Management of the hyperlipidaemic patient

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The evidence from epidemiology, controlled trials, clinical findings in genetic hyperlipidaemias, animal studies and cell biology is consistent in indicating that hypercholesterolaemia is causally related to coronary heart disease (CHD) [1,2]. Hence, treatment of elevated cholesterol levels is indicated to reduce the risk of *de novo* development of CHD [3]. Such treatment, for example by nicotinic acid, also decreases the incidence of myocardial infarction in patients who already have overt CHD [4], albeit to only a modest extent, appears to retard progression of peripheral [5] and coronary atherosclerosis [6] and leads to regression of atherosclerotic lesions in laboratory animals [7, 8].

Despite earlier controversy, recent analyses have re-established that hypertriglyceridaemia is a risk factor for CHD in persons with low levels of high density-lipoprotein (HDL) cholesterol [9]. Since supportive evidence from other sources is lacking, there is a less rigorous case for treatment of elevated triglyceride levels. However, there is reason to believe that the smaller triglyceride-bearing lipoprotein particles of plasma (eg intermediate density lipoprotein (IDL)) are, like the cholesterol-rich low density lipoprotein (LDL) atherogenic in man and in animals [10]. A further clear indication for the treatment of marked hypertriglyceridaemia is the risk of acute pancreatitis when levels exceed about 10 mmol/l [11]. Hypertriglyceridaemia commonly results from underlying causes that require correction in their own right, notably obesity, over-indulgence in alcohol and diabetes mellitus.

Approach to the hyperlipidaemic patient

Four aspects of the clinical examination may be referred to. The frequency and age of presentation of CHD in first degree relatives should be noted, as clues to the presence of a major genetic hyperlipidaemia. Tendon and cutaneous xanthomas should be sought as part of routine examination. The presence of further CHD risk factors should be noted, particularly cigarette use, hypertension, diabetes mellitus and use of oral contraceptive drugs. Other common causes of secondary hyperlipidaemia are hypothyroidism, diuretic drugs, retinoids and renal and hepatic disease. Their presence offers a therapeutic opportunity.

Two baseline cholesterol and triglyceride measurements, in the fasted state, are required, and HDL cholesterol should be measured at least once. HDL cholesterol measurement helps to refine the assessment of CHD risk; and it is necessary to recognise mild hypercholesterolaemia due to markedly elevated HDL levels (>2 mmol/l), a condition not requiring therapy.

Lipid levels requiring therapy

The bases for defining desirable levels of plasma lipids have recently been revised [1,12,13]. In a study of 361,000 men [14], CHD incidence was least in those with cholesterol levels below 5 mmol/l; it increased moderately steeply and linearly with levels in the range 5–6.5 mmol/l, then rose much more steeply with levels exceeding 6.5 mmol/l. The majority of patients with major genetic lipoprotein disorders conferring a very high risk of CHD have levels exceeding 8 mmol/l [11].

Since the cholesterol-CHD relationship is continuous and graded, the intensity of lipid-lowering therapy should similarly be graded. The most vigorous therapy is appropriate for those with the highest levels (>6.5 mmol/l) while more limited dietary counselling is suitable for the larger number of patients found to have mild hypercholesterolaemia (5–6.5 mmol/l).

These cut-off points are not absolute; other factors also modulate the choice of therapy. More vigorous treatment is justified by high overall risk of CHD (taking into account family history and additional risk factors), by younger age, by early-onset CHD and, in patients who have undergone coronary artery bypass grafting (CABG), by the need to preserve graft patency. Hence, it is the patient who is treated, and not the laboratory report. Table 1 illustrates this graded approach to therapy modified from the recent report by the European Atherosclerosis Society [13].

There is general agreement that the goal of therapy should be to attain plasma cholesterol levels as close to 5 mmol/l as possible [12,13], corresponding to LDL cholesterol levels of <3–3.5 mmol/l.

Dietary treatment of hyperlipidaemia

Diet is the mainstay of treatment for all primary hyperlipidaemias, although drug therapy is additionally necessary in a minority of patients.

Weight control in the overweight patient is the simplest and one of the most effective measures for reducing elevated triglyceride and cholesterol levels, the improvement persisting after weight reduction is completed. The

high risk of CHD in obesity is mediated in part by its association with hyperlipidaemia and low levels of HDL cholesterol, with hypertension and with glucose intolerance, all of which are ameliorated by weight reduction. Obesity, particularly of truncal distribution, is also a risk factor independent of these associations.

Even moderate weight reduction is followed in most patients by lowered blood lipid levels; but where attainable the goal is to achieve a weight-for-height in the middle of the desirable range, ie corresponding to body mass index 22–23 [15]. Reduction of obesity also improves responsiveness to lipid-lowering drugs.

A target weight should be agreed with the patient, who should understand that a loss of 0.5–1 kg per week is the desirable rate. The duration of hypocaloric dieting can be approximately estimated. Daily exercise appropriate to the patient's age, cardiorespiratory status and fitness is of value. The patient should be seen as frequently as possible to enhance motivation.

The lipid-lowering diet is prescribed for indefinite use; it may be isocaloric, or may initially be combined with a reducing regime during a period of weight loss, if required. The several individual changes of nutrient intake have additive effects on plasma lipid levels [16]. They comprise:

1. An increased consumption of foods providing complex carbohydrate and soluble forms of fibre; these include cereal products (bread, oats-based breakfast cereals), root vegetables, legumes and leafy vegetables, rice and fruit. A three-fold increase in soluble fibre intake is desirable.

2. Reduction in the use of foods with high saturated fat content. Such foods are often, but not always, of animal origin. Their major fatty acids are palmitic acid, which is saturated, and oleic acid, which is mono-unsaturated. The intake of saturated fatty acids is reduced to about half of that in a typical British diet, ie to less than 10 per cent of food energy. Decreased use of such foods brings the total fat intake from 40 to less than 30 per cent of energy in the diet as initially prescribed; but poor response may be overcome in some patients by a further reduction of total fat to 20–25 per cent of energy and of saturated fatty acids to 5–7 per cent of energy. Further reduction is unacceptable to many patients. Important sources of saturated fatty acids include butter, hard margarine, cream, whole milk, full fat cheeses, red meats except for the very lean cuts now becoming available, baked goods, many convenience foods and shortening.

3. Reduction in dietary cholesterol to 200 mg/day (and for hyporesponders, subsequently to 100 mg/day) since intake of cholesterol is a significant determinant of IDL cholesterol levels. The provisions under paragraph (2) lessen cholesterol intake; other cholesterol-containing foods that need to be restricted are egg yolk, liver and other offal and crustacean shellfish; by removing poultry and fish skin the content of cholesterol in these foods is decreased. Molluscs (mussels, oysters) contain little or no cholesterol.

4. Increased use of fish, turkey, chicken, veal and game, all high-protein foods that are low in saturated fatty acids.

Table 1. The graded management of hyperlipidaemia.

Lipid levels (mmol/l)	
Cholesterol 5–6.5	Take overall risk, cardiovascular status into account. Emphasise need for dietary changes as recommended to whole population, and for weight control and avoidance of smoking; exceptionally, more stringent diet and/or medication indicated.
Cholesterol 6.5–7.8	Take age, overall risk, cardiovascular status into account. Prescribe formal lipid-lowering diet, with energy restriction if overweight; monitor response and re-emphasise diet as necessary. Consider adding drug therapy if response persistently inadequate, particularly in young patients at high CHD risk
Cholesterol > 7.8	Full investigation is required, for underlying causes and for characterising the lipoprotein disorder. Prescribe formal lipid lowering diet with energy restriction if overweight; monitor response. Provide appropriate drug therapy for those with inadequate diet response; continue to monitor response.
Triglyceride 2.3–5.6	Identify and deal with underlying causes. Energy restriction if overweight. Lipid-lowering diet. Exceptionally, triglyceride-lowering drug therapy for non-responders at very high risk.
Triglyceride > 5.6	As above, but drug therapy more commonly required especially if pancreatitis has occurred.
Combined hyperlipidaemia (cholesterol > 6.5 and triglyceride > 2.3)	Consider possible diagnosis of remnant hyperlipoproteinaemia or familial combined hyperlipidaemia. Dietary management. Drug management for poor responders.

These, together with legumes such as beans and lentils, and low-fat milk products, become the major protein sources. Fatty fish are allowable as well as white fish, since they provide a class of polyunsaturated fatty acids that is especially effective in reducing serum triglyceride levels.

5. Increased use of skimmed and/or low-fat milk and its products.

6. Use of soft margarines based on polyunsaturated seed oils (corn, sunflower) as spreads, and of such oils and olive oil for cooking purposes. There is insufficient data to permit dogmatic recommendations on the optimal intake of polyunsaturated fatty acids (particularly linoleic acid) derived from seed oils, still less on that of fish oils or of oils providing mono-unsaturated fatty acids such as olive oil. The conventional view, that intake of seed oils should allow the intake of polyunsaturated fatty acids to equal but not exceed intake of saturated fatty acids, has much to commend it; a few comments on this aspect of the diet are apposite:

(a) uptake of linoleic acid-rich oils has increased several fold in the USA in the past 30 years, and is the main nutritional reason for the fall in average serum cholesterol levels in recent decades [17]. This secular reduction is associated with and may well have contributed to the declining mortality from and incidence of CHD in the USA [18]; non-cardiovascular diseases such as common cancers have shown no increase during this period.

(b) Dietary CHD prevention trials showing a reduction in CHD morbidity have all employed an increased polyunsaturated fat intake in partial substitution for saturated fats.

(c) Retrospective and prospective studies of adipose tissue and plasma fatty acid patterns (which reflect dietary intake) have shown an inverse relation between CHD and the percentage of dietary linoleic acid; no statistically significant relation has emerged between CHD and other fatty acids such as oleic acid or eicosapentanoic acid within populations.

With close compliance, marked reduction in serum cholesterol and triglyceride can be attained by such a diet [16] especially when a desirable body weight is already present or can be attained. However, there is a wide individual variation in response (possibly on a genetic basis); also patients with familial hypercholesterolaemia are relatively diet-resistant. Compliance is also variable. Reductions of cholesterol of 15–25 per cent, and of triglyceride by 20–40 per cent can usually be obtained [16]. Thus, dietary treatment should suffice in the great majority of patients with cholesterol levels up to 7–7.5 mmol/l and/or with triglyceride not exceeding 5–6 mmol/l. Compliance is best achieved by the combined efforts of doctor and dietitian. Dietary change is a gradual process; some authorities advise the introduction of only a proportion of the whole dietary 'package' at each session. Certainly several months should be allowed for achieving maximum dietary response.

The rare hypertriglyceridaemic disorder, the chylomicronaemia syndrome, is managed by a diet that differs from the above. Strict reduction in all natural fats, to 10–25 per cent dietary energy, is necessary to reduce the gross hypertriglyceridaemia sufficiently to avert pancreatitis. Moderate use of medium-chain triglyceride is advantageous.

Drug treatment of hyperlipidaemia

The indications for drug therapy of hyperlipidaemia are listed in Table 2. The great majority of patients with

Table 2. Indications for drug therapy of primary hyperlipidaemia.

Disorder	Purpose of drug therapy
Major genetic hyperlipidaemias	
Familial hypercholesterolaemia	Reduction of CHD risk or progression
Remnant ('Type III') hyperlipoproteinaemia	Reduction of CHD risk and peripheral vascular disease risk or progression
Familial endogenous hypertriglyceridaemia	Prevention of relapsing pancreatitis
Milder hyperlipidaemic states	Reduction of CHD risk or progression in patients judged to be at high risk of CHD, when assiduous attempts at dietary treatment have failed to achieve acceptable lipid levels.

heterozygous familial hypercholesterolaemia, remnant hyperlipoproteinaemia and familial hypertriglyceridaemia achieve acceptable control only when treated by diet together with medication. The use of drug treatment for 'common' ('polygenic') hypercholesterolaemia is less often indicated. In patients in whom the maximum effect of diet leaves serum cholesterol levels substantially higher than 5 mmol/l, and/or LDL cholesterol levels substantially above 3.5 mmol/l, and whose overall risk of CHD is judged to remain high, drug treatment may be appropriate. Additional factors favouring drug therapy are younger age and revascularisation procedures (CABG, angioplasty or peripheral vascular surgery).

Lipid-lowering drugs fall into two broad categories.

Group I drugs. Group I includes bile acid sequestrants (colestipol and cholestyramine), probucol and the new (not yet licensed) inhibitors of cholesterol synthesis, symvastatin and SQ31000; the major effect of these drugs is reduction of elevated serum cholesterol due to raised levels of LDL. Symvastatin also reduces triglyceride levels, which are increased by sequestrant drugs that are the present treatment of choice in familial hypercholesterolaemia. Of currently available drugs, the bile acid sequestrants are the most effective single treatment for marked hypercholesterolaemia, and there is good evidence of their safety. The usual dosage is 2–3 sachets twice daily with meals. Unfortunately, they are not easy to use, having gastrointestinal side effects. With experience, reasonable compliance can be achieved in most patients. These drugs are also remarkably expensive. Absorption of other drugs may be impeded.

Many patients with familial hypercholesterolaemia do not respond adequately to diet and the maximum tolerated dose of a sequestrant drug. The most effective available drug for combination therapy is gemfibrozil, and good results have been obtained with nicotinic acid, bezafibrate and probucol.

Probucol is more readily accepted by patients. It is less

effective than sequestrants, with which it shares gastrointestinal side effects; it is also far less expensive. Its cholesterol-lowering effect results from a decrease in levels of both LDL and HDL; since the former is the desired effect it is essential to monitor levels of LDL cholesterol during therapy.

The cholesterol synthesis inhibitors promise a dramatic improvement in our ability to manage hypercholesterolaemia, though fuller long-term studies must become available before their use is justified.

Group II drugs. Group II hypolipidaemic drugs have more general effects on the lipoprotein system. They produce greater reduction in triglyceride than cholesterol, reducing very-low density lipoprotein and IDL and increasing HDL. In hypertriglyceridaemic states they tend to increase LDL levels (which are often initially low). In pure hypercholesterolaemia they have a moderate LDL-lowering effect when used alone, but this is additive with the effect of Group I drugs; the differing modes of action often result in very effective two-drug treatment.

Group II drugs are used as monotherapy in remnant ('Type III') hyperlipoproteinaemia, in which they are highly effective, and in familial endogenous hypertriglyceridaemia when triglyceride levels persist above 5 mmol/l, despite dietary treatment and attention to underlying causes.

Group II comprises clofibrate and the related drugs gemfibrozil and bezafibrate, and nicotinic acid used in pharmacological dosage (3–6 g/day); the fish oil preparation Maxepa may be included in this group since its use in high dosage (15–30 g/day) is particularly effective in familial hypertriglyceridaemia.

Though nicotinic acid has been shown to reduce CHD recurrences, it is a difficult drug to use; it is largely prescribed in specialised centres. Flushing with initial use, dyspepsia, hyperuricaemia and abnormal liver function are the most prominent problems. Of the fibrate family of drugs, clofibrate has been most extensively studied. Untoward effects include dyspepsia and increased risk of cholesterol gallstones, and in one of the two major trials there was an increase in non-cardiovascular mortality. All fibrate drugs potentiate the effect of warfarin and occasionally cause impotence and abnormalities of liver function. It is not certain whether newer fibrate drugs promote gallstone formation, but in a large-scale study of gemfibrozil the rate of appearance of new asymptomatic stones was probably no greater than in the untreated population. Fish oils have yet to undergo large-scale, long-term scrutiny for untoward effects. Patients should be monitored for any marked increase in LDL levels. Highly unsaturated fatty acids are prone to lipid peroxidation, which can lead to gross pathology in adipose tissue and myocardium in animals; but the encapsulated preparation Maxepa is protected against peroxidation by the addition of alpha-tocopherol.

The selective use of lipid-lowering drugs can reduce the risk of CHD and the progression of atherosclerosis. Since the benefit is mediated by lipid reduction, the ongoing lipid response of the patient must be monitored, and it is fruitless to continue therapy that is ineffective. Fortunately the majority of hyperlipidaemic patients can be improved by judicious treatment with currently available drugs; compounds now under investigation promise a striking improvement in effectiveness and tolerability.

References

1. Blackburn, H., Lewis, B., Wissler, R. W. and Wynder, E. L. (1979) *Preventive Medicine*, **8**, 609.
2. Mann, J. I. (1987) *Lipid Review*, **1**, 25.
3. Joint Working Party of Royal College of Physicians and British Cardiac Society (1976) *Journal of the Royal College of Physicians*, **10**, 213.
4. Coronary Drug Project Research Group (1986) *Journal of the American College of Cardiology*, **8**, 1245.
5. Duffield, R. G. M., Lewis, B., Miller, N. E. *et al.* (1983) *Lancet*, **ii**, 639.
6. Brensike, J. F., Levy, R. I, Kelsey, S. F. *et al.* (1984) *Circulation*, **69**, 313.
7. Wagner, W. D., St Clair, R. W. and Clarkson, T. B. (1980) *American Journal of Pathology*, **100**, 633.
8. La Ville, A., Woolf, N. and Lewis, B. (In preparation.) Prevention of atherosclerosis in genetically-hyperlipidaemic rabbits by inhibition of cholesterol synthesis.
9. Castelli, W. B. (1986) *American Heart Journal*, **112**, 432.
10. Steiner, G., Schwartz, L., Shumak, S. and Poapst, M. (1987) *Circulation*, **75**, 124.
11. Lewis, B. (1976) *The hyperlipidaemias: clinical and laboratory practice*. Oxford: Blackwell Scientific.
12. Steinberg, D. (chairman) (1985) Report of NIH Consensus Conference. *Journal of the American Medical Association*, **253**, 2080.
13. European Atherosclerosis Society (1987) Policy statement on prevention of coronary heart disease. *European Heart Journal*, **8**, 77.
14. Martin, M. J., Hulley, S. B., Browner, W. S., Kulley, L. H. and Wentworth, D. (1986) *Lancet*, **ii**, 933.
15. Royal College of Physicians (1983) Report on obesity. *Journal of the Royal College of Physicians*, **17**, 3.
16. Lewis, B., Hammett, F., Katan, M. B. *et al.* (1981) *Lancet*, **ii**, 1310.
17. National Center for Health Statistics—NHCBI Collaborative Lipid Group (1987) *Journal of the American Medical Association*, **257**, 937.
18. Havlik, R. J. and Feinleib, M. (eds) (1979) *Proceedings of the conference on the decline in coronary heart disease mortality*. Bethesda: US Department of Health, Education and Welfare.