Secondary dyslipidaemia

Abstract

Plasma lipid levels are determined by the interplay of environmental and genetic factors. Occasionally environmental factors may alter lipid levels significantly, resulting in secondary dyslipidaemia. The lipid phenotype in secondary dyslipidaemia is very variable (e.g. predominant hypercholesterolaemia, hypertriglyceridaemia or changes in high-density lipoprotein cholesterol) and is dependent on the inciting secondary factor and the genetic and metabolic background. Some common causes of secondary hyperlipidaemia include hypothyroidism, diabetes, nephrotic syndrome, cholestatic liver disease and drugs such as retinoids, antiretroviral medications and glucocorticoids. Secondary dyslipidaemia should be addressed before lipid-lowering drugs are prescribed.

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Introduction

Plasma lipoprotein levels are determined by a complex and multifaceted interaction between genetic and environmental factors, “environment” referring in this case to both external factors, such as diet, lifestyle, drugs and alcohol, and internal factors, such as medical disorders or altered physiological states such as pregnancy. In some individuals genetic factors will be the predominant influence; in patients with familial hypercholesterolaemia (FH), low-density lipoprotein cholesterol (LDLC) elevation is mainly determined by genes but may still be influenced by diet or drugs. Secondary factors such as nephrotic syndrome may cause severe LDLC elevation in previously normolipidaemic individuals, yet LDLC will not be elevated to the same extent in all individuals with similarly severe nephrotic syndrome.

This article will review some environmental factors that may alter lipoprotein concentrations from the “set point” determined by the genetic background. Patients in whom dyslipidaemia is wholly or at least partially due to such secondary causes are said to have secondary dyslipidaemia. Identifying patients with secondary dyslipidaemia is important, as treatment of the secondary cause may make lipid-lowering therapy unnecessary, or allow the dyslipidaemia to be controlled with lower doses of lipid-lowering medications. In other patients routine lipid screening may identify dyslipidaemia, with subsequent screening for secondary causes identifying hitherto unexpected disorders, such as hypothyroidism, by “stealth”. It is thus important for all practitioners treating dyslipidaemia to be familiar with the secondary causes of dyslipidaemia, so that unnecessary treatment may be avoided or recognised disorders identified.

Endocrine disorders

Hypothyroidism

Hypothyroidism is probably one of the most common secondary causes of dyslipidaemia in clinical practice and is often missed. Many hypothyroid patients do not fit the clinical stereotype of an elderly, overweight woman wearing a thick jersey in summer, who has dry skin, constipation, slowed mentation, a croaky voice and myxoedema. Recent-onset hypothyroidism in particular may cause significant dyslipidaemia without hypothyroidism being clinically obvious.

Thyroid hormones interact with lipoprotein metabolism at multiple points. The most common lipid abnormality seen in hypothyroidism is elevated LDLC. Hypothyroid patients express fewer LDL receptors on the liver cell surface because thyroid hormones promote LDL-receptor gene transcription. Hypothyroid patients thus have reduced LDL catabolism secondary to insufficient LDL receptor on hepatocytes. Decreased LDL receptor expression also impairs clearance of remnant lipoproteins [chylomicrons and very low-density lipoproteins (VLDLs), from which triglyceride has been partially removed] and hypothyroidism may precipitate dysbetalipoproteinaemia, which is characterised by severe mixed hyperlipidaemia due to high levels of remnant lipoproteins.
Larger triglyceride-rich lipoproteins may also accumulate in hypothyroidism due to both decreased hepatic clearance and decreased peripheral lipolysis, as the activity of lipoprotein lipase and hepatic lipase is reduced in hypothyroidism. Thyroid hormones also promote the transcription of apolipoprotein A-V, which is an important co-factor in triglyceride metabolism. In genetically predisposed patients, hypothyroidism may thus precipitate hypertriglyceridaemia.

Severe hypothyroidism may be associated with high levels of high-density lipoprotein cholesterol (HDLC). This effect is mainly mediated via the effect thyroid hormones have on hepatic lipase, although reduced activity of cholesteryl ester transfer protein (CETP) may also play a role.

A thyroid function test for thyroid stimulating hormone (TSH) should thus be routinely requested before lifelong lipid-lowering therapy is started. Deteriorating lipid levels, despite good medication adherence in previously well-controlled patients, are also an indication for thyroid function evaluation. Hypothyroid patients are more likely to experience statin-induced myalgia or rhabdomyolysis. Patients with hypothyroidism should not be started on lipid-lowering therapy unless they remain significantly dyslipidaemic despite receiving adequate thyroid replacement therapy for two to three months. Thyroid hormone therapy usually improves the lipid profile markedly, but patients with underlying genetic disorders of lipoprotein metabolism may still require lipid-lowering therapy. Repeat lipid evaluation following thyroid hormone prescription and restoration of the euthyroid state is thus essential.

Subclinical hypothyroidism is characterised by elevated TSH with normal T4 levels. The prevalence of subclinical hypothyroidism in the general population may be as high as 4-10%, and up to 20% in females over the age of 60 years. The management of subclinical hypothyroidism is controversial and there are few large randomised studies from which evidence-based recommendations can be derived. Some of the proposed indications for thyroxine are prevention of overt hypothyroidism, as thyroid function often deteriorates further, treatment of symptoms such as fatigue, lack of energy and depression, and vascular risk reduction.

This article will only review dyslipidaemia and vascular risk reduction as possible indications for treating subclinical hypothyroidism. In epidemiological studies, higher TSH levels correlate with higher LDLC, although the absolute increase in LDLC is small. Each one milliunit rise of TSH has been estimated to increase LDLC by 0.08 mmol/L in men and 0.16 mmol/L in women. Treatment of subclinical hypothyroidism lowers lipids most in patients with the highest baseline TSH (>10 mU/L) and highest baseline total cholesterol (>6.2 mmol/L). Subclinical hypothyroidism is also associated with elevated levels of C-reactive protein (CRP) in some, but not all, studies. The data on cardiovascular risk in subclinical hypothyroidism are conflicting, but the majority of studies indicate increased risk particularly in those with a TSH >10 mU/L. As yet, no study has determined cardiovascular outcomes of thyroxine replacement in patients with subclinical hypothyroidism, but treatment can be considered in those with high baseline cholesterol and cardiovascular risk, particularly if the TSH is > 10 mU/L. Sufficient thyroxine should be prescribed to normalise the TSH, but overtreatment should be avoided because of associated risks such as atrial fibrillation and osteoporosis.

Insulin resistance and diabetes

Insulin resistance is an important pathophysiological component in the genesis of the metabolic syndrome and type II diabetes. The dyslipidaemia of insulin resistance is characterised by moderate hypertriglyceridaemia, low HDLC and normal to moderately elevated levels of LDLC. The LDL particles are often small and dense. This constellation of lipid abnormalities is often called diabetic dyslipidaemia or the atherogenic lipid phenotype. The risk of atherosclerosis is high with this lipid phenotype and is often underestimated on superficial inspection of the lipid profile, as neither the total cholesterol nor the LDLC are usually markedly elevated.

Treatment of diabetic dyslipidaemia is an important component of global vascular risk reduction in type II diabetes. Statin therapy is indicated in most patients with type II diabetes in addition to lifestyle modifications. The main lipid effect of statin therapy is LDLC reduction, and statin monotherapy therefore often does not comprehensively control all the components of diabetic dyslipidaemia. Residual vascular risk is high in type II diabetes, despite aggressive lowering of LDLC. Combining statins with fibrates or niacin, which lower triglycerides and increase HDLC, is thus an attractive potential strategy to further lower vascular risk. In the recently published ACCORD study, fenofibrate or placebo was added to simvastatin in high-risk diabetics irrespective of baseline lipids, i.e. the trial did not specifically aim to include patients with low HDLC or high triglycerides. Combination therapy was not more effective than statin monotherapy in the overall cohort, but there was a trend towards better outcomes in the subgroup of patients with the lowest HDLC and the highest triglycerides. Combination lipid-lowering therapy can thus currently not be routinely recommended in the management of diabetic dyslipidaemia and individualised treatment decisions should be based on careful analysis of the lipid phenotype, assessment of vascular risk and the costs and risks of combination therapy.

Diabetes may precipitate severe hypertriglyceridaemia in genetically predisposed patients. Patients with newly diagnosed hypertriglyceridaemia should always be screened...
for undiagnosed diabetes. Severe hypertriglyceridaemia in diabetes is managed with tight glycaemic control, dietary fat restriction and fibrates.

**Cushing's syndrome**

Glucocorticoid excess, as seen in Cushing's syndrome, may be associated with elevated LDL-C and triglycerides. Cardiovascular risk is further increased by hypertension and dysglycaemia, which occur frequently in Cushing's syndrome. Long-term cardiovascular mortality is increased in patients with Cushing's disease and this increased risk persists after successful treatment of hypercortisolaemia. Cardiovascular risk factor control is therefore an important component of the long-term management of patients with Cushing's syndrome. Glucocorticoid therapy can have similar adverse metabolic consequences to endogenous glucocorticoid excess.

**Renal disease**

**Nephrotic syndrome**

Severe hypercholesterolaemia is characteristic in nephrotic syndrome. Hypercholesterolaemia is usually due to high LDL-C but, in genetically predisposed individuals (homozygosity for the E2 isoform of apolipoprotein E), remnant lipoproteins may accumulate, resulting in a severe mixed hyperlipidaemia (dysbetalipoproteinaemic phenotype). The pathophysiology of hypercholesterolaemia in nephrotic syndrome is not perfectly understood, but the severity of dyslipidaemia correlates with the degree of proteinuria. Proteinuria may lead to loss of LDL receptors in addition to increasing hepatic lipoprotein output. Combined with decreased VLDL and chylomicron clearance, these mechanisms may lead to marked hyperlipidaemia. Hyperlipidaemia often resolves or improves markedly if the underlying renal disease enters remission. Statins are effective lipid-lowering agents for the dyslipidaemia associated with nephrotic syndrome and are generally prescribed, unless the underlying renal disease is expected to respond rapidly to treatment.

**Chronic kidney disease**

Chronic kidney disease with reduced glomerular filtration rate (usually less than 50 ml/minute) is often associated with mild hypertriglyceridaemia, low HDLC, increased lipoprotein(a) and normal to slightly reduced total cholesterol and LDL-C. Uraemia downregulates the expression of the lipolytic enzymes hepatic lipase and lipoprotein lipase. Apolipoprotein C-III, which inhibits lipolysis, is also increased in renal failure. The dyslipidaemia is often further modified by concomitant diseases such as diabetes or medications such as steroids or calcineurin inhibitors.

Patients with renal failure are at very high risk of cardiovascular disease. The recently completed Study of Heart and Renal Protection (SHARP) showed that treating patients with renal disease who had lost at least 50% of their glomerular filtration rate with the combination of simvastatin 20 mg and ezetimibe 10 mg reduced the major atherosclerotic event rate by about one-sixth compared to placebo. Two previous trials in patients on dialysis had failed to show any benefit from statin treatment. Once patients require dialysis, their vascular disease may be too advanced for statins to be effective. Non-lipid-related mechanisms, such as vascular calcification, arrhythmias and non-ischaemic cardiomyopathy, are also likely to be important contributors to mortality and would not be influenced by statins.

Statins (or the combination of a statin with ezetimibe) are the preferred lipid-lowering treatment for patients with chronic renal disease. Severe hypertriglyceridaemia may require fibrate treatment but the fibrate dose must be carefully adjusted to the renal function, as renal elimination is a major pathway in the clearance of fibrates.

**Hepatic disease**

**Cholestasis**

Patients with cholestatic liver disease often have severe hypercholesterolaemia, and total cholesterol levels of 15 mmol/L or more are not unusual. The high total cholesterol is due to the accumulation of an abnormal lipoprotein called lipoprotein X. Lipoprotein X forms spontaneously in the circulation of patients with biliary stasis or lecithin cholesterol acyltransferase (LCAT) deficiency. Lipoprotein X does not have a structural apolipoprotein (such as apolipoprotein B in VLDL or LDL) and has an aqueous core. The major components of lipoprotein X are phospholipids and unesterified cholesterol. Lipoprotein X frequently causes pale white cutaneous xanthomata (the aqueous core of lipoprotein X does not contain carotene) and may also cause pseudohyponatraemia and a neuropathy. The definite identification of lipoprotein X requires specialised laboratory techniques, but the clinical scenario of severe hypercholesterolaemia in patients with cholestasis is highly suggestive. Low apolipoprotein B relative to the total cholesterol may also be a clue to the presence of lipoprotein X.

Lipoprotein X has antioxidant properties and may reduce the atherogenicity of LDL by preventing oxidative damage. Limited clinical data suggest that patients with chronically high levels of lipoprotein X do not have excess atherosclerotic risk. However, these data cannot be regarded as conclusive, since the liver disease responsible for the accumulation of lipoprotein X often limits the lifespan of patients and atherosclerosis may thus not become clinically manifest. Lipoprotein X is cleared mainly via the reticuloendothelial system and statins are not effective in reducing lipoprotein X. Lipoprotein X levels fall rapidly once the biliary obstruction has been relieved.
Acute intermittent porphyria

Total cholesterol and LDLC are elevated in some patients with acute intermittent porphyria. High HDLC is also a relatively frequent finding. Symptomatic patients usually have more severe hypercholesterolaemia, but elevated lipids have also been found in asymptomatic patients. The mechanisms leading to hyperlipidaemia in acute intermittent porphyria are not perfectly understood, but porphyrogenic chemicals have been shown to increase hepatic sterol synthesis and low hepatic lipase activity may account for the HDLC elevation.

Miscellaneous disorders

Anorexia nervosa

The reported frequency of hypercholesterolaemia in anorexia nervosa is highly variable, ranging from about 20% to as high as 70%. The most common lipid abnormality is high LDLC, although HDLC elevation has been described as well. The hypercholesterolaemia of anorexia nervosa is somewhat paradoxical, as malnutrition is usually associated with hypolipidaemia and anorexic patients obsessively avoid consuming triglycerides and cholesterol. Refeeding anorexic patients lowers lipid levels, although patients gain weight and consume more fat. The mechanisms leading to hypercholesterolaemia in anorexia nervosa are not well understood. Some potential explanations include a general reduction in protein catabolism, including LDL removal, functional hypothyroidism and increased lipolysis.

Bulimia is also associated with hypercholesterolaemia and possibly mild hypertriglyceridaemia. The lipid changes are often not as marked as in anorexia nervosa, where nutrient intake is more restricted.

Systemic lupus erythematosus

Premature atherosclerosis is a characteristic feature of systemic lupus erythematosus (SLE) and contributes substantially to premature mortality. The most common lipid phenotype is high HDLC, although HDLC elevation has been described as well. The hypercholesterolaemia of anorexia nervosa is somewhat paradoxical, as malnutrition is usually associated with hypolipidaemia and anorexic patients obsessively avoid consuming triglycerides and cholesterol. Refeeding anorexic patients lowers lipid levels, although patients gain weight and consume more fat. The mechanisms leading to hypercholesterolaemia in anorexia nervosa are not well understood. Some potential explanations include a general reduction in protein catabolism, including LDL removal, functional hypothyroidism and increased lipolysis.

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HIV infection

Human immunodeficiency virus (HIV) infection may be associated with dyslipidaemia, usually mild hypertriglyceridaemia with a low HDLC. The total cholesterol and LDLC may also be decreased. More advanced immunosuppression is associated with increasing severity of dyslipidaemia. Antiretroviral therapy may also provoke dyslipidaemia.

Pregnancy

Pregnancy is associated with profound alterations in physiology and metabolism. Lipid metabolism is not exempt from these changes, and pregnancy is associated with increases in both LDLC and triglycerides. Most of the increase in lipid levels is observed by the second trimester. Lipid increases usually do not exceed the 95th centile and are of no clinical consequence in most women. Occasionally severe hyperlipidaemia may develop in genetically predisposed women. Of most concern is the development of severe hypertriglyceridaemia, as this may provoke acute pancreatitis. Pancreatitis in pregnant patients often has a poor outcome and foetal loss is not infrequent. Hypertriglyceridaemic patients should be counselled about the risks of pregnancy and pregnancy should only be considered after evaluation by a lipid specialist, followed by tight monitoring of lipids during pregnancy.

Statins are frequently prescribed to young female patients with familial hypercholesterolaemia. The safety of statins during pregnancy has not been adequately established, and they are contraindicated during pregnancy. Patients should be counselled on adequate contraception and discontinue statins prior to stopping contraception if they plan to fall pregnant. Statins can be resumed once the infant has been weaned.

Lifestyle

Diet and obesity

There is large variability in population average lipid levels between various countries, reflecting at least in part different dietary habits. Population average cholesterol has risen in many countries, as the diet has become more westernised and the consumption of animal products has increased. The effect of diet in the individual is more difficult to predict, as individual lipid responses to dietary changes are fairly variable and, to a large degree, genetically determined. However, dietary modification has many benefits that go beyond changes in serum lipids and should therefore be encouraged and maintained in all patients, even if the achieved reduction in serum lipids “disappears” the patient.

Alcohol

In epidemiological studies, moderate alcohol intake is associated with reduced cardiovascular mortality.
This effect is partially mediated by the modest increase in HDLC associated with alcohol consumption.\textsuperscript{70} Excess alcohol intake may have deleterious lipid effects and the most common problem is severe hypertriglyceridaemia.\textsuperscript{71} Unfortunately alcohol intake is not always declared honestly and ancillary clues such as a high mean corpuscular volume and a high aspartate aminotransferase relative to the alanine aminotransferase may be helpful. Cessation or reduction of alcohol intake often improves the dyslipidaemia.

Smoking
One of the many deleterious effects of smoking is a modest reduction in HDLC levels. In a recently published randomised study, smoking cessation was associated with a mean increase of 0.06 mmol/L in HDLC, despite a 4.6 kg weight gain. HDLC increased most in women and the effect size was not linked to the baseline smoking intensity.\textsuperscript{72}

Drugs
There are many drugs that can have a deleterious effect on lipid metabolism. This article will only discuss selected drugs that are relatively frequently associated with dyslipidaemia.

Retinoids
Retinoids are frequently prescribed for the treatment of acne and other dermatological disorders and are also important in the treatment of some forms of leukaemia. Retinoids bind to the nuclear hormone receptor retinoid X receptor and increase the transcription of apolipoprotein C-III, which inhibits the action of lipoprotein lipase.\textsuperscript{73} Hypertriglyceridaemia is a well-described complication of retinoid therapy, and cases of acute pancreatitis have been described.\textsuperscript{74,75} Baseline lipid assessment with follow-up measurements on therapy are essential. Patients with elevated baseline triglycerides are at particular risk of developing severe hypertriglyceridaemia, and retinoids should only be prescribed if there are no therapeutic alternatives and patients are willing to adhere to a diet very low in fat and a tight monitoring schedule.

Antiretroviral therapy
Antiretroviral therapy (ART) is associated with the lipodystrophy syndrome characterised by fat redistribution, insulin resistance and dyslipidaemia.\textsuperscript{76-79} Two of the major clinical concerns related to ART-induced dyslipidaemia are acute pancreatitis, secondary to severe hypertriglyceridaemia, and increased cardiovascular risk in those with hypercholesterolaemia or mixed hyperlipidaemia. Protease inhibitors, especially ritonavir, are strongly implicated in the development of severe hypertriglyceridaemia.\textsuperscript{79,80} The management of ART-associated dyslipidaemia is guided by the lipid phenotype (predominant hypertriglyceridaemia or hypercholesterolaemia) and clinical circumstances: is acute pancreatitis the primary concern or is there excess cardiovascular risk mandating treatment? Possible treatment strategies include lifestyle modification, changing ART and lipid-lowering medications. Fibrates are generally prescribed for predominant hypertriglyceridaemia, while statins are used in those with predominant hypercholesterolaemia. Protease inhibitors are potent inhibitors of the cytochrome P450 isoenzyme system, which metabolises many drugs, including most statins.\textsuperscript{83,84} Simvastatin should be avoided in patients taking protease inhibitors, as it is particularly affected by this interaction; pravastatin or rosuvastatin would be better choices.

Steroids
The lipid effects of glucocorticoids are similar to those seen in Cushing’s syndrome. Anabolic steroids can reduce HDLC dramatically (up to 50% decrease) and may also raise LDL.\textsuperscript{85,86} Oestrogen raises HDLC in most women but may trigger severe hypertriglyceridaemia in predisposed women.\textsuperscript{87,88} Progesterone may increase LDL and decrease HDLC slightly, but some of the newer progestogenic compounds are neutral with regard to the lipid profile.

Anti-hypertensive therapy
Thiazide diuretics may increase triglycerides and LDL, with a concomitant reduction in HDLC. The negative metabolic effects of thiazides tend to occur at doses that are not commonly prescribed anymore. Beta blockers may also cause mild hypertriglyceridaemia, but this is also not a major problem in routine clinical practice.\textsuperscript{89,90} Both these drug classes have shown mortality reductions if prescribed in the correct clinical setting, and concerns about possible dyslipidaemia associated with their use should not prevent their prescription where appropriate.

Immunosuppressive therapy
Hyperlipidaemia is a common clinical problem in transplant recipients and immunosuppressive therapy is an important contributing factor. Cyclosporin, sirolimus and prednisone are the agents most frequently implicated in the genesis of hyperlipidaemia. Cyclosporin use is usually associated with LDL hypercholesterolaemia, but low HDLC has also been reported and is thought to be due to direct inhibition of apolipoprotein A1 gene expression.\textsuperscript{91,92} There is a high risk of drug-drug interactions when cyclosporin and statins are co-prescribed, and such patients should be managed at a specialist level. Sirolimus commonly induces hypertriglyceridaemia, which may be difficult to control.\textsuperscript{93,94}

Antipsychotics
Second-generation antipsychotic drugs, such as quetiapine or olanzapine, may cause weight gain, dyslipidaemia, hypertension and diabetes mellitus.\textsuperscript{95-97} These negative metabolic effects are important, as baseline cardiovascular risk is often high in patients with psychiatric disorders, because of high smoking rates and frequent sedentary lifestyles. It is advisable to assess and monitor cardiovascular risk factors in patients receiving antipsychotics.
Conclusion
Secondary factors may contribute significantly to dyslipidaemia in some patients. The presence of secondary factors may be obvious, as in the deeply jaundiced patient with cholestasis, or subtle and easily missed, as in the patient with recent-onset hypothyroidism. Awareness and identification of secondary factors may allow one to avoid unnecessary lipid-lowering treatment if the underlying problem, such as hypothyroidism, can be corrected.

One should not reflexively prescribe lipid-lowering drugs to hyperlipidaemic patients before attempting to answer the following questions: Why is this patient hyperlipidaemic? Is this a genetic disorder, such as familial hypercholesterolaemia, and other family members are at risk, or are there modifiable secondary factors that need correction before life-long treatment is started?

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