An ABC of HDL

a paradigm shift in managing lipid disorders

There has been renewed interest in the protective role of high density lipoprotein (HDL) against atherosclerosis and coronary heart disease (CHD), chiefly owing to new research showing that raising HDL may diminish the risk of clinical cardiovascular events. The burgeoning body of work on HDL is rapidly generating a new paradigm for the management of lipid disorders in clinical practice.

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HDL metabolism: reverse cholesterol transport

The lipoprotein HDL is a macromolecular complex of lipids (cholesterol, triglycerides and phospholipids) and proteins (apolipoproteins [apo] and enzymes). The plasma concentration of HDL-cholesterol is determined chiefly by the production and catabolism of its principal apoproteins, called apo A-I and apo A-II. Importantly, the concentration of cholesterol in HDL is also dependent on an exchange process between HDL and triglyceride-rich lipoproteins (i.e. chylomicrons, chylomicron remnants and very low density lipoproteins [VLDL]). Thus, when plasma triglyceride concentrations are elevated (e.g. hypertriglyceridaemia of obesity and type 2 diabetes) there is an increased exchange of cholesterol for triglycerides and thus a low plasma HDL-cholesterol concentration. This mechanism involves a protein called cholesteryl ester transfer protein (CETP) that in the future may be therapeutically important.

Reverse cholesterol transport is a process that shuttles cholesterol from peripheral tissues back to the liver directly via HDL and other lipoproteins, such as low density lipoprotein (LDL) and VLDL (Figure 1). Reverse cholesterol transport is a physiological pathway for maintaining cholesterol homeostasis in the face of the 0.5 to 1 g of cholesterol generated each day by peripheral tissues. The first step in this process is the movement of cholesterol out of cells via a newly discovered membrane protein, called ATP-binding cassette transporter A1

IN SUMMARY

- **The antiatherogenic effect of HDL is mediated by both enhanced reverse cholesterol transport and direct mechanisms on the arterial wall.**
- **The first approach to raising HDL-cholesterol is to identify the cause of a low level.**
- **Correcting hypertriglyceridaemia usually increases low HDL-cholesterol, but specific elevation in HDL-cholesterol may be needed in some patients.**
- **Lifestyle modifications should aim to improve body weight and insulin resistance in obese subjects.**
- **Drugs are often needed to optimise the lipid profile and elevate HDL-cholesterol.**
- **Patients taking statins will often require adjunctive therapy, such as gemfibrozil, fenofibrate or fish oil, to raise HDL-cholesterol.**
- **In patients with type 2 diabetes or the metabolic syndrome, plasma HDL-cholesterol should be raised above 1.2 mmol/L.**

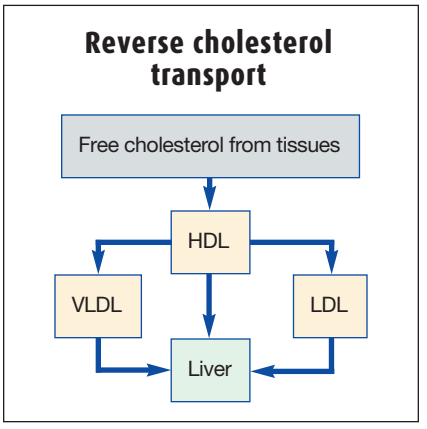

Figure 1. HDL is involved in reverse cholesterol transport, where cholesterol is taken from the tissues and shuttled in the circulation in HDL, VLDL and LDL back to the liver for metabolism and excretion in bile.

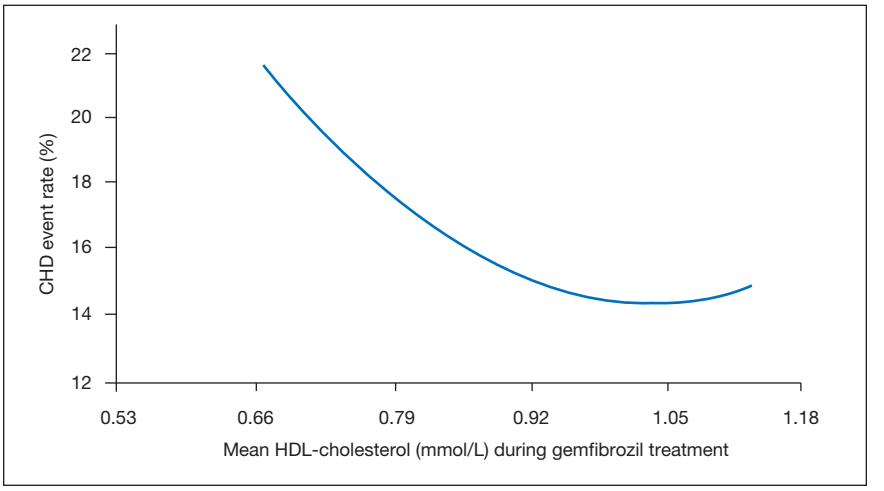

Figure 2. Relation between the reduction in coronary events and elevation in plasma HDL-cholesterol concentration during gemfibrozil treatment in the Veterans Affairs-HDL Intervention Trial (VA-HIT).[2]

(ABCA1). HDL occupies centre stage in reverse cholesterol transport, and this mechanism underscores its effectiveness against accumulation of cholesterol in arteries.

Evidence for a protective effect of HDL-cholesterol

The idea that elevated HDL-cholesterol protects against CHD comes chiefly from epidemiological studies. Collectively, these suggest that on average a 10% increase in plasma HDL-cholesterol independently decreases the CHD risk by 8% in men and 12% in women. Recent clinical trials suggest also a similar benefit from raising plasma HDL-cholesterol levels. An earlier statin trial, the Scandinavian Simvastatin Survival Study (4S), showed that a 1% increase in HDL translates into a 1% decrease in CHD risk.[1] In statin trials, however, the benefits from lowering LDL-cholesterol are, as expected, greater than those from increasing HDL-cholesterol because the effect of these agents on HDL-cholesterol is only modest. Also, patients with low HDL-cholesterol in these trials derive less proportional benefit from statins than do those with high HDL-cholesterol.

In the fibrate trials (e.g. the Veteran Affairs-HDL Intervention Trial [VA-HIT] and Helsinki Heart Study[2,3]), the effects attributable to changes in HDL-cholesterol are more impressive than those in the statin trials, with a 1% increase in HDL-cholesterol translating into a 3% reduction in CHD risk, even in the face of no change in LDL-cholesterol.

Specifically, three clinical trials recently reported on the benefits of lipid-regulating therapy in subjects with normocholesterolaemia and low HDL-cholesterol.

- The VA-HIT results suggest that when LDL-cholesterol levels are optimal, increasing HDL-cholesterol with reduction in triglyceride-rich lipo - proteins may be an efficacious approach for decreasing the incidence of coronary events in secondary prevention.[2] This applies especially to obese patients with insulin resistance (including type 2 diabetes), dyslipidaemia (high triglycerides with low HDL-cholesterol) and/or hypertension (>130/85 mmHg) – i.e. patients with the metabolic syndrome. (A subgroup analysis from the Helsinki Heart Study, a primary prevention trial, showed that the cardiovascular benefit of gemfibrozil was greatest in subjects with obesity, high triglycerides and low HDL-cholesterol.[3]) In VA-HIT, a 0.15 mmol/L increase in plasma HDL-cholesterol was associated with an 11% decrease in CHD (Figure 2), roughly equivalent to that predicted from epidemiological data.
- Subgroup analysis from the Bezafibrate Infarction Prevention (BIP) trial showed that in hypertriglyceridaemic patients with previous myocardial infarction, bezafibrate is an effective treatment for dyslipidaemia when triglyceride levels are greater than 2.2 mmol/L.[4]
- The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) results have implications for primary prevention in the general population for subjects with low HDL-cholesterol in whom increased risk of CHD appears to be diminished with statin therapy.[5] However, the cost-effectiveness of this approach will remain a significant issue.

In these three trials the safety of fibrate and statin therapies in treating patients with low HDL-cholesterol was reaffirmed.

Experimental evidence lends strong

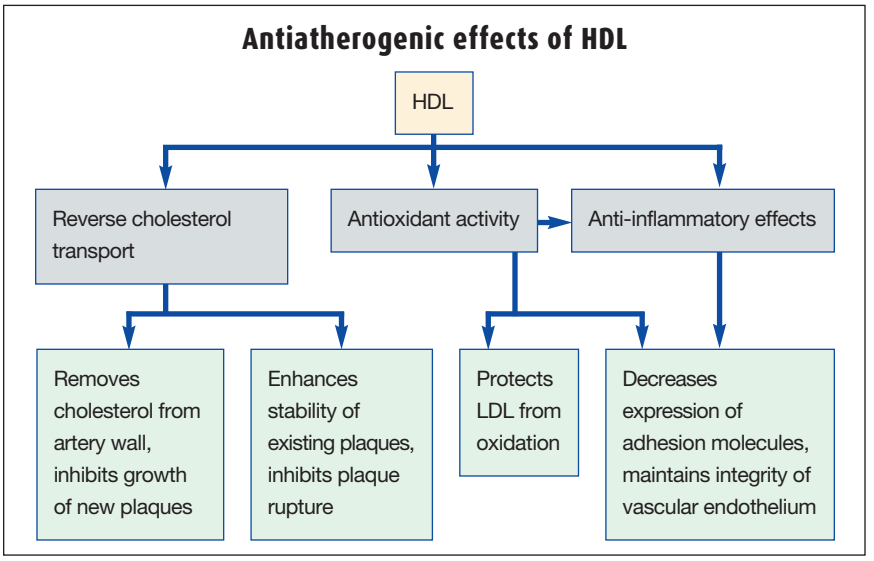

Figure 3. The antiatherogenic effects of HDL are mediated by reverse cholesterol transport and by direct mechanisms on the arterial wall.

Case 1. Low HDL-cholesterol in a man with a family history of CHD

A 47-year-old man whose mother had died of a myocardial infarction when aged 42 years had the following fasting lipid results: total cholesterol, 4.4 mmol/L; triglycerides, 1.8 mmol/L; HDL-cholesterol, 0.6 mmol/L; LDL-cholesterol 3.0 mmol/L. Apart from this, he had no other cardiovascular risk factors.

Discussion

This man does not have central obesity, diabetes or secondary causes for low HDL-cholesterol, and given the family history, he probably has a genetic cause for low HDL-cholesterol. The genetic disorder, familial hypoalphalipoproteinaemia, may be seen in up to 25% of patients with premature CHD. Its heritability is not clearly defined. The molecular defect is now thought to relate to a deficiency in a newly discovered ATP-binding cassette transporter (ABCA1) that moves cholesterol from cells to HDL particles.

In the absence of cardiovascular disease, this patient should initially be treated with lifestyle measures: exercise, Mediterranean-type diet and possibly regular alcohol intake of two to three standard drinks per day, although the latter may be risky owing to potential abuse. He should be investigated strictly for latent atherosclerosis and CHD, with an exercise stress test, stress echocardiogram or myocardial perfusion scan, and possibly also carotid ultrasonography.

If established coronary or carotid atherosclerosis is suggested, he should be treated with drugs in addition to lifestyle measures. Gemfibrozil, or preferably fenofibrate (Lipidil), should be used as first measure. There is, however, clinical trial evidence that the combination of simvastatin and nicotinic acid may benefit such patients with CHD, but the tolerability of the nicotinic acid preparation available in Australia is poor.

Raising an isolated low HDL-cholesterol level can be very difficult, and achievement of the target level of greater than 1.0 mmol/L would require the use agents still in development, such as cholesteryl ester transfer protein inhibitors.

support to the findings from epidemiology and clinical trials showing that HDL protects against CHD. In summary, the new data indicate that HDL has intrinsic antiatherosclerotic properties (i.e. anti-inflammatory, antioxidant, antimitotic, anticoagulant, antiaggregatory and profibrinolytic). These antiatherogenic properties are determined by the apo A and enzyme (e.g. paraoxonase) contents, and the phospholipid composition, of the HDL particle. Thus, HDL-cholesterol elevation protects against atherosclerosis via both reverse cholesterol transport and nonlipid pathways (Figure 3).

Detection of patients with low HDL-cholesterol

Disorders of lipid metabolism

Clinicians should always consider that a low plasma HDL-cholesterol concentration may be due to a primary (genetic) or secondary disorder of lipid metabolism.

Primary disorders

A genetic cause for low HDL-cholesterol (e.g. familial hypoalphalipoproteinaemia; see Case 1) may be present in 20% of patients with premature coronary artery disease (CAD) and normal or slightly elevated levels of LDL-cholesterol. A low plasma HDL-cholesterol may be seen in association with other genetic disorders of lipid metabolism, such as:

- primary chylomicronaemia
- familial hypertriglyceridaemia
- familial dysbetalipoproteinaemia (type III hyperlipidaemia)
- familial combined hyperlipidaemia.

In these situations, the low plasma HDL-cholesterol is most certainly a consequence of the elevation in plasma triglyceride and the increased exchange of cholesterol and/or triglycerides between HDL and triglyceride-rich lipoproteins, as explained earlier.

Very rare genetic disorders that specifically lower HDL-cholesterol include Tangier disease and lecithin cholesterol: acyltransferase deficiency.

Secondary disorders

In clinical practice, a low plasma HDL-cholesterol is more often associated with other disorders that increase plasma triglycerides – e.g. central obesity, insulin resistance, type 2 diabetes mellitus (see Case 2) and renal disease (chronic renal failure or nephrotic proteinuria).

Unfavourable lifestyle circumstances, such as low physical activity and cigarette smoking, can also contribute to a low plasma HDL-cholesterol. It is important to obtain a drug history since beta blockers, thiazide diuretics and androgenic progestins may also depress plasma HDL-cholesterol levels. Insulin resistance and hypertriglyceridaemia often explain a low HDL-cholesterol level within populations; hence, low HDL-cholesterol is one of the cardinal features of the metabolic syndrome.

Laboratory aspects

An accredited laboratory should measure HDL-cholesterol as part of a fasting lipoprotein profile. However, under current Medicare arrangements HDL-cholesterol has to be specified on the requesting form for the laboratory to carry out the assay – i.e. requesting a 'lipid profile' is not enough.

Interference with HDL-cholesterol measurement may occur if patients have hypertriglyceridaemia (>12 mmol/L) or increased lipoprotein remnant concentrations (e.g. those with familial dysbetalipoproteinaemia and type 2 diabetes).

The value of measuring the concentration of HDL-cholesterol is underscored by its requirement:

- to estimate the concentration of non-HDL-cholesterol (total cholesterol minus HDL-cholesterol), which reflects the atherogenic remnant particles, and
- to calculate the LDL-cholesterol using the Friedewald equation – i.e. LDL-cholesterol equals total cholesterol minus HDL-cholesterol minus [triglycerides divided by 2.2]. (Note that the Friedewald formula does not

Case 2. Use of statin–fibrate combination plus further approaches

A 46-year-old man presented with a BMI of 31 kg/m^2 (a BMI of ≥25 kg/m^2 is overweight and ≥30 kg/m^2 obese), waist circumference of 102 cm, hypertension and type 2 diabetes. He had been treated with an antidiabetic diet, glipizide (Melizide, Minidiab) and metformin. He was also taking atenolol for blood pressure that was well controlled at 130/75 mmHg. Fasting blood lipid results were as follows: total cholesterol, 8.7 mmol/L; triglycerides, 25 mmol/L; HDL-cholesterol, 0.5 mmol/L.

Discussion

A low HDL-cholesterol level invariably accompanies this level of hypertriglyceridaemia and poor glycaemic control. At this level of triglycerides, LDL-cholesterol cannot be calculated by the Friedewald formula. Nephrotic range proteinuria due to diabetic nephropathy and hypertriglyceridaemia due to alcohol abuse may contribute to the dyslipidaemia, but this man did not have any of these precipitants. Hypothyroidism should be excluded routinely by measurement of the plasma thyroid stimulating hormone level.

Initially the patient should be treated rigorously with a hypocaloric, high complex carbohydrate diet to achieve at least a 5% reduction in body weight, along with a 'start slow, go slow' exercise program.

Case continued

After 6 months of dieting and moderate exercise, the patient's weight fell to 92 kg, but he remained dyslipidaemic with a total cholesterol of 5.0 mmol/L; triglycerides, 9.0 mmol/L; and an HDL-cholesterol, 0.6 mmol/L.

Discussion continued

This picture suggests that he may have a background genetic hyperlipidaemia, such as familial hypertriglyceridaemia or familial combined hyperlipidaemia. The latter would be supported more clearly by a family history of premature cardiovascular disease, which was not clear from the history, nor confirmed in a pedigree study. Familial dysbetalipoproteinaemia (type III hyperlipidaemia) is very uncommon and the absence of apo E2 homozygosity excluded this disorder.

Case continued

The patient was started on 40 mg of atorvastatin (Lipitor) but after two months the lipid profile still remained abnormal: cholesterol, 3.4 mmol/L; triglycerides, 4.0 mmol/L; HDL-cholesterol, 0.8 mmol/L. After adding gemfibrozil 600 mg twice daily, the triglycerides fell to 3.1 mmol/L and the HDL-cholesterol increased to 1.0 mmol/L. Plasma renal biochemistry was confirmed to be normal before adding the fibrate, an important check since risk of myositis with this combination is increased in patients with renal impairment. The patient's plasma creatine kinase and liver enzymes were checked every three months and remained normal.

Discussion continued

Further approaches to achieving a more optimal lipid profile could include more rigorous weight reduction with the assistance of sibutramine (Reductil), as well as improvement in insulin sensitivity with a glitazone, both of which have been shown to increase HDL-cholesterol. With sibutramine, blood pressure will need to be monitored since this may rise by a few mmHg. If significant CHD is excluded with standard cardiology tests, changing this patient's antihypertensive medication from a beta blocker to an ACE inhibitor or angiotensin II-receptor blocker may help with the lipid profile.

apply if the triglyceride concentration exceeds 4.5 mmol/L or the patient has familial dysbetalipoproteinaemia.)

Some diagnostic laboratories report the total cholesterol to HDL-cholesterol, or the LDL-cholesterol to HDL-cholesterol, ratios along with an assessment of CHD risk based on the results of the Framingham Heart Study. The validity of HDL-cholesterol ratios can be misleading, especially at extreme ends of total or LDL-cholesterol values.

We see no practical value at present in measuring the apo A-I, apo A-II or HDL-cholesterol subfractions in routine clinical practice.

Guidelines for management: which target level?

Invariably, every set of guidelines worldwide for the management of lipid disorders includes low HDL-cholesterol as an important factor for assessing cardiovascular risk and guiding the type and intensity of lipid-regulating therapy. Guidelines agree that a plasma level of HDL-cholesterol below 1.05 mmol/L is undesirable and increases the individuals' 10-year risk of a cardiovascular event, especially in the presence of other risk factors. The Australian guidelines propose as a therapeutic target a plasma level of HDL-cholesterol greater than 1.0 mmol/L, but any degree of elevation of HDL-cholesterol is likely to be beneficial even if the recommended target is not achieved. Surprisingly, neither the American guidelines (NCEP III) nor the European guidelines give an HDL-cholesterol goal for therapy.

In our view, a low HDL-cholesterol is a critical risk factor for CHD among patients with insulin resistance and type 2 diabetes (and by extension all individuals at high risk of CHD) that merits the use of appropriate therapeutic goals. The American Diabetes Association has recommended that HDL-cholesterol should be raised above 1.2 mmol/L in patients with type 2 diabetes; this may be appropriate also for patients with the metabolic syndrome. We believe that now LDL-cholesterol treatment targets have been well defined, guidelines should be revised to set an HDL-cholesterol target above 1.2 mmol/L in all high risk individuals. The inverse relation between HDL-cholesterol and coronary risk is continuous, so that any targets set are arbitrary but operationally useful. We have not found that the ratios of total cholesterol or LDL-cholesterol to HDL-cholesterol are of value in our clinical practice.

Generally, the approach to managing patients with low HDL-cholesterol has to be seen in the context of other risk factors and, particularly, the coexistent level of LDL-cholesterol. Our preferred recommendation is that in high risk patients (e.g. those with diabetes and/or the metabolic syndrome) LDL-cholesterol should be lowered to below 2.6 mmol/L with a statin and appropriate lifestyle modification. Attention should then be given to increasing HDL-cholesterol to above 1.0 mmol/L, with a target of greater than 1.2 mmol/L in high risk patients. A fibrate or fish oil may be added to statin therapy. If plasma LDL-cholesterol at diagnosis is below the desirable level, a fibrate may be used initially as monotherapy if HDL-cholesterol is low (see Case 3).

Table 1. Lifestyle and constitutional factors affecting HDL-cholesterol

Increases HDL-cholesterol	Decreases HDL-cholesterol
Weight loss	Obesity
Exercise	Physical inactivity
Alcohol	Cigarette smoking
High fat diet	High carbohydrate diet
Female gender	Male gender

Therapy for raising HDL-cholesterol

The first approach to managing low plasma HDL-cholesterol is to identify and remedy the cause (e.g. diabetes, obesity). Isolated depression in HDL-cholesterol in primary prevention should be treated with lifestyle modifications alone; drug treatment for isolated low HDL-cholesterol (with fibrates or niacins) should be considered only in patients with a history of CHD and after excluding and treating secondary disorders.

Lifestyle modifications

Lifestyle modifications are the first therapeutic step and involve weight reduction, smoking cessation and regular (aerobic) physical exercise (Table 1). They may benefit other cardiovascular risk factors (such as hypertension, endothelial dysfunction, hyperglycaemia and coagulopathy) apart from low HDL-cholesterol.

Smoking cessation may increase HDL-cholesterol by up to 10%, and a similar benefit may accrue from a 4 to 5 kg weight loss in obese patients. A fat-modified diet high in monounsaturates may have a more favourable effect on HDL metabolism than a low saturated fat, high carbohydrate diet. This is because of the decreased tendency of the former to induce hypertriglyceridaemia, which as noted earlier can lower plasma HDL-cholesterol levels. All fats, including dietary cholesterol, increase plasma HDL-cholesterol. Total fat intake may be increased up to 35% of energy intake provided that the intake of saturated fats and transunsaturated fatty acids are kept low (<10%). The 'Atkins Diet' (high fat, low carbohydrate, low energy) has recently been shown to be more effective in achieving weight loss and raising

plasma HDL-cholesterol in obese subjects, but this diet is 'unnatural' and its long term safety is questionable.

Aerobic physical exercise increases HDL-cholesterol and is more effective in those people who are initially hypertriglyceridaemic.

Regulation of alcohol intake is important. A modest intake (e.g. a maximum of two standard drinks a day for women and four for men [one standard drink equals 120 to 150 mL of wine or 8 to 10 g of alcohol]) may increase HDL-cholesterol by as much as 10%. This is particularly the case in individuals who metabolise alcohol slowly via the enzyme alcohol dehydrogenase.

The contribution of an elevation in HDL-cholesterol to the cardiovascular benefit of lifestyle changes is not known.

Review coexisting medications

As well as adverse lifestyle factors, medications (e.g. beta blockers, thiazide diuretics, and androgenic progestins) can decrease plasma HDL-cholesterol (Table 2, and see Case 4). These should be identified and, where appropriate, replaced with agents that have more favourable effects on HDL-cholesterol.

Lipid-regulating drugs

Statins, fibrates and nicotinic acid

Despite appropriate lifestyle modifications, many patients, particularly those with insulin resistance, type 2 diabetes or obesity, will require pharmacotherapy. Drugs that increase HDL-cholesterol include statins, fibrates and nicotinic acid (Table 2). The efficacy of these agents in increasing HDL-cholesterol is in part related to their triglyceride-lowering effect (Table 3). The mechanisms whereby these drugs increase HDL-cholesterol relate to complex effects on the production and catabolism of the apo A of the HDL particle.

In Australia, fenofibrate (Lipidil) has now been registered. This agent is a more specific and potent fibrate than gemfibrozil and has an excellent long term safety record.

Newer statins

Newer statins on the horizon but not yet available in Australia, such as rosuvastatin (Crestor), show promise in preliminary clinical trials in correcting the dyslipoproteinaemia in the metabolic syndrome and type 2 diabetes, including the low levels of HDL-cholesterol. Compared with other statins, rosuvastatin is more potent in lowering LDL-cholesterol and maintains a sustained elevation in HDL-cholesterol up to the maximum dosage of 40 mg daily. The drug interaction profile of rosuvastatin also compares favourably with that of other statins. Pitavastatin is another highly potent statin, but has not yet been trialled in Australia.

Ezetimibe

Ezetimibe (Ezetrol) is an inhibitor of a specific cholesterol transport system in the gut and thereby decreases the delivery of cholesterol to the liver. It has just been registered in Australia and its major use is as adjunctive therapy to statins to lower elevated LDL-cholesterol. It has a modest effect in elevating HDL-cholesterol and potentially could be used very successfully in combination with fenofibrate in patients with the metabolic syndrome and diabetes, but experience is limited.

Statin–fibrate combination

The currently available statins are generally not very effective in elevating HDL-cholesterol and require the addition of a fibrate or fish oil. In clinical trials statin–fibrate combinations have been reported to increase HDL-cholesterol by as much

Table 2. Drugs affecting HDL-cholesterol levels

Increases HDL-cholesterol	Decreases HDL-cholesterol
Nicotinic acid	Androgens
Fibrates	Antiretroviral agents
Statins	Beta blockers
Phenytoin (Dilantin)	Nicotine
Alcohol	Prednisolone
Fish oils	Progestins
Ezetimibe (Ezetrol)	Retinoic acid
Cholestyramine (Questran Lite)	Thiazide diuretics
Colestipol (Colestid Granules)	
Carbamazepine (Tegretol, Teril)	
Oestrogens	
Insulin	

Table 3. Drug effects on plasma HDL-cholesterol and triglycerides

Drug group	HDL-cholesterol	Triglycerides
Niacins	Increase by 10-35%	Decrease by 20-50%
Fibrates	Increase by 10-15%	Decrease by 20-50%
Statins	Increase by 5-10%	Decrease by 10-25%
Resins	Increase by 3-5%	Increase by 0-20%
Ezetimibe	Increase by 2-4%	Increase by 0-5%

as 30%. The use of a statin with gemfibrozil is associated with a small but significant risk of myositis and rhabdomyolysis, and certain precautions should be followed if using this combination (e.g. measure creatine kinase before treatment and regularly thereafter). Table 4 lists some caveats and guidelines on the use of statin–fibrate combinations, which should be reserved for high risk patients (i.e. those with more than a 2% risk of cardiovascular events per year – typically those with the metabolic syndrome including type 2 diabetes).

Fenofibrate is being trialled in the Fenofibrate In Event Lowering in Diabetes (FIELD) study. It has a very long safety record as monotherapy and when administered with statins will be a safer option than gemfibrozil for combination regimens.

Statin–fish oil combination

A statin–fish oil combination is potentially safer than a statin plus a fibrate. Statins plus fish oils can effectively correct the dyslipidaemia of insulin resistance, including increasing HDL-cholesterol. In a recent clinical trial, we reported that atorvastatin (40 mg/day) and fish oils (e.g. Blackmores Fish Oil 1000 mg, 3 to 4 g/day) have independent and additive effects in correcting dyslipidaemia in the metabolic syndrome, the combination increasing HDL-cholesterol levels by 13%.[6]

Nicotinic acid

The use of nicotinic acid (niacin, vitamin B_3) is popular in North America for treating dyslipidaemia and raising HDL-cholesterol, but the preparation available in Australia is generally unsuitable as a result of side effects (e.g. palpitations and flushing). An extended-release preparation has recently been approved in North America and may become available in Australia.

Nicotinic acid preparations are subject to drug interactions (e.g. with alcohol) and may increase blood glucose in patients with diabetes and uric acid levels in patients predisposed to gout.

Other HDL-cholesterol elevators

Oestrogens are effective in increasing HDL-cholesterol, but the use of hormone

Case 3. The metabolic syndrome in a man with no history of CHD or diabetes

A 50-year-old man presented with central obesity and hypertension, but no history of cardiovascular disease or diabetes mellitus. His BMI was 28 kg/m^2, blood pressure 150/95 mmHg, fasting insulin 38 mU/L (upper normal limit is 15 mU/L) and glucose 6.1 mmol/L. Medication comprised atenolol, bendrofluazide (Aprinox) and ramipril (Ramace, Tritace) taken once daily. Fasting serum lipid profile was: total cholesterol, 4.9 mmol/L; triglycerides, 3.1 mmol/L; HDL-cholesterol, 0.9 mmol/L; LDL-cholesterol, 2.6 mmol/L.

Discussion

This patient has the metabolic syndrome with insulin resistance and almost certainly impaired glucose tolerance (IGT). His lipid profile meets the entry criteria for the VA-HIT trial and he could be treated initially with gemfibrozil or fenofibrate (Lipidil).

The efficacy of fibrates in decreasing cardiovascular events in patients with this lipid profile is greatest in those who are insulin resistant. Insulin resistance may be measured with a fasting insulin level or by calculating the homeostasis model assessment (HOMA) score (insulin level in mmol/L multiplied by glucose level in mmol/L, divided by 22.5; upper normal limit is 4). If he has IGT there is good trial evidence for the prevention of diabetes over four years with exercise and a hypo-caloric diet high in complex carbohydrates that achieves a 5 to 10% reduction in body weight.

Both lifestyle measures and fibrates should be used in this patient, but before adding a fibrate, plasma renal, muscle and liver biochemistry need to be checked; fibrates are also contraindicated in patients with clinical evidence of cholelithiasis, since these drugs increase the lithogenicity of bile. If the HDL-cholesterol still remains depressed his antihypertensive therapy should be reviewed because both atenolol and bendrofluazide may exacerbate hypertriglyceridaemia and depress HDL-cholesterol. If necessary the atenolol could be switched to pindolol (Barbloc, Visken), a beta blocker that does not affect HDL levels, and the bendrofluazide to indapamide (also lipid neutral).

Table 4. Use of statin plus fibrate combinations for dyslipidaemias

- Avoid use in patients with significant liver, muscle or renal dysfunction.
- Avoid use in patients with significant elevation in liver and/or muscle enzymes (>3 times the upper reference limit).
- Avoid use in patients on polypharmacy and in the elderly.
- Avoid use in patients taking drugs known to impair cytochrome P450 3A4 mixed function oxidase – e.g. macrolide antibiotics, azole antifungals, cyclosporin.
- Do not use if there is lack of physician and/or patient commitment to close clinical and laboratory monitoring.
- Teach patients to recognise muscle symptoms.
- Discontinue therapy if muscle symptoms are present and/or creatine kinase is greater than 3 times the upper reference limit.

Case 4. Very low HDL-cholesterol and high LDL-cholesterol in a fit, muscular man

A fit, muscular 41-year-old man presented to his GP requesting a cholesterol test. His BMI was 25 kg/m^2 and blood pressure 130/70 mmHg and he was on no medications. There was no family history of premature cardiovascular disease or death. The lipid profile was: total cholesterol, 7.5 mmol/L; HDL-cholesterol, 0.2 mmol/L; triglyceride, 2.0 mmol/L; LDL-cholesterol 6.8 mmol/L.

Discussion

The patient has the rare combination of extremely low HDL-cholesterol and high LDL-cholesterol levels. His glucose, renal function, liver function and thyroid function tests were all normal, thus excluding a number of the common secondary causes of dyslipidaemia and low HDL-cholesterol. The HDL-cholesterol concentration would be consistent with the genetic condition, familial hypoalphalipoproteinaemia, whereas the LDL-cholesterol level would be consistent with familial hypercholesterolaemia. However, the patient had no peripheral stigmata of lipid disorders, and in particular no corneal arcus, xanthelasma or xanthomata and a negative family history of premature CHD, making familial hypercholesterolaemia unlikely.

Anabolic steroid use may result in extreme alteration in plasma lipids and lipoproteins.

Case continued

When questioned, the patient admitted to joining a gym and self-administering exogeneously an androgenic-anabolic steroid (oxandrolone) with the aim of 'bulking up'. The atherogenic lipid profile was reversible after discontinuation of the anabolic steroids.

Discussion continued

Anabolic steroids lower plasma HDL-cholesterol by increasing the degradation of HDL by the liver. The HDL lowering effects of testosterone are modest compared with agents such as oxandrolone, nandrolone and stanozolol. Misuse of anabolic steroids can be especially risky in the present context in subjects with familial dyslipidaemias; prolonged use may also increase liver enzymes and result in cholestasis, which itself can induce marked hypercholesterolaemia.

replacement therapy is not recommended for the treatment of dyslipidaemia in postmenopausal women owing to the adverse results of recent clinical trials.

Improvement in glycaemic control in patients with diabetes with the use of lifestyle changes, some oral antidiabetic agents and, possibly, insulin will lower hypertriglyceridaemia and reciprocally increase HDL-cholesterol levels. The insulin sensitisers, glitazones, have also been reported to increase levels of HDL-cholesterol, but their effect on the levels of triglycerides are variable.

The weight-reducing drug, sibutramine (Reductil) has been reported to have a specific HDL-cholesterol elevating effect independent of the degree of weight loss, but the mechanism for this effect is unknown.

Novel agents being developed for regulating HDL metabolism include:

- inhibitors of cholesteryl ester transfer protein (CETP), which controls cholesterol and triglyceride shunting between HDL and other lipoproteins
- stimulators of the ATP-binding cassette transporter A1 (ABCA1), a newly identified protein that moves cholesterol from tissues to HDL.

Conclusion

A low plasma HDL-cholesterol level is often seen in patients with central obesity, the metabolic syndrome and type 2 diabetes mellitus. There is now a good rationale for raising HDL-cholesterol in these and other patients at high risk of cardiovascular disease. Continuing research should strengthen this novel paradigm for managing lipid disorders. The incremental benefits of adding a fibrate, fish oils or 'pipeline agents', such as CETP inhibitors, to a statin in high risk patients with the metabolic syndrome, including diabetes, are clearly burning questions for future clinical endpoint trials. MT

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A list of further reading is available on request to the editorial office.

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An ABC of HDL

a paradigm shift in managing lipid disorders

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