Secondary dyslipidaemia

FRANS MARITZ
MB ChB, MMed (Int), FCP (SA), PhD

Head
Internal Medicine Karl Bremer Hospital Bellville

Senior Lecturer
Endocrine Unit Department of Internal Medicine Tygerberg Hospital and University of Stellenbosch Tygerberg

Frans Maritz was a specialist in general medicine at Tygerberg Hospital, University of Stellenbosch, but now heads Internal Medicine at Karl Bremer Hospital where he manages the Cardiovascular Risk and Lipid Clinic. His special interest is lipidology, in particular the insulin resistance syndrome and the non-lipid effects of statins.

Disorders associated with secondary dyslipidaemia are some of the commonest causes of morbidity and mortality in the South African population. This article outlines the causes and management of these disorders.

Dyslipidaemia predisposes to atherosclerosis, and where hypertriglyceridaemia is severe, also to pancreatitis. Although most cases of dyslipidaemia have a primary genetic pathogenesis, a significant proportion of patients have a secondary cause that can be modified (Table I). In many populations secondary causes, in particular the insulin resistance (IR) syndrome (e.g. metabolic syndrome, syndrome X), play a dominant role in causing dyslipidaemia and in the genesis of coronary artery disease (CAD). Secondary causes of dyslipidaemia should always be considered and may be important for several reasons:

- they uncover other underlying diseases that require specific treatment
- they may explain why a previously treatable dyslipidaemia has become resistant to treatment
- they may point to an alternative and possibly a safer treatment.

Although most cases of dyslipidaemia have a primary genetic pathogenesis, a significant proportion of patients have a secondary cause that can be modified.

In most cases of dyslipidaemia, a modifiable secondary factor will be found. Even where the treatment of the contributory secondary cause results only in a small change in the lipogram, the aggressive management of the modifiable secondary cause is justifiable and cost-effective, as this may forestall costly increases in lipid-lowering medication.

The secondary causes may conveniently be remembered by the mnemonic of 5 ds (Table I):

- **d**iet
- **d**iabetes
- other **d**isorders of metabolism
- **d**rugs
- **d**iseases (non-metabolic).

Pharmacogenetic studies, including those on the effect of genes on diet and environmental factors, indicate that genes play a role in determining how lipid profiles react to the environment. This also applies to how a person reacts when exposed to one of the secondary causes of dyslipidaemia, and explains why only a percentage of those exposed to a secondary cause will develop dyslipidaemia. This additional genetic influence is often responsible for some perturbation in the metabolism of lipoprotein particles, most often the triglyceride (TG)-rich particles. Under normal metabolic conditions these patients may be entirely normal, but when exposed to one of the secondary causes this 'excessive metabolic load' precipitates an ever-worsening cycle of impairment in lipoprotein metabolism. This may result in extremely high lipid (in particular TG) levels or a chylomicronaemia syndrome, which can in turn precipitate an attack of pancreatitis. It is worth emphasising that the majority of patients with an extremely high total cholesterol (TC) level (> 15 mmol/l) very seldom have increased low-density lipoprotein cholesterol (LDL-C) levels such as those with familial hyper-

cholesterolaemia. Usually these patients have very high TG levels, almost invariably precipitated by a secondary cause of which poorly controlled diabetes mellitus is the commonest.

The management of secondary dyslipidaemia should not focus on the lipid profile of the patient.The patient should be treated as a whole — including all the other co-existent non-lipid risk factors. After dealing with the secondary cause, a risk assessment must be made by taking all the risk factors into account.The lipid profile must be judged and managed by the company it keeps — a person with an isolated hypercholesterolaemia and no other risk factors may not require pharmacological treatment, whereas a person with a lower cholesterol level may need aggressive therapy because of massive cumulative risk.

SECONDARY CAUSES OF DYSLIPIDAEMIA

Secondary causes of dyslipidaemia tend to produce characteristic changes that may aid in finding the cause (Table II).

Diet

One should question the patient regarding dietary saturated fat and cholesterol intake, as these can raise the LDL-C level. Similarly, the patient should be questioned about alcohol and carbohydrate intake, as well as recent weight gain, as these can increase the plasma TG level.Where the doctor's time is at a premium, a referral to a capable dietician is well worth while.

One should remember that some eating disorders such as anorexia nervosa may present with dyslipidaemia, in which case, paradoxically, an increase in the caloric intake may be indicated.

Table I. Causes of secondary dyslipidaemia

Diet
- Excess of saturated fats
- Caloric excess
- Weight gain
- Alcohol
- Anorexia nervosa

Diabetes
- Poorly controlled type 1 diabetes
- Type 2 diabetes

Other disorders of metabolism
- Hypothyroidism
- Pregnancy
- Obesity

Drugs

Cardiovascular drugs
- Thiazide diuretics
- Beta-adrenergic blockers
- Amiodarone

Endocrine drugs
- Anabolic steroids
- Glucocorticoids
- Oestrogens

Other drugs
- Retinoids
- Cyclosporine
- Antiretroviral therapy

Diseases (non-metabolic)
- Biliary obstruction
- Chronic renal disease
- Systemic lupus erythematosus
- Nephrotic syndrome

Diabetes

Type 1 diabetes

The lipogram of patients with well-controlled type 1 diabetes frequently reflects the lipid profiles of the general population, i.e. these patients also inherit the other sets of genes that determine the lipid profiles of the general population. However, where the diabetes is poorly controlled, additional dyslipidaemia may result, usually in the form of increased TG and low high-density lipoprotein cholesterol (HDL-C) levels. While these changes are generally modest, occasionally the severely raised TG level of a chylomicronaemia syndrome is observed and pancreatitis may develop.

Insulin resistance and type 2 diabetes

A large proportion of the population has IR as part of the IR syndrome (e.g. metabolic syndrome, syndrome X).There is a strong correlation between IR and all the markers of atherosclerosis, and IR is a strong predictor for the future development of CAD. It is not surprising that in some populations of South Africa IR is the commonest phenotype seen in patients presenting with acute coronary syndrome (ACS).

As IR progresses, the body is able to compensate by secreting more insulin to maintain normoglycaemia. Hyperinsulinaemia may have adverse effects and many years may pass before failure of the

Table II. Lipid profile of secondary causes of dyslipidaemia

Secondary cause	High cholesterol (high LDL-C)	TG excess mild to moderate (high VLDL)	Low HDL-C	Severe TG excess: chylomicronaemia syndrome
Diet	Saturated fats, caloric excess, anorexia	Weight gain, alcohol	Low-fat diet	Alcohol and fat with genetic lipid disorder
Drugs	Diuretics, glucocorticoids, cyclosporin	Retinoids, beta-blockers, oestrogens, glucocorticoids	Anabolic steroids, progestins, beta-blockers, cigarettes	Glucocorticoids, oestrogen, genetic lipid disorder
Disorders of metabolism	Diabetes poorly controlled, hypothyroidism, pregnancy	Type 2 diabetes, obesity, pregnancy	Type 2 diabetes, obesity	Diabetes poorly controlled, hypothyroidism with genetic lipid disorder
Diseases	Nephrotic syndrome, biliary obstruction	Chronic renal failure with/ without dialysis, nephrotic syndrome	Chronic renal failure with/ without dialysis	SLE (rare)

LDL-C = low-density lipoprotein cholesterol; TG = triglyceride; VLDL = very low-density lipoprotein; HDL-C = high-density lipoprotein cholesterol; SLE = systemic lupus erythematosus.

pancreatic beta-cells supervenes. Only then will glucose levels rise, with the development of impaired glucose tolerance and type 2 diabetes. Type 2 diabetes may conveniently be seen as the end result of another disease present for a long time, namely IR. In the 'pre-diabetic' phase of the IR syndrome these patients have the same risk factors as type 2 diabetics, including dyslipidaemia, and are equally prone to develop macrovascular disease. Indeed, many of these 'pre-diabetic' IR patients die of their macrovascular disease before ever developing impaired glucose tolerance and diabetes. By the time type 2 diabetes is diagnosed, the damage has already been done and macrovascular disease and CAD are established. Remember that type 2 diabetics without clinical CAD have as high a probability of experiencing an adverse cardiac event as a non-diabetic who already has clinical CAD. Accordingly, type 2 diabetic patients, taking their lipogram into consideration, should be managed as for secondary prevention. It is tragic that these 'pre-diabetic' IR patients, who are so prone to develop CAD, are more often than not viewed as being 'healthy' and do not receive the attention and risk factor modification they require!

The abnormalities of the lipid profile seen in type 2 diabetics can resemble those of IR.The dyslipidaemia resulting from IR (and type 2 diabetes) is often subtle, with seemingly minor changes, and it is therefore not surprising that this atherogenic lipid phenotype is often poorly managed.

The dyslipidaemia of this IR is manifested by the following:

- Raised TG levels. The TG level is usually only slightly raised (< 3 mmol/l), but at times a chylomicronaemia syndrome with massively raised TG levels may develop in genetically susceptible individuals.
- Decreased HDL-C levels. The HDL-C level is very often at, or just below, the lower limit of normal.This usually accompanies the raised TG level, and the high TG/low HDL syndrome is often missed.
- Post-prandial lipaemia. After a fatty meal the TG level rises higher and stays raised longer than normal.The post-prandial hypertriglyceridaemia affects cholesterol ester exchange with LDL, and subsequent modulation of TG-rich LDL by HDL yields small LDL species.This has still not been standardised for clinical investigative use.
- Small dense LDL particles. These patients invariably have 'small dense LDL' particles, a family of LDL particles that are cholesterol-enriched, very prone to oxidisation and accordingly extremely atherogenic.
- Hyper-ApoB. Because of the small dense LDL particles, the

number of LDL particles per unit volume is increased. Bearing in mind that LDL particles contain only one ApoB molecule per lipoprotein particle, IR patients may manifest with increased ApoB levels or hyper-ApoB. The ApoB/LDL-C ratio may be increased, which is a reasonably good marker for IR but is not yet accepted for general use. Similarly, the measurement of LDL size is difficult and not cost-effective.

- IR patients inherit a set of genes determining their IR and also their characteristic lipid profile. However, as in type 1 diabetes, these patients also inherit a totally different cluster of genes that determine the lipid profiles in the rest of the population. These genes may simultaneously but independently raise the LDL-C level, which must be managed in its own right.

The IR syndrome is accompanied by the following other components of a cardiovascular risk factor cluster that must be managed as well:

- Hypertension.
- Central obesity. This is part of the disease and not very easy to get rid of.
- Impaired glucose tolerance or overt type 2 diabetes.
- Increased fibrinogen. This decreases with fibrate treatment. It is uncertain whether it translates into a reduction of cardiovascular mortality.
- Increased plasminogen activator type 1 (PAI-1). This impaired endogenous thrombolysis is almost invariably present. Advice as to its modification is uncertain.

The treatment of these IR patients is as follows:

- **Lifestyle modification.** These patients eat well because they live well. Lifestyle modification has been shown to be extremely cost-effective and pays tremendous dividends with regard to reductions in cardiovascular mortality.
- **Dietary advice,** incorporating caloric restriction for weight loss and low fat intake, can be very effective but requires proper motivation of the patient. A sympathetic dietician can be of great value.
- **Lipid-modifying drugs** . Statins predominantly decrease LDL-C levels and have lesser effects on TG and HDL-C levels, whereas fibrates have a major effect on lowering TG and raising HDL-C levels but little effect on LDL-C levels. Despite this it is still advised that treatment be started with a statin, as these drugs have additional non-lipid-lowering effects on the vessel wall, which are beneficial. Where TG levels are markedly raised (> 5 mmol/l) treatment may be started with a fibrate or a fibrate may be added to a statin to improve the TG level further and raise the HDL-C level.

Drugs should always be considered as contributory to a dyslipidaemia.

Other disorders of metabolism

Hypothyroidism may present via an increased TC and LDL-C level, which can be normalised with thyroid replacement therapy. Occasionally hypothyroidism precipitates dysbetalipoproteinaemia or hypertriglyceridaemia. Some lipid clinics see a selected group of patients in whom the incidence of hypothyroidism is high. However, the incidence of hypothyroidism in general practice is low enough to question the cost-effectiveness of performing routine thyroid function tests. Certainly, thyroid function tests should be borne in mind where the pre-test probability of hypothyroidism is high.

In **pregnanc y** lipid levels continue to rise with each trimester, but this is most dramatic during the second trimester. Pregnancy may unmask an underlying genetic defect that can give rise to severe hypertriglyceridaemia and pancreatitis. This can usually be controlled by diet and the lipid profile usually normalises postpartum.

Obesity is often associated with abnormal lipograms, but many severely obese patients do not have dyslipidaemia. However, patients with central obesity and increased hip/waist ratios are prone to dyslipidaemia. These patients are part of the IR syndrome discussed above and should be treated aggressively.

Drugs

Drugs should always be considered as contributory to a dyslipidaemia.

Cardiovascular drugs

Thiazide diuretics affect the lipid profile in a dose-dependent fashion. Low-dose (12.5 mg/day) hydrochlorothiazide is metabolically safe. Beta-blockers also affect the lipid profile of patients, but this adverse effect is not universal. These agents have a profound beneficial effect on cardiovascular mortality and careful consideration should be given before withholding these drugs, even in diabetics! Amiodarone may cause dyslipidaemia directly, but also by causing hypothyroidism.

Endocrine drugs

Anabolic steroids profoundly lower HDL-C levels soon after use. Glucocorticoids have a potent effect on the lipid profile, which is aggravated by secondary weight

gain and glucose intolerance. In susceptible persons alpha-oestrogens can cause dramatic increases in TG levels. Transdermal administration may have less input on plasma lipids.

Other drugs

Retinoids used for acne can have profound effects on the lipid profile, especially on TG levels. One should check for dyslipidaemia before and during treatment. The lipogram normalises promptly after discontinuation of treatment. Cyclosporin can contribute to dyslipidaemia observed after transplantation, and may be aggravated by the associated administration of steroids and by weight gain. Importantly, it can also interact with some statins, the dosage of which must be adjusted in this situation.Antiretroviral therapy is being used increasingly. The protease inhibitors can cause a secondary lipodystrophy and dyslipidaemia associated with severe increases in TC and TG levels.

Non-metabolic diseases

Liver disease

Cholestasis can be associated with severe increases in TC levels, which are partially comprised of lipoprotein-X. Impaired liver function may be associated with impaired production of lipoproteins and this should be considered if treatment results appear to be too good to be true.

Renal disease

Chronic renal failure can be linked to dyslipidaemia and may be aggravated by dialysis. Raised TC levels are a common feature of the nephrotic syndrome.

Only rarely does systemic lupus erythematosus (SLE) cause dyslipidaemia via the production enzyme inhibitors that impair lipoprotein metabolism.

TREATMENT OF SECONDARY DYSLIPIDAEMIAS

The management of secondary dyslipidaemia should follow the general principles listed below:

- Discontinue the suspected drug and substitute with a lipid-neutral drug.
- Treat the underlying disorder.
- Apply the appropriate dietary fat restriction.
- Lipid-modifying agents. With severely raised TG levels, fibrates may be needed as an adjunct to the above.Where the LDL-C level does not normalise with the conservative approach, statins may be used.

CONCLUSION

Secondary and contributory causes of dyslipidaemia should always be considered. Patients have much to gain, both health wise and wealth wise, from recognition and appropriate management of these causes.

IN A NUTSHELL

In many populations secondary causes play a dominant role in causing dyslipidaemia and in the genesis of coronary artery disease (CAD).

Genes also play an important role in secondary dyslipidaemia.

Extremely raised total cholesterol levels (> 15 mmol/l) are usually a manifestation of a severe hypertriglyceridaemia.

Poorly controlled diabetes is the commonest secondary cause of massively raised triglyceride levels.

Insulin resistance correlates strongly with the development of macrovascular disease.

In some populations the insulin resistance syndrome is the commonest phenotype seen in patients with acute coronary syndromes.

Type 2 diabetes may conveniently be regarded as the end result of another disease that has been present for a long time, namely insulin resistance.

'Pre-diabetic' insulin-resistant patients should be managed aggressively to prevent the progression of macrovascular disease.

FURTHER READING

Colagiuri S, Best J. Lipid-lowering therapy in people with type 2 diabetes. *Curr Opin Lipidol* 2002; **13:** 617-623.

Components of the 'metabolic syndrome' and incidence of type 2 diabetes — **http://www.medscape.com/viewarticle/442152**

Grundy SM. Approach to lipoprotein management in 2001. National Cholesterol Guidelines. *Am J Cardiol*. 2002; **90:** 11i-21i.

Pathogenesis and epidemiology of metabolic abnormalities — **http://www.medscape.com/viewarticle/441490 (accessed 10 January 2003).**

The obesity epidemic: prevention and treatment of the metabolic syndrome — **http://www.medscape.com/viewprogram/2015 (accessed to January 2003).**

Update on the management of dyslipidemia — **http://www.medscape.com/viewarticle/442031 (accessed to January 2003).**