanese patients with type 2 diabetes.

Obesity

Obesity is associated with a number of deleterious changes in lipoprotein metabolism, including high serum levels of TC, LDL-C, VLDL-C, and TG, and a reduction in serum HDL-C concentration of about 5 percent (*61*). Loss of body fat can reverse hypercholesterolemia and hypertriglyceridemia. However, improvements in serum levels of TC, HDL-C, and Apo A-I were primarily limited to patients with LDL subclass A (LDL peak particle size ≥ 26 nm), and one-third of patients with LDL subclass B (LDL peak particle size ≤ 25.5 nm), albeit a small-sized study of obese subjects with a mean age of 60 years (*62*).

Cushing's syndrome

Cushing's syndrome is caused by over-secretion of cortisol, which induces central obesity, impaired glucose tolerance, and dyslipidemia. Cortisol increases hepatic VLDL production, and patients with Cushing's syndrome show elevations of serum cholesterol and TG (*63*). The meta-analysis showed that Cushing's syndrome was associated with IMT thickening, carotid arterial plaque development, and endothelial dysfunction (*64*).

Cushing's syndrome can be a cause for secondary dyslipidemia and is associated with progression of atherosclerosis.

Pheochromocytoma

Pheochromocytoma is a rare neuroendocrine tumor arising from chromaffin cells of the adrenal medulla. The varied signs and symptoms of pheochromocytoma mainly reflect the hemodynamic and metabolic actions of catecholamines produced and secreted by the tumor. Increased catecholamines may activate HSL which increase serum FFAs, and enhance hepatic VLDL production. However, phenotypes of dyslipidemia due to pheochromocytoma and effect of its treatment on dyslipidemia varies by case reports (*65-67*).

Drugs

Among the most common causes of secondary dyslipidemia are drugs used for other indications. Causative drugs which induce dyslipidemia are shown in Table 3.

Table 3. Causative drugs which induce dyslipidemia

Causative drugs	LDL-C	TG	HDL-C
Diuretics (thiazide)	→	↑	→
β-blockers	→	↑	↓
Steroid	↑	↑	↑
Estrogen	↓	↑	↑
Progesterone	↑	↓	↓
Immunosuppressants	↑	↓	No available data
Anti-HIV drugs	↑	↑	↓
Atypical antipsychotics	→	↑	↓
Retinoids	↑	↑	↓

Diuretics

The meta-analysis of clinical trials, which investigated the effects of antihypertensive agents on lipids, showed that the use of diuretics, especially thiazides, in the treatment of hypertension has been associated with increased TC, LDL-C and TG levels (*68*). Among thiazide diuretics, chlorthalidone led to a greater increase in LDL-C, whereas indapamide did not alter TG levels at all. The effects of diuretics on TG were diminished over time, but the effects on cholesterol levels were not associated with study duration (*68*).

β-blockers

The conventional *β*-blockers exert adverse effects on weight, heart rate, and lipid and glucose metabolism, which may impair glucose tolerance, leading to elevations of TG and VLDL and a reduction in HDL (*69*). They may have a negative impact on total energy expenditure, which leads to weight gain (*70*). However, β-blockers with cardioselectivity and intrinsic sympathomimetic activity (ISA) decreased TC and LDL-C levels and increased HDL-C (*68,71,72*). Pindolol, a cardioselective β-1 blocker with ISA, lowered TG and increased HDL-C. However, atenolol, a cardioselective β-1 blocker without ISA, reduced HDL-C levels and did not affect TC and LDL-C levels (*72*).

Steroid

Steroids increase hepatic VLDL production and HDL production, which induce elevations of serum levels of TG, LDL-C and HDL-C. The effects of steroid treatment on serum lipids may vary depending on the daily dose and duration of steroid treatment (*73*). Corticosteroid-treated transplant recipients showed increased frequency of hypercholesterolemia and hypertriglyceridemia, with elevations of both LDL-C and HDL-C levels (*74-77*). Short-term prospective studies of the effects of prednisone in healthy men and patients with various disorders requiring corticosteroid therapy have shown an increase in TC by 8-17% and an increase in HDL-C by 36-68%, with insignificant changes in LDL-C levels (*78,79*).

Estrogen, Progesterone

Estrogen increases hepatic VLDL production, suppresses HL activity, and increases expression of LDL receptors (*80-82*). These effects of estrogen eventually decrease LDL-C and increase HDL-C and TG (*83*). Progesterone acts as an antagonist for estrogen, increases LDL-C, and decreases TG and HDL-C (*83*). Therefore, the effects of female hormones on serum lipids vary depending on the ratio of estrogen to progesterone included in drugs. When estrogen and progesterone are used as hormone replacement therapy for menopausal disorders or as treatment for prostate cancer, it is known to affect lipid metabolism in a dose-dependent manner. However, dyslipidemia is rarely a problem with low-dose pills intended for contraception.

Immunosuppressants

A longitudinal cohort review of 102 outpatient pediatric liver recipients surviving greater than 6 months and immunosuppressed with cyclosporine and prednisone was undertaken (*84*). Half of the children had a mean cholesterol greater than 75th percentile (170 mg/dl); 20% were above the 95th percentile; 56% had a mean TG level greater than 140 mg/dl. Switching from cyclosporine to tacrolimus was significantly associated with decrease of TG, Apo A1, Apo B, LDL-C, HDL-C, and TC levels (*85*). Switching from cyclosporine to tacrolimus was associated with a more favorable cardiovascular risk profile by improving dyslipidemia. Since the patients undergoing transplant surgery are young, it is necessary to observe the effects of immunosuppressants on future cardiovascular events.

Anti-human Immunodeficiency Virus (HIV) drugs

Anti-HIV drugs improve endothelial function due to an improvement of chronic inflammation by HIV reduction. However, recently, anti-HIV drugs have been reported to increase the development of myocardial infarction. The prospective observational study of 23,437 patients infected with HIV showed that the incidence of myocardial infarction increased from 1.53 per 1,000 person-years in those not exposed to protease inhibitors to 6.01 per 1,000 person-years in those exposed to protease inhibitors for more than 6 years (*86*). The increased exposure to protease inhibitors is associated with an increased risk of myocardial infarction, which is partly explained by dyslipidemia (*86*). Elevations of TG, TC, and LDL-C and HDL-C reduction are commonly observed as dyslipidemia due to protease inhibitors (*87,88*). In a variety of anti-HIV drugs, protease inhibitors may cause dyslipidemia, while integrase inhibitors, a new-generation anti-HIV drug, have a minimal impact on serum lipid profile (*89*).

Atypical antipsychotics

Atypical antipsychotics such as olanzapine induce obesity and insulin resistance (*90*), which induce TG elevation and HDL-C reduction (*91*).

Retinoids

Hypertriglyceridemia is a metabolic complication of systemic retinoid therapy, which may occur in up to 17% of individuals treated with such therapy (*92*). Apo

C-III appears to be a target gene for retinoids acting via retinoid X receptor. The increased Apo C-III expression may contribute to hypertriglyceridemia due to retinoid therapy (*92,93*). LDL-C elevation and HDL-C reduction are also induced by systemic retinoid therapy (*92*).

Alcohol intake

Moderate alcohol intake induces elevations of HDL-C and Apo A-I, which might be anti-atherogenic (*94*). However, over-consumption of alcohol increases inflammatory cytokines, deteriorates insulin resistance (*95*), and results in an increase of VLDL. Patients with over-consumption of alcohol usually show type IV dyslipidemia. Alcoholism was associated with 7-day myocardial infarction fatality in the crude analysis (*96*), and is a risk factor for ischemic stroke (*97*).

Smoking

Cigarette smoking is associated with an increase in TG, a decrease in HDL-C and the deterioration of insulin resistance (*98*). The effect of smoking was more prominent if adjusted for concomitant alcohol intake; in such patients, smoking was associated with a 5 to 9 mg/dL decline in serum HDL-C (*99*). These effects are reversible within one to two months after smoking cessation (*100,101*). Smoking also causes the production of dysfunctional HDL3 particles that are characterized by an increased sensitivity to glycation and a reduced antioxidative capacity; it also impairs HDL function including cellular cholesterol efflux (*102,103*). Smoking is one of crucial risk factors for atherosclerosis (*104,105*).

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