The role of HDL-C in diabetes and the metabolic syndrome

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Article points

1. HDL-C transports excess cholesterol back to the liver. Every 2–3% rise is associated with a 2–4% reduction in cardiovascular disease risk.
2. HDL-C rises are linked to triglyceride reduction.
3. Consensus is that an HDL-C level of >1.0mmol/l should be achieved in patients with established coronary heart disease (CHD).
4. Fibrates and nicotinic acid (niacin) raise HDL-C levels. Recent studies have focused on statins plus nicotinic acid, e.g. ARBITER 2 study.
5. Strategies that raise HDL-C have an important preventive role in CHD.

Key words:

- HDL-cholesterol
- LDL-cholesterol
- Nicotinic acid
- Targets
- Guidance

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People with diabetes or the metabolic syndrome are at increased risk of myocardial infarction. The most important lipid intervention when reducing the risk of coronary heart disease is reduction of low-density lipoprotein cholesterol; however, there is similar evidence of risk reduction with an increased high-density-lipoprotein cholesterol (HDL-C) level. This article looks at the role of HDL-C in people with diabetes and the metabolic syndrome.

Reduction of low-density lipoprotein cholesterol (LDL-C) is the single most important lipid intervention that will reduce coronary heart disease (CHD). Epidemiological work has consistently shown that each 1% reduction in LDL-C results in a reduction of 1.0–1.5% in the risk of major cardiological events. In both primary and secondary prevention studies, meta-analysis of LDL-C lowering strategies has shown a 12–38% reduction in LDL-C and a relative risk reduction of 19–35% in overall risk (Hennekens and Ridker, 1999).

Benefit of raising HDL-C

There is similar convincing evidence in relation to the importance of high-density-lipoprotein cholesterol (HDL-C). HDL-C is the 'scavenger' lipoprotein. Its function is to transport excess cholesterol back to the liver for further metabolism. Every 2–3% rise in HDL-C (around 0.03 mmol/l) has been associated with a reduction in risk of 2–4%, independent of the level of LDL-C (Gordon et al, 1989; Phillips et al, 1993; Brown et al, 1990). The preventive effect of HDL-C seems more important in post-menopausal women. Meta-analysis of US studies suggests that an increase of 0.026 mmol/l (1 mg/dL) is associated with a reduction in coronary events of 2% in men but 3% in women, independent of other risk factors, such as LDL-C (Sharrett et al, 2001; Gordon and Rifkind, 1989).

Studies of HDL-C

The metabolism of HDL-C and triglyceride are inextricably linked. Strategies that raise HDL-C are invariably associated with a reduction in triglycerides. In the Veterans Affairs HDL-C Intervention trial (VA-HIT; Rubins et al, 1999), the fibrate gemfibrozil was compared with placebo in men with dyslipidaemia typical of the metabolic syndrome. At one year, though mean LDL-C remained the same in both groups, mean HDL-C was 6% higher and mean triglyceride levels were 31% lower in the fibrate group than in the group receiving placebo. These changes in the treatment arm were associated with a 22% and 25% reduction in myocardial infarction and stroke respectively. So reduction of HDL-C is associated with improvements not only in surrogate measures but also in outcomes.

Combined LDL-C/HDL-C strategies

The logical conclusion is that a therapeutic

Table 1. Desirable lipid levels in patients at risk of CHD, diabetes and the metabolic syndrome.

Lipid	Desirable level	Authority
Total cholesterol	<5.0 mmol/L	Cardiovascular National Service Framework (Department of Health, 2000) Joint European Societies (1998)
LDL-cholesterol	<3.0 mmol/l	Joint European Societies (1998)
HDL-cholesterol	>1.03 mmol/L	European Consensus Panel on HDL-cholesterol (2004)

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1. Increasing HDL-C by 6% reduced triglycerides by 31% and was associated with 22% and 25% reduction in myocardial infarction and stroke incidence respectively.
2. Lowering LDL-C and raising HDL-C could reduce the risk of coronary events by 60–80%.
3. Type 2 diabetes and the metabolic syndrome are associated with a particularly atherogenic pattern of dyslipidaemia, leaving them at especial risk of developing CHD and at the same risk of suffering myocardial infarction (MI) as people without diabetes who have already had an MI.
4. There is a consensus that an HDL-C of >1.0mmol/l should be achieved in people with established CHD.
5. Two therapies are particularly useful in raising HDL-C: the fibrates and nicotinic acid.

approach which combines lowering of LDL-C with raising of HDL-C could reduce risk of coronary events by 60–80%. This is of particular importance in type 2 diabetes, in pre-diabetes and in the metabolic syndrome, all of which are associated with a particularly atherogenic pattern of dyslipidaemia:

- raised triglycerides
- unchanged or raised LDL-C rendered more atherogenic because of a raised triglyceride load (known as small dense LDL-C)
- lowered HDL-C, less able to 'scavenge' cholesterol effectively because of a high triglyceride load
- increased very-low density lipoprotein (containing triglyceride).

This particular pattern of dyslipidaemia goes some way to explaining why people in these groups are at especial risk of developing CHD and why patients with diabetes who have not yet suffered a myocardial infarction are at the same risk as people without diabetes who have (Watkins, 2003). The risk of CHD in patients with pre-diabetes and the metabolic syndrome is less well established. However, it is logical that increased risk should not suddenly begin with the diagnosis of full-blown diabetes, but rather that it should extend some way back through the duration of pre-diabetes metabolic imbalance. This is known to exist for 10 to 15 years before frank diabetes develops.

General Medical Services contract

The new General Medical Services contract has obscured the importance of HDL-C by focusing clinical attention upon LDL-C. For patients with both established CHD and diabetes, GPs now have a single lipid target of 5.0 mmol/l for LDL-C (British Medical Association, 2003). Authorities have argued that for patients at risk of CHD, and particularly those with diabetes and the metabolic syndrome, consideration of HDL-C should also be included (European Consensus Panel on HDL-C, 2004). Examples of the desirable lipid levels for patients at risk of CHD are shown in *Table 1*.

While there is a consensus that an HDL-C of >1.0 mmol/l should be achieved in patients with established CHD, some guidelines have suggested that in women it should be even higher (>1.3 mmol/l) (Mosca et al, 2004; American Diabetes Association, 2004).

The ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol 2 study

Two therapies are particularly useful in raising HDL-C – the fibrates and nicotinic acid (niacin). The latter agent has a greater effect on HDL-C. Recent interest, therefore, has focused upon the combined benefits of statins plus nicotinic acid therapy in patients with a history of CHD. The results of the ARBITER 2 study (ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol; Taylor et al, 2004) were presented at the American Heart Association meeting in New Orleans in November 2004. These data showed that, compared with a statin alone, the combination of statin and prolonged-release nicotinic acid (Niaspan) significantly slowed progression of atherosclerosis, as measured by carotid intima-media thickness (CIMT), among individuals with established coronary risk and moderately low HDL-C.

In the patients taking a statin plus prolonged-release nicotinic acid, HDL-C increased by 21% and CIMT remained unchanged. In the group taking statin alone, HDL-C was unchanged at one year and CIMT had progressed significantly. Somewhat surprisingly, the difference in CIMT between the two groups was only significant in those individuals who did not have insulin resistance. Nevertheless, the researchers concluded that the addition of

Table 2. Intervention level and targets for LDL-C and non-LDL-C (triglyceride is seen as an independent risk factor in ATP-III).

Intervention level	LDL-C target mmol/l (mg/dL)	Non-HDL-C target mmol/l (mg/dL)
No coronary heart disease (CHD), <2 risk factors	<4.1 (160)	<4.9 (190)
No CHD, 2+ risk factors	<3.4 (130)	<4.1 (160)
CHD or CHD risk equivalent	<2.6 (100)	<3.4 (130)

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1. The ARBITER 2 study compared a statin alone with statin plus prolonged-release nicotinic acid.
2. HDL-C was increased by 21% and carotid intima-media thickness remained the same with combined statin plus nicotinic acid therapy.
3. Researchers concluded that addition of prolonged-release nicotinic acid to statin therapy slowed the rate of atherosclerosis among individuals with known CHD and moderately low HDL-C.
4. Weight loss, exercise and stopping smoking will also increase HDL-C levels.
5. ATP III guidance (2001) has a comprehensive secondary lipid strategy.
6. ATP III sees triglycerides as an independent CHD risk factor with an intervention level at or above 2.3 mmol/l. As triglycerides and HDL-C are linked, no HDL-C target is given.
7. The first management strategy is behavioural change.

prolonged-release nicotinic acid to statin therapy slowed the rate of progression of atherosclerosis among individuals with known CHD and moderately low HDL-C.

Concern has been expressed that nicotinic acid may increase the glucose level in patients with impaired fasting glucose (but not yet diabetes) or the metabolic syndrome, based upon earlier reports. However, recent analyses of pooled double-blind data have shown no increased effect other than that which would be expected from the natural progression to diabetes in this type of case (Insull et al, 2004).

Lifestyle and HDL-C

Several lifestyle changes have also been shown to raise HDL-C. Weight loss, exercise and stopping smoking will raise HDL-C. So too will food and drinks such as red wine, orange juice, beans, fish, olive oil, oat bran, onions, soy products and soluble fibre (Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III [ATP III], 2001).

Building HDL-C management into current practice

The guidance in ATP III, which is perhaps the most comprehensive current guidance regarding secondary lipid strategy, reinforces the consensus that where risk of CHD is >2 % per year, LDL-C is still the prime target. However, after optimal progress towards target LDL-C is achieved, the dyslipidaemia of the metabolic syndrome becomes a secondary target (ATP III, 2001).

ATP-III sees triglycerides as an independent risk factor with an intervention level at or above 2.3 mmol/l and three levels of LDL-C and non-HDL-C target, depending upon the exact level of CHD risk (see *Table 2*). No target level for HDL-C is given, though, because triglycerides and HDL-C are linked. The European Consensus panel has provided a general target for HDL-C of >1.03 mmol/l.

Management strategies

Management options in CHD, metabolic syndrome and diabetes are given in *Table 3*. The first management strategy is behavioural – appropriate diet, weight loss, exercise and smoking cessation. Dietary fat is also a key consideration with an emphasis on reducing saturated fats:

- total fat should be in the range 25–30 %
- saturated fat <7 % of total calories
- polyunsaturated fat up to 10 % of total calories
- monounsaturated fat up to 20 % of total calories.

In practice, most of this will already have been done when reducing overall CHD risk and introducing a statin. After this, where maximal tolerable statin levels have been reached yet LDL-C targets are not achieved, ATP III (2001) suggests treatments that target HDL-C and triglycerides should be considered. Target lipid levels for triglycerides and HDL-C from the Joint European Societies and the European Consensus Panel are shown in *Table 1*.

Conclusion

The level of guidance suggested by ATP-III (2001) is perhaps too complex for everyday general practice; but the targets regarding triglycerides and HDL-C are eminently practical. The emerging consensus demonstrates that at all levels of cardiovascular risk, after reduction of LDL-C, strategies which lower triglycerides and raise HDL-C have an important preventive role. ■

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'At all levels of cardiovascular risk, after LDL-C reduction, lowering of HDL-C and triglycerides has an important preventative role.'

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Table 3. Management options in CHD, the metabolic syndrome and diabetes

Target	Action	Review
Overweight and obesity	Reducing diet calories	Dietitian/nurse review
Lack of exercise	Exercise programme	Review by exercise team
Smoking	Smoking cessation programme	Review by nurse
Raised LDL-C	Statin	Review with liver function tests in three months
Low HDL-C	Fibrate, nicotinic acid Advise dietary change, exercise	Review in three months
High triglycerides	Fibrate, nicotinic acid Advise dietary change, exercise	Review in three months
Impaired fasting glucose (IFG) or impaired glucose tolerance	Diet, weight loss, exercise	Review as appropriate (oral glucose tolerance test if IFG persists)
Raised HbA_{1c} (if the person has diabetes)	Diet Hypoglycaemic agents that target insulin resistance	Review in three months
Hypertension	Hypotensive agents	Review as appropriate
Hyper-coagulable state	Aspirin for CHD patients	Medication review Check uric acid
Albuminuria	ACE inhibitor or angiotensin II antagonist	Monitor albumin/creatinine ratio and renal function regularly