Dyslipidaemia and the metabolic syndrome

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Introduction

Patients with the metabolic (or dysmetabolic) syndrome have a cluster of cardiovascular risk factors that place them at extremely increased risk of coronary heart disease, stroke and, consequently, reduced survival.[1]

There is considerable overlap between the traditional cardiovascular risk factors and the factors that make up the metabolic syndrome (Table 1).

The metabolic syndrome comprises a number of unfavourable factors which have developed through a complex interplay of genetic and environmental influences. These factors often exacerbate the effect of others, thereby multiplying the cardiovascular risk (Figure 1).

However, the inter-relation between the risk factors can be used as a target for intervention, mainly lifestyle modification. This is most apparent in the benefits of even modest weight loss, in terms of reducing development of diabetes, increasing insulin sensitivity, improvement of the dyslipidaemic profile (see below) and improving blood pressure control.

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The dyslipidaemic profile

Individuals with the metabolic syndrome, and in fact the majority of obese people per se, tend to have a typical lipid profile including:

- increased total cholesterol
- increased LDL cholesterol
- increased triglycerides
- decreased HDL cholesterol.

The elevated triglyceride levels are due to an excess of VLDLs, synthesised in excess as a result of hyperinsulinaemia. Obesity also contributes to this increase in VLDL production due to increased free fatty acid flux from adipose tissue to liver.

It is widely accepted that all four of these factors (individually and in combination) result in increased cardiovascular risk.[2,3] Although the evidence relating total cholesterol and risk is undisputable, it does appear that a moderately elevated triglyceride level, usually associated with a low HDL, also increases risk.[4] But the situation becomes even more ugly when one analyses the lipid components further.[3] For example, people with the metabolic syndrome tend to have a greater proportion of their LDL as the more atherogenic small dense particles.

Table 1. Cardiovascular risk factors and the metabolic syndrome

Classical cardiovascular risk factors	The metabolic syndrome
Age	Obesity – especially abdominal/visceral
Gender	Dyslipidaemia
Obesity – especially abdominal/visceral	High triglycerides
Dyslipidaemia	Low HDL cholesterol
High total and/or LDL cholesterol	Hypertension
High triglycerides	Diabetes or impaired glucose tolerance
Low HDL cholesterol	Insulin resistance
Hypertension	
Diabetes mellitus	
Smoking	
Family history	

Management of dyslipidaemia in the metabolic syndrome

1. Lifestyle measures

The importance of weight loss cannot be underestimated. Apart from the reduction in blood pressure and improvement in insulin sensitivity, even modest weight loss can improve the dyslipidaemia in these patients and thereby reduce cardiovascular risk.[5]

Not only are LDL and triglyceride levels reduced, but there is a small increase in HDL level if weight loss is sustained. The latter increase can also be aided by regular exercise. It seems that exercise and weight loss have independent, additive beneficial effects on the lipid profile.[6] Regular exercise is particularly effective in increasing HDL.

There is evidence that weight loss in patients with type 2 diabetes or impaired glucose tolerance, and probably the majority of patients with metabolic syndrome, results in a favourable change in LDL size away from the small dense atherogenic molecules. Specific dietary advice should focus on reduction of calories, total and saturated fats and adoption of a Mediterranean style diet (high levels of fruit, vegetables, whole-grain foods with low levels of red meat and moderate alcohol consumption). The consumption of fish oils based on omega-3 fatty acids can reduce triglyceride levels.

2. Drug therapy

The 'when', 'who' and 'what with' questions need to be asked before prescribing any therapy, but more so when treating an asymptomatic patient or condition. Treatment of all dyslipidaemias is based on sound evidence for reducing disease and death.[7–9] The patient with metabolic syndrome (without overt diabetes) is already identified as having at least three times the risk of cardiovascular events, be it myocardial infarction or stroke.[1] Thus, early and aggressive correction of the dyslipidaemia is imperative to ameliorate the cardiovascular risk. Once diabetes has developed in any individual, this confers a risk equivalent to that of coronary disease.[2] Patients with cardiovascular disease and/or diabetes should receive lipid modifying therapy early as per evidence-based guidelines.[10] It should be stressed however that these treatment levels are guidelines only and, as the body of evidence grows, even lower levels should be used to initiate drug therapy, and to aim for when monitoring therapy (Table 2). Although the benefits of lifestyle measures, especially of diet and weight loss, have been discussed, these are notoriously difficult to achieve and maintain, and drug therapy should not be withheld in this high-risk group of patients.

The choice of lipid lowering therapy essentially lies between the fibrates and the statins (Table 3). Traditionally, on the basis of reasonable evidence, the fibrates have been the agent of choice to lower triglyceride levels and elevate HDL levels, and in so doing, achieve some clinical benefit.[11] They result in a modest reduction in LDL cholesterol, less than can be achieved with a statin. There is an increasing amount of evidence that statins reduce cardiovascular events in high-risk patients[12] (such as the metabolic syndrome patients) and this benefit appears to be partly due to 'non-lipid-lowering' effects such as improving endothelial function and an anti-inflammatory effect. Interestingly the benefit of treatment with simvastatin in one of the largest trials undertaken suggests equal benefit regardless of baseline HDL or triglyceride levels.[12] Although this might imply that all high-risk patients be treated with simvastatin, it is still a little unclear as to the relative importance/risk of the individual lipid components. It is probably too early to do away with the fibrates as first line therapy in some dyslipidaemic patients with mildly elevated total cholesterol.

It should also not be forgotten that a number of patients will not be able to tolerate statins and would benefit, albeit to a lesser degree, with fibrate therapy.

Figure 1.

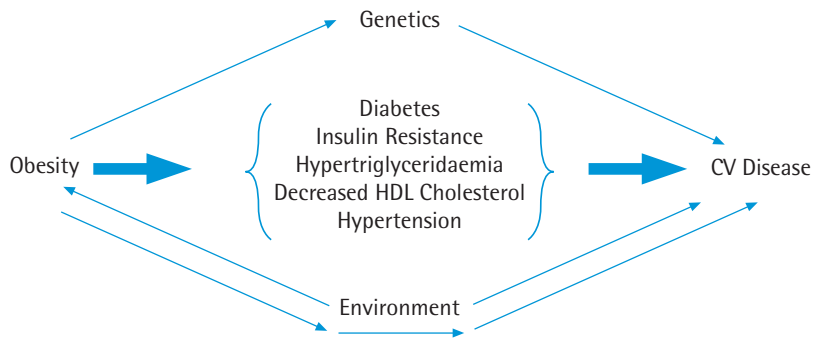

Table 2. Optimum lipid levels

Total Cholesterol	< 4.0 mmol/l
LDL Cholesterol	< 2.5 mmol/l
HDL Cholesterol	> 1.0 mmol/l
TC:HDL ratio	< 4.5
Triglycerides	< 2.0 mmol/l

Table 3. Effects of lipid-lowering drugs on lipids

Drug group	Examples	Lipid effects
HMG Co-A Reductase Inhibitors (Statins)	Simvastatin Atorvastatin Pravastatin	↓↓LDL, ↓TG, ↑HDL
Fibric Acid Derivatives (Fibrates)	Bezafibrate Gemfibrozil	↓LDL, ↓↓ TG, ↑HDL
Nicotinic Acid	Nicotinic acid	↓LDL, ↓↓TG, ↑HDL
Bile-acid binding resins	Cholestyramine	↓LDL

There also remains a small group of patients whose lipid profile cannot be optimised by a statin alone and may require combination therapy, usually with a fibrate. However, such combination therapy needs to be monitored closely because of the small risk of increased muscle or liver toxicity.

Other types of lipid modifying therapies such as nicotinic acid and cholestyramine are seldom used, but may be of benefit in drug intolerant or resistant cases.

A promising new treatment for type 2 diabetes (and possibly impaired glucose tolerance), the glitazones, may help improve the dyslipidaemia in these patients, by increasing HDL and reducing small dense LDL.[15]

Concurrent antihypertensive therapy may affect the lipid profile of any patient. Historically, beta-blockers have received bad press due to the tendency of most agents to slightly increase LDL and/or reduce HDL. This effect has not been shown to negate the cardioprotective benefit of these agents in patients with established ischaemic heart disease, or heart failure. Patients in the latter group are now being prescribed beta-blockers in increasing numbers and it is important that such patients do not miss out on proven life-saving therapies because of such concerns.[13] The patient's dyslipidaemia should be managed with appropriate proven therapies as above.

Similarly, there is overwhelming evidence for the cardioprotective effects of ACE inhibitors in not only diabetic patients, but also those at high risk of developing cardiovascular disease and/or diabetes.[14] Thus, patients with the metabolic syndrome should be prime candidates to receive ACE inhibitors whether hypertensive or not.

Conclusions

The patient with the metabolic syndrome is at high risk of subsequent cardiovascular events. Risk reduction needs to start early, be aggressive and ongoing. Weight loss is imperative but drug therapy of dyslipidaemia is usually required and (based on good evidence) considered essential if diabetes is present.

Evidence for cardiovascular risk reduction in such high-risk patients favours prescription of statins and ACE inhibitors.

Key Points

- Patients with the metabolic syndrome have a cluster of cardiovascular risk factors that place them at extremely increased risk of coronary heart disease, stroke and consequently, reduced survival.
- Even modest weight loss reduces the development of diabetes, increases insulin sensitivity, improves the dyslipidaemic profile and improves blood pressure control.
- A promising new treatment for type 2 diabetes (and possibly impaired glucose tolerance), the glitazones, may help improve the dyslipidaemia in these patients, by increasing HDL and reducing small dense LDL.
- Patients with the metabolic syndrome should be prime candidates to receive ACE inhibitors whether hypertensive or not.

References

1. Groop L. The dysmetabolic syndrome. J Intern Med 2001; 250:105–120.
2. Dyslididaemia Advisory Group. NHF clinical guidelines for the assessment and management of dyslipidaemia. NZ Med J 1996; 109:224–32.
3. Scott R. Emerging risk factors for cardiovascular disease. New Ethicals J Nov 2001; 13–18.
4. Bainton D, Miller NE, Bolton CH, Yarnell JW, Sweetnam PM, Baker IA, Lewis B, Elwood PC. Plasma TG and HDL-cholesterol as predictors of ischaemic heart disease in British men. Br Heart J 1992; 68:60–66.
5. Goldstein D. Beneficial health effects of modest weight loss. Int J Obesity 1992; 16:397–415.
6. Wood P. The effects on plasma lipoproteins of a prudent weight-reducing diet, with or without exercise, in overweight men and women. NEJM 1991; 325:461–6.
7. Scandinavian Simvastatin Survival Study (4S). Randomised trial of cholesterol lowering in 4 444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S) Lancet 1994; 344:1383–9.
8. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. West of Scotland coronary prevention study. NEJM 1995; 333:1301–7.
9. Lipid Research Clinics Programme (LIPD trial). JAMA 1984; 251:351–64 and 365–74. NEJM 1998; 339:1349–57.
10. National Heart Foundation. Guidelines for management of dyslipidaemia 2002.
11. Manninen V, Elo MO, Frick MH, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, et al. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. JAMA.1988 Aug 5; 260(5):641–51.
12. Heart Protection Study Group. MRC/BHF heart protection study of cholesterol lowering in 20 536 high-risk individuals. Lancet, July 6, 2002; 360:7–22.
13. MERIT-HF Study Group. Metoprolol CR/XL randomised intervention trial in congestive heart failure. Lancet 1999; 353:2001–07.
14. HOPE Investigators. The heart outcomes prevention evaluation study. NEJM 2000; 342:154–60.
15. Rosiglitazone in type 2 diabetes mellitus. Adis Drug Evaluation, 2002.