Dietary management of familial hyperlipidaemias

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The rising incidence of coronary heart disease (CHD) in affluent populations has focused attention onto predisposing risk factors, among them high blood levels of cholesterol and triglyceride. In some inherited disorders characterized by hyperlipidaemia the risk of developing CHD is extremely high, and attempts at preventing CHD should in the main concentrate on these individuals in view of the magnitude of their risk, although some advice on a prudent diet and life style may be offered to the general population.

The lipids in the blood are transported in combination as lipoproteins, and the familial disorders are classified according to which lipoprotein is present in excess. The common inherited disorders predisposing to CHD are familial hypercholesterolaemia (familial hyperbetalipoproteinaemia, Type IIa), familial hypertriglyceridaemia (familial hyperprebetalipoproteinaemia, Type IV), and familial combined hyperlipidaemia (Type IIb). Familial hyperchylomicronaemia (Type I) apparently does not predispose to CHD, and will be considered separately.

Familial hypercholesterolaemia (FH)

FH, a dominantly inherited condition is the commonest familial lipoprotein disorder; in fact it is one of the commonest of all inherited conditions, having an incidence in the population of 0·3–0·5%. Individuals with the disorder have a high risk of CHD in early adult life; 50% of males will have had a coronary heart attack by the age of 50 years (Slack, 1969); for the females the risk is less, the comparable figure being 12%, but nevertheless considerably greater than for individuals who do not have the disorder. The risk of CHD in an individual with FH is much greater than the risk of CHD in an individual with the same plasma cholesterol and betalipoprotein concentration due to other causes.

Although tendon and skin xanthomata, and corneal arcus may occur in patients with FH, clinical features of the disease are inconstant, and diagnosis is established by measurement of plasma lipids and lipoproteins in the relatives of individuals known to have FH, or to have had premature CHD. The finding of raised plasma cholesterol and betalipoprotein concentrations, and the demonstration of familial occurrence establishes the diagnosis. Biochemical evidence of FH is always present in childhood, but diagnosis may be difficult during the first year of life (Darmady *et al.* 1972).

The aim of the treatment in FH is to lower the plasma cholesterol (and betalipoprotein) concentration to within the normal range; it is hoped, but not yet

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confirmed, that normalization of the plasma lipids will reduce the incidence of premature CHD. As it is unlikely that atherosclerosis is fully reversible the earlier in life that FH is diagnosed and treatment initiated, the more likely it is to be effective.

Apart from treatment to lower plasma cholesterol, special attention should be paid to other risk factors in patients with FH. Combinations of risk factors for CHD summate in their effect, so in patients with FH special attention should be paid to other risk factors apart from hypercholesterolaemia. Patients should be warned of the risks of smoking and taking the contraceptive pill, and should be encouraged to pursue an active life style. Blood pressure should be measured regularly and any hypertension detected should be treated, and obesity should be prevented.

Dietary treatment of hypercholesterolaemia has in the past concentrated on altering the amount and type of dietary fat. Alternative dietary approaches to cholesterol lowering have been advocated, including a vegan diet (Sanders *et al.* 1978), and increasing intakes of yoghurt (Hepner *et al.* 1979), soybean protein (Carroll *et al.* 1978) and guar gum (Jenkins *et al.* 1979), but these have not yet been evaluated in patients with FH.

Dietary fat modification to lower plasma cholesterol involves consideration of three aspects; decreasing the amount of saturated fat, increasing the polyunsaturated fat, and reducing dietary cholesterol intake. Strict restriction of ordinary (mainly saturated) dietary fat intake is needed to cause significant lowering of plasma cholesterol in FH. Such diets tend to be monotonous and unattractive. Furthermore, if the diet remains isoenergetic in spite of reduction in the total fat intake, there will be increased carbohydrate intake which may give rise to hypertriglyceridaemia in some individuals.

Polyunsaturated fats have some hypocholesterolaemic action. When they are used in partial substitution for dietary fat they exert benefit not only by their own hypocholesterolaemic effect, but also by lowering saturated fat intake, and by improving palatability, and thus compliance. By utilizing maize or sunflower oils in cooking, and commercially available polyunsaturated margarine and cheese, an attractive diet can be devised.

The amount of cholesterol in the diet has received considerable attention. The concensus of current opinion is that the dietary cholesterol content has only a slight effect on serum cholesterol concentration in most individuals and attention to dietary cholesterol content alone achieves little in reducing serum cholesterol concentration. The major sources of dietary cholesterol are eggs and offal, and as eggs have a high fat content a diet low in animal fat is likely to cause a reduction in dietary cholesterol.

Most currently recommended diets for FH are similar to that recommended by the Inter-Society Commission for Heart Disease Resources (1970) which laid down these guidelines. (a) Energy intake to be adjusted to achieve and maintain optimal weight. (b) Less than 35% of total dietary energy to come from fat, with the use in moderation of unsaturated fats within this limit so that only about 10%

of dietary energy comes from saturated fat. (c) Reduction in dietary cholesterol to less than 300 mg/d. Utilizing diets constructed along these lines it is possible in the short term to lower plasma cholesterol in FH by about 20%, although there is wide variation between individuals (Segall *et al.* 1970; Kwiterovich *et al.* 1970; Schlierf *et al.* 1977; Glueck, Fallat & Tsang, 1973). Even with a significant reduction, plasma cholesterol concentrations remain above the normal range in many patients.

In the longer term, dietary treatment of FH is less successful (West *et al.* 1975; Schlierf *et al.* 1977). Compliance with the diet is difficult, especially if the individual eats away from home. In our own series only about 20% of children with FH maintained satisfactory cholesterol lowering with diet as the only form of treatment. Nevertheless, we feel dietary fat modification should be the first treatment tried in all patients with FH.

We have recently tried the effect of supplementing the diet with liquid safflower oil in a few children, taken as a medicine in a dose of 15 ml twice daily, in an attempt to increase their polyunsaturated fat intake. The mean pre-treatment plasma cholesterol level of 7·9 mmol/l was lowered to 7·3 mmol/l (−8%) by dietary management in four children. Continuation of the diet plus additional safflower oil reduced the level further to 6·3 mmol/l (−20%). Results are variable and it is too early to draw definite conclusions, but in some children there does seem to be benefit, at least in the short term.

If diet alone is insufficient to reduce the plasma cholesterol to within normal limits, or if compliance is poor, drug treatment may be needed. Cholestyramine, an anion exchange resin, is then usually the drug of choice, and usually the diet can be liberalized once the patient is established on the resin.

Familial hypertriglyceridaemia

This condition is due to elevated plasma concentrations of pre-betalipoprotein, which is synthesized in the liver for the transport of endogenously synthesized triglyceride. Familial hypertriglyceridaemia is inherited as a dominant condition but the disorder is only infrequently manifest in childhood. Furthermore, the type IV lipoprotein pattern is common in adults and in many does not appear to have a genetic background.

Endogenous hypertriglyceridaemia is often associated with obesity, and in such individuals the main aim of dietary therapy is to reduce body-weight to normal. If achieved, this usually leads to normalization of the plasma lipids. In forty children (mean age 13 years) with familial hypertriglyceridaemia (type IV), Glueck *et al.* (1977) report that a diet in which 20% of energy was derived from protein, 40% from carbohydrate and 40% from fat, with a polyunsaturated:saturated fat value of 1·5 resulted in normalization of serum triglyceride (below 1·58 mmol/l 140 mg/100 ml) in twenty-nine of the children during the first 6 months of treatment. In thirteen children treated for 8–12 months, mean triglyceride concentration decreased from 3·2 mmol/l (290 mg/100 ml) to 1·68 mmol/l

(149 mg/100 ml). In some patients reductions of dietary carbohydrate, particularly sucrose may be of marked benefit.

If dietary modifications are ineffective, drug therapy will probably be required, with clofibrate usually the drug of first choice.

Familial combined hyperlipidaemia (Type IIb)

In type IIb disorders there is both hypercholesterolaemia and hypertriglyceridaemia due to increased concentrations of both beta- and pre-beta-lipoproteins. Familial combined hypertriglyceridaemia has only been delineated as a separate condition relatively recently, and there is still some dispute about its mode of inheritance. In a study of the offspring of thirty-three families, Glueck, Fallat, Buncher *et al.* (1973) investigated thirty-five children under 13 years of age, of whom sixteen (45%) were found to have some form of lipid abnormality. However, only three had a type IIb pattern and the remainder had either a type IIa pattern (ten) or a type IV pattern (three).

Initial treatment using a modified fat diet as for FH, together with weight reduction if indicated, will usually result in improvement in the hyperlipidaemia, but long-term dietary management is only acceptable to a minority of patients.

Familial hyperchylomicronaemia

This recessive condition is due to a deficiency of the enzyme lipoprotein lipase. Chylomicrons are lipoprotein macromolecules formed in the intestinal absorptive cell, and they transport dietary triglycerides and cholesterol into the lymph. When the chylomicrons reach the capillaries of adipose tissue they are exposed to the enzyme lipoprotein lipase which is activated by a surface protein on the chylomicrons. This results in the hydrolysis of the contained triglyceride, and the free fatty acids thus liberated enter the fat cell. Absence of lipoprotein lipase leads to a build up of chylomicrons in the blood, and there is deposition of triglyceride in the skin as eruptive xanthomata, and in the fundi (lipaemia retinalis). Episodes of abdominal pain frequently occur, and there may be hepatosplenomegaly.

Although plasma triglyceride levels may be very high, and plasma cholesterol is usually also raised, familial hyperchylomicronaemia apparently does not predispose to CHD, and the aim of treatment is therefore the amelioration and prevention of symptoms rather than an attempt to normalize the plasma lipids. When the patient is first seen, and the initial diagnosis made, it is usually because of eruptive xanthomata, or abdominal pain. The diagnosis may first be suspected from the turbid appearance of the plasma, which on standing separates into a creamy layer above and a clear infranatant.

The institution of a virtually fat-free diet leads to gradual clearing of the chylomicrons from the plasma over a few days, and a concommittant improvement in symptoms. Once symptoms have been abolished some fat may be re-introduced into the diet. Individual patients vary widely in their fat tolerance, and one titrates diet fat against plasma lipids and clinical features until the maximum amount of dietary fat that can be tolerated is established. There appears to be little increase in

diet fat tolerance with age, and patients will probably need to remain on quite severe fat restriction for life. Medium chain triglycerides (MCT), as they are absorbed via the portal system and not as chylomicrons, can be useful diet supplements to add variety and fat energy to the diet.

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