Secondary dyslipidaemia

There are frequently secondary causes of dyslipidaemias, often reversible.

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While many of the dyslipidaemias have a familial or genetic basis, there is no denying that secondary causes often coexist. These causes may aggravate or even cause the dyslipidaemia. As they are potentially reversible with treatment, it is important to identify the underlying secondary causes in all patients presenting with dyslipidaemia (Table I).

Lifestyle

Diet is regarded as the major reason for the enormous variation in cholesterol levels worldwide. The role of a capable dietician cannot be overemphasised, particularly as proper dietary analysis is not prioritised during medical training. Populations with a high intake of saturated fats and cholesterol tend to have higher serum cholesterol and low-density lipoprotein cholesterol (LDLC) levels. Hypertriglyceridaemia is often seen in patients with high caloric intake, rapid weight gain and obesity. Interestingly, it is also seen in up to one-third of women suffering from anorexia nervosa or bulimia. The reason is unknown, but decreased catabolism coupled with diminished bile salts turnover has been postulated.

Table I. Commoner causes of secondary dyslipidaemia

- **Drugs**
  - Amiodarone
  - Anabolic steroids
  - Antiretrovirals (especially protease inhibitors)
  - Beta blockers
  - Glucocorticoids
  - Immunosuppressants, e.g. cyclosporine
  - Retinoids
  - Sex steroids (androgens, oestrogens)
  - Thiazides
- **Endocrinopathies**
  - Acromegaly
  - Cushing's syndrome
  - Diabetes mellitus
  - Metabolic syndrome and obesity
  - Hypothyroidism
- **Gastrointestinal and hepatic disease**
  - Acute intermittent porphyria
  - Cholestatic liver disease
  - Intestinal malabsorption
- **Lifestyle**
  - Anorexia nervosa, bulimia
  - Cigarette smoking
  - Diet
  - Excessive alcohol consumption
  - Stress
- **Miscellaneous**
  - HIV infection
  - Pregnancy
  - Systemic lupus erythematosus
- **Renal disease**
  - Nephrotic syndrome
  - Chronic renal failure

Physical stress. It is unknown why serum cholesterol levels decrease during physical stress. The decrease may be due to the diminished uptake and synthesis of cholesterol. There is an increase in triglyceride levels that may persist for several weeks once the patient has recovered fully. The effects of mental stress on lipid levels are unknown. It is important to note that serum lipid levels may be misleading if checked within a 3-month period of any major illness or surgery.

Cigarette smoking is associated with a modest drop in serum high-density lipoprotein cholesterol (HDLC) levels and may be a contributory factor in the development of insulin resistance (IR). The effects of smoking appear more prominent if adjusted for alcohol. These changes are reversible and benefits are seen within 2 months of cessation of smoking.

Alcohol is widely recognised as one of the commoner causes of dyslipidaemia, predominantly hypertriglyceridaemia. One should not forget that beer and wine may be major components of diet and may also contribute to obesity and weight gain. Normally fatty acids are the main substrate in the postprandial state. However, alcohol is oxidised in preference to all other substrates. There is very little direction for the postprandial surge in fatty acid flux apart from triglyceride synthesis. Although alcohol is the major aetiological agent in pancreatitis, up to 10% of cases can be attributed to hypertriglyceridaemia. The effect of moderate regular uptake of alcohol (10 g ethanol=300 ml beer or 1½ glasses of wine daily) is to raise the HDLC levels by 0.03 - 0.05 mmol/l. While some patients are remarkably honest about their alcohol consumption, this is not always the case. Clues to the abuse of alcohol are an elevated gamma-glutamyl transferase (γGT) level, a raised mean corpuscular volume (MCV), a low serum urea and a 'flipped' aspartate aminotransferase:alanine aminotransferase (AST:ALT) ratio. If alcohol has been a major contributor to dyslipidaemia, the patient should be advised to refrain from alcohol intake for 4 - 6 weeks, after which a fasting lipogram should be done.

Endocrinopathies

Obesity. With the move to a western lifestyle, South Africa has seen an upsurge in the prevalence of obesity. While the causes may

be multifactorial, there is no denying the deleterious changes in lipid metabolism, e.g. high serum concentrations of cholesterol, LDLC and triglycerides, with a decrease in HDLC.

The metabolic syndrome is characterised by the variable coexistence of hyperinsulinaemia (with resultant IR and type 2 diabetes mellitus), obesity, dyslipidaemia, and hypertension. The pathogenesis of the metabolic syndrome is mainly obesity and a sedentary lifestyle coupled with a calorie-rich diet, but still largely unknown genetic factors clearly interact, leading to the syndrome. Dyslipidaemia, coupled with IR, appears to be the hallmark of the metabolic syndrome. The ensuing hyperinsulinaemia is associated with increased serum free fatty acid levels, raised triglycerides, moderately raised LDLC, and decreased HDLC. The severity of the dyslipidaemia is associated with the degree of IR.

Type 1 diabetes mellitus. The lipogram in a well-controlled type 1 diabetic is similar to that in the general population. With poor control one sees an increase in triglyceride concentrations and a decrease in HDLC levels, which may be reversed with improvement in diabetes control.

Type 2 diabetes mellitus is reaching epidemic proportions in both the developing and developed world. With the increase in obesity, the situation can only worsen. Type 2 diabetes is by no means a benign disease. It is currently the leading cause of end-stage renal disease, non-traumatic lower-extremity amputations and blindness in adults. There is also a two-fold increase in cerebrovascular accidents and up to three-quarters of type 2 diabetics have, or will develop, co-morbid cardiovascular disease. The cost of prevention and treatment of both micro- and macrovascular complications is astronomical. The dyslipidaemia tends to mimic that seen in IR, with hypertriglyceridaemia and low HDLC levels. Greater IR is associated with an increase in LDLC particles that are smaller, dense and more atherogenic.

The treatment of dyslipidaemia associated with obesity, the metabolic syndrome and diabetes should be aggressive owing to the increase in cardiovascular risk and mortality. A diet low in saturated fat, cholesterol, refined carbohydrate and simple sugars should be coupled with physical activity (a minimum of 30 - 40 minutes 5 times weekly). The importance of weight loss (by means of exercise and caloric restriction) and stress management should be emphasised. One should not forget the need for pharmacotherapy if appropriate (statins and, where necessary, fibrates).

Hypothyroidism is commonly associated with an increase in serum cholesterol concentrations due to increased LDLC levels. The high levels of LDLC are due to a decrease in receptor-mediated LDLC catabolism. Less consistently, there is an increase in triglyceride levels due to a decrease in triglyceride clearance mediated by low lipoprotein lipase activity. Recent research has shown an increase in the HDLC concentrations, the major component being an increase in the HDL_2C subfraction. Because of the subtle clinical presentation of hypothyroidism, most centres recommend thyroid function testing in all patients with unexplained or poorly explained dyslipidaemia. In patients with true hypothyroidism, there is a dramatic decrease in cholesterol and triglyceride levels once thyroxine has been administered. This reduction can however take several months.

Gastrointestinal and hepatic disease

Crohn's and coeliac disease. Intestinal malabsorption as seen in conditions such as Crohn's and coeliac disease tends to cause a decrease in serum cholesterol levels. This is primarily owing to the malabsorption of cholesterol and bile salts. Serum triglyceride levels are frequently normal and HDLC levels may be low.

Cholestatic liver disease (e.g. primary biliary cirrhosis) may be accompanied by hypercholesterolaemia caused by the accumulation of an abnormal lipoprotein, i.e. lipoprotein X. Lipoprotein X is degraded by the reticulo-endothelial system and is virtually devoid of triglycerides. Clinical findings include peripheral and palmar xanthomata, and possibly xanthomatous peripheral neuropathy. Lipoprotein X levels return to normal once the biliary obstruction has been relieved. Where biliary obstruction cannot be relieved (e.g. in primary biliary cirrhosis) treatment becomes problematic. Diet may be helpful, while fibrates may have a paradoxical effect on the cholesterol level. The use of statins carries a small risk of accumulation and toxicity.

Acute intermittent porphyria. In one-third of patients suffering from acute intermittent porphyria there is an associated increase in total cholesterol and LDLC levels. The underlying mechanisms for these changes are unknown. As a general principle, pharmacotherapy should be used with caution.

Renal disease

Nephrotic syndrome. One of the characteristics of the nephrotic syndrome is the associated increase in cholesterol level – predominantly due to the increase in LDLC. There may be an increase in triglyceride levels and a decrease in HDLC. The mechanism behind the dyslipidaemia associated with the nephrotic syndrome is poorly understood, but a directly proportional relationship has been established between the rise in lipid levels and the degree of proteinuria. Dyslipidaemia may also be seen in patients with a minimal decrease in serum albumin.

Chronic renal failure *per se* has been linked to dyslipidaemia. There is an increase in triglyceride levels with little or no effect on cholesterol concentrations, while HDLC concentrations tend to fall. The effect is partly due to the decreased activity of lipoprotein lipase. The dyslipidaemia becomes more profound with the progression of renal insufficiency and usually appears when the estimated glomerular filtration rate is approximately 50 ml/min. In haemodialysis heparin is routinely used, depleting lipoprotein lipase, which may further exacerbate the problem. Peritoneal dialysis may result in carbohydrate-induced hypertriglyceridaemia. After renal transplantation many of the abnormalities in the lipid profile may return to normal, provided that good renal function has been established. In 25% of patients the dyslipidaemia may however persist.

Dyslipidaemia in patients with chronic kidney disease should be actively treated owing to the significant contribution of dyslipidaemia to the development of cardiovascular disease. There is no just reason for withholding statin therapy. Fibrates should be used carefully as they are primarily renally excreted. The safe administration of ezetimibe in patients with renal insufficiency is currently being evaluated.

Miscellaneous

During pregnancy altered metabolism causes many changes to the normal physiology. A significant increase is seen in cholesterol levels, especially during the second trimester, while triglycerides tend to peak in the third trimester. However, it is not uncommon to see increased levels as each trimester progresses. One should be aware of a dramatic rise in triglyceride levels, which may precipitate pancreatitis. Dyslipidaemia during pregnancy can usually be controlled by diet. The use of statins is contraindicated owing to the possible increased risk of congenital abnormalities. Lipid levels tend to return to baseline values within 6 weeks of delivery.

Systemic lupus erythematosus (SLE). Recent evidence suggests that dyslipidaemia can also occur in patients with connective tissue disorders such as SLE – partially

owing to the chronic inflammatory state. Immunosuppressive therapy and steroids also play a contributory role. Hypercholesterolaemia may occur in up to 50% of patients. There is a decrease in HDLC levels and an increase in triglyceride levels.

Human immunodeficiency virus (HIV). With the ever-increasing burden of HIV, the physician should be aware that untreated HIV infection tends to increase triglyceride levels and decrease serum cholesterol and HDLC – a response common to most chronic illnesses.

Drugs

With the ever-expanding repertoire of pharmacological agents available to the practitioner, it is virtually impossible to keep track of all side-effects and drug interactions.

Highly active antiretroviral therapy (HAART) for the treatment of HIV has led to the discovery that these drugs may be associated with the development of dyslipidaemia and lipodystrophy. The components of HAART most likely to be responsible are the protease inhibitors, especially ritonavir. Because of the increased use of HAART, it is currently considered to be one of the more common causes of drug-induced dyslipidaemia. Dyslipidaemia associated with HAART is most commonly seen in hypertriglyceridaemia (probably due to an overproduction of very-low-density lipoprotein cholesterol (VLDLC)), followed by an increase in total cholesterol and a decrease in serum HDLC. The management of HIV and HAART-associated dyslipidaemia requires a sensible diet, followed by a modification in HAART therapy and the introduction of pharmacotherapy, i.e. fibrates or statins, if necessary. Liver enzymes should be closely monitored with the use of statins.

Due to a constantly changing lifestyle, chronic conditions such as hypertension and cardiac failure are becoming quite common. **Amiodarone**, a commonly used antiarrhythmic agent, is well described as causing an increase in serum cholesterol concentration owing to an increase in the LDLC level. These changes are independent of any changes in thyroid function. One cannot doubt the benefit of **beta blockers**. Cardioselective and non-cardioselective beta blockers consistently increase the VLDLC level. There is also a decrease in serum HDLC levels with an increase in triglyceride level. The effects of the **thiazide diuretics** are dose dependent, causing an increase in total cholesterol, triglycerides, VLDLC and LDLC levels. There is no evidence to suggest that loop diuretics differ in their effects.

Steroids. The prescription of steroids (anabolic and sex steroids, as well as glucocorticoids) is common practice. Glucocorticoids as a group of drugs have a potent effect on the lipid profile, which is potentiated by secondary weight gain and glucose intolerance, i.e. an increase in LDLC and often in VLDLC. The rise in triglycerides is minimal unless diabetes develops. Prednisolone may increase serum HDLC levels. Anabolic steroids raise serum LDLC levels and cause a marked decrease in HDLC levels. Considerable attention has been devoted to the possible benefits and potential harm of the oral contraceptive pill (OCP) and hormone replacement therapy (HRT). Classically the OCP contains both oestrogen and progesterone which, due to their mineralocorticoid and glucocorticoid properties, tend to raise blood pressure and impair glucose tolerance. Oestrogens cause an increase in VLDLC and HDLC levels, while progesterone causes an increase in LDLC and a decrease in HDLC levels. Menopause, whether natural, after surgery, or premature, causes an increase in the total cholesterol level immediately after ovarian involution. Oestrogens administered after the menopause lower the serum LDLC level and may raise HDLC levels.

Retinoids. While the dermatological effects of retinoids are clearly seen, one has to take cognisance of the dyslipidaemia associated with their use. Increases in triglycerides are seen after the administration of vitamin A and its derivatives. It is recommended that a fasting lipogram be checked before and during treatment. The triglyceride levels promptly return to normal after discontinuation of therapy.

Immunosuppressants. The use of immunosuppressants, e.g. cyclosporine, after transplant may cause an increase in total cholesterol and LDLC levels. Severe hypertriglyceridaemia may occur in patients receiving concomitant steroid therapy. Careful consideration should therefore be given to the treatment of dyslipidaemia in patients receiving immunosuppressive therapy because of potential drug interaction.

In conclusion, the identification and treatment of secondary causes of dyslipidaemia many negate the need for pharmacotherapy, thus saving the patient expense and potential side-effects (expected and unexpected) of these drugs.

Further reading

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In a nutshell

- Secondary causes of dyslipidaemia are numerous and may aggravate or cause the condition.
- Secondary causes are of vital importance to the practitioner owing to them being modifiable, treatable or potentially reversible.
- South Africans are becoming more sedentary and obese, with catastrophic health consequences. In essence we have become a 'hypercholesterolaemic artherogenic' society.
- The treatment of dyslipidaemia associated with obesity, the metabolic syndrome and diabetes should be aggressive owing to the increase in cardiovascular risk and mortality.
- Hypothyroidism is an important secondary cause of dyslipidaemia, but may not be recognised owing to the variable and subtle clinical presentation.
- All patients should be cautioned with regard to cigarette smoking, alcohol intake, stress management and diet.
- Drugs should always be considered as contributory to dyslipidaemia.