Can nutrition favourably affect serum lipids?

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Many short- and long-term studies have looked at lipid-lowering in man, and some have looked at vascular disease. In some studies multiple interventions have been made, making the effects of the diet element difficult to interpret. Altering one element will alter, at the same rate, one or more other elements in the diet. In animal studies these elements can be more closely controlled, but will not be considered in great detail in the present paper.

The question 'Can nutrition favourably affect serum lipids?' can be interpreted in a narrow sense, but perhaps returning extreme values of serum lipids towards the average is not the only objective of treatment. Thus, when nutritional interventions are undertaken not just lipid-lowering should be considered, but also prevention of heart disease. It is the epidemic of macrovascular disease, and particularly coronary artery disease, that is of concern. There has been a considerable fall in ischaemic heart disease mortality in the USA of 3% per annum, with a fall of 40% from 1967 to 1983. Between 1952 and 1983 the incidence of stroke has fallen by 70%. Many alterations in lifestyle have occurred and the precise reasons for this fall are not apparent. From the point of view of lipids and nutrition it was in 1963 that the American Heart Association advised a reduction in fat. The egg intake has fallen by 35%. The intake of polyunsaturated vegetable oil, which was less than 2% of energy in 1950, is now 7%.

In contrast to the USA, the failure to alter the increased rates of coronary artery disease in the UK in the 1970s may be linked to the increasing percentage of energy obtained from fat, and largely from saturated fat. Fat intake increased from 39·8 to 51·4 kg/person per year from 1900 to 1957. In the next 15 years fat intake, as a percentage of total energy, had increased from 36 to 42%. Keys (1970) showed in eighteen male populations in seven countries a positive linear correlation (r +0·89) between serum cholesterol and the percentage of energy obtained from saturated fat, and others have had similar findings (McGill, 1968; Hankin *et al.* 1970).

Concentrations of serum lipids vary widely within, and especially between, communities. For example, the mean serum cholesterol in eastern Finland is 6·95 mmol/l, 2·5 times higher than that in the Pacific islands (Luyken & Jansen, 1960; Keys, 1967). Serum triglyceride concentrations also vary geographically, tending to follow the variation in serum cholesterol (Bang *et al.* 1971; Lewis *et al.* 1974*a*,*b*). Migrating populations develop lipid levels corresponding to those in the host country (Gordon, 1957; Toor *et al.* 1960; Epstein, 1967), suggesting that environmental factors may be important, and may include diet. The prevalence of hypercholesterolaemia (greater than 6·7 mmol/l) in Japanese living in Japan was 3·2% but rose to 12·4 and 16·3% in Japanese living in Hawaii and California respectively (Gordon, 1957).

Fat intake correlates well with serum cholesterol levels in epidemiological studies across communities (Keys, 1967, 1970; McGill, 1968). This is only occasionally found within communities (Easty, 1970), where a more homogeneous overall diet intake has less effect than variation in physical activity, genetic and psychosocial factors. Various dietary constituents do, however, affect serum lipids, and many studies of dietary manipulation support this.

Dietary cholesterol

The presence of compensatory mechanisms render man, unlike certain laboratory animals, relatively unresponsive to changes in dietary cholesterol (Keys *et al.* 1965; Connor *et al.* 1964). Wide variation between individuals in responsiveness to dietary cholesterol (Keys *et al.* 1956) render it difficult to detect statistically significant changes. With a very large dietary intake of cholesterol, levels of serum cholesterol may increase markedly, by 2 mmol/l. However, the variations in cholesterol intake commonly found in Western communities would account for a change of as little as 0·2–0·3 mmol/l (Keys *et al.* 1965). Reductions in intake of foods high in saturated fat, with reduction in a few other foods, will reduce cholesterol intake considerably, from about 800 mg/d to about 300 mg/d.

Dietary saturated and unsaturated fat

Vegetarian communities have been found to have low serum cholesterol levels (Groen *et al.* 1952; Kinsell *et al.* 1952; Jolliffe, 1961), as have hypertensive subjects treated with a low-fat, rice diet (Keys, 1950).

Serum lipid levels are influenced by the quantity and nature of dietary fatty acids, by chain length, stereoisomeric differences and degree of unsaturation. Fatty acids of C_{10} chain length or less, or C_{18} or more, have little effect. Lauric, myristic and palmitic acids (C_{12}, C_{14} and C_{16} respectively) increase cholesterol levels, the last being the most important in human diets (Hashim *et al.* 1960; Grande *et al.* 1970).

Dietary saturated fat tends to increase cholesterol levels compared with an unsaturated fat diet, and this rise can be reversed by supplementation with polyunsaturated fat (Ahrens *et al.* 1955; Bronte-Stewart *et al.* 1956). On an adequate-energy diet the replacement of saturated fat by polyunsaturated fat will lower serum lipids, in normal and hyperlipidaemic subjects. Cholesterol reductions of about 15% occur within 2 weeks, while the triglyceride reductions are larger. While the diet continues the effect is maintained. Where a polyunsaturated-fat supplement is added to an otherwise-unaltered diet, with a consequent increase in energy intake, a similar effect is still seen (Lewis, 1976).

Fat-modified diets in man and animals appear to increase conversion of cholesterol to bile acids, and increase faecal bile acid excretion.

Dietary carbohydrate and fibre

With an isoenergetic diet a major reduction in total fat intake to 5 g/d, with a compensatory increase in carbohydrate, profoundly affects serum lipids in the short term. Cholesterol falls by about 30%, while there may be a temporary rise in serum triglycerides. This effect may be related to a high refined carbohydrate intake, while high fibre intake may be beneficial.

Three phases of triglyceride response to a high carbohydrate intake may be detected. Initially triglyceride levels fall when carbohydrate is fed or injected. Carbohydrate (and insulin), by decreasing non-esterified fatty acid turnover, decrease the supply of non-esterified fatty acids to the liver for re-esterification to triglyceride, and hence to very-low-density lipoproteins (VLDL). There is also increased peripheral uptake of plasma triglyceride possibly due to induction of lipoprotein lipase (*EC* 3.1.1.34). The second phase, of carbohydrate-induced hypertriglyceridaemia, commences at about 2 d and is maximum at 2–3 weeks, being more pronounced in men and postmenopausal women. Those with higher basal triglyceride levels tend to show a proportionately larger response, while energy restriction tends to limit the effect. A third phase of adaptation

occurs in the majority of individuals, with a fall in serum triglyceride concentrations over 1–4 months. Mancini *et al.* (1973) showed that the magnitude of the hypertriglyceridaemic second-phase response to high carbohydrate intake varied considerably, but was about 2·5-fold.

The findings on comparing different carbohydrate sources are conflicting, but there may be relatively little difference between sucrose and starch intake. High fibre intake may not affect serum lipids greatly, if insoluble fibre such as cellulose or lignin is considered. Bagasse, a lignin-rich fibre source, was shown not to change significantly the serum concentrations of cholesterol or triglyceride, although intestinal transit was increased and faecal bile acid and fat excretion rose (Walters *et al.* 1957). Other studies have indicated falls in serum lipids on soluble gel-forming fibre-containing diets (Jenkins *et al.* 1975; Kay, 1976).

Dietary alcohol

Zieve (1958) described a syndrome in alcoholics of gross hypertriglyceridaemia with fatty infiltration of the liver and haemolysis, but the full syndrome is rare. However, alcohol is often associated with moderate or severe hypertriglyceridaemia, and is second only to diabetes as a cause of secondary hyperlipidaemia. Withdrawal of alcohol may lead to normalization of lipid levels, unless there is an underlying familial hypertriglyceridaemia. Effects of alcohol on clearance of serum triglycerides may be modest, and the major effect of alcohol is to increase VLDL synthesis. Alcohol oxidation is mediated by alcohol dehydrogenase (*EC* 1.1.1.1) and is NAD-linked. A resulting rise in NADH:NAD ratio would decrease fatty acid oxidation in the liver and increase fatty acid availability for triglyceride synthesis (Lieber & Schmid, 1961; Fex & Olivecrona, 1969).

In the USA alcohol contributes 5% of energy intake and for those Americans admitting to any alcohol intake it supplies 10% of total energy. While the studies at Framingham, USA, show alcohol to be a powerful univariate protective factor against coronary artery disease, the effects of alcohol in the general population may be different from those in susceptible hyperlipidaemic subjects.

Energy intake

Adiposity and VLDL-triglyceride concentrations may be positively related within populations (Lewis *et al.* 1974*a,b*), although not between populations. Hyperlipidaemia may be associated with insulin resistance, and the degree of central truncal adiposity. An evanescent hypertriglyceridaemia and a more-persistent moderate hypercholesterolaemia may follow marked overfeeding (Olefsky *et al.* 1975).

During negative energy balance serum triglycerides, and to a lesser extent serum cholesterol, fall. If patients are then maintained on an adequate-energy diet at a leaner weight, then the concentrations of serum triglycerides may remain lower, suggesting that both adipose tissue mass and energy balance are important.

Dietary protein

The possible effects of different amounts and sources of protein have been less clearly studied in man, but may affect serum lipids. One controlled study of effects of different protein and fibre sources was carried out by Kritchevsky (1980) in rabbits fed on a hypercholesterolaemic diet for 10 months. The diet contained (g/kg): 400 sucrose, 250 protein, 150 fibre, 140 coconut oil, 50 salt mix, 10 vitamin mix. Casein was more hyperlipidaemic than soya-bean protein, while lower concentrations of serum cholesterol and triglycerides were seen with lucerne (*Medicago sativa*) compared with either

cellulose or wheat straw. These rabbits were subsequently killed and the aortic arches and thoracic aortae examined for atheroma. Aortic changes were proportional to the changes in lipid levels, and related to the dietary manipulation.

Dietary treatment of various hyperlipidaemic states

Considering these various factors a simple plan for clinical management of the hyperlipidaemias can be put forward, involving first weight reduction towards the desirable weight-for-height. Second, total fat and particularly saturated fat should be reduced, with a partial-only replacement with polyunsaturated fats. This prudent diet may also include an increase in the amount of soluble fibre. This will control the majority of moderately hyperlipidaemic patients, drug therapy being needed in a minority.

The value of weight reduction as opposed to just fat reduction can be regularly demonstrated. Cholesterol and low-density-lipoprotein (LDL)-cholesterol will fall, as will triglycerides and VLDL-triglycerides. Falls in serum triglycerides should be associated with a rise in high-density-lipoprotein (HDL)-cholesterol.

Mancini *et al.* (1980) studied twelve type II hyperlipidaemic patients on an adequate-energy fat-modified diet. Energy from saturated fat was very considerably reduced to 5%, with polyunsaturated fats increased to 14% and a high polyunsaturated:saturated ratio was achieved; protein was consequently high. Cholesterol and LDL-cholesterol fell significantly by 15 and 21% respectively, although the reductions of about 35% in serum triglycerides and VLDL-triglycerides were not significant. In a similar study of sixteen type IV hyperlipidaemic subjects the reductions in triglycerides were greater than 50%. There was a fall in total serum cholesterol, and a rise in HDL-cholesterol. However, the LDL-cholesterol levels rose, probably partly reflecting increased catabolism of the VLDL.

In the rare type III hyperlipidaemia, chylomicron and VLDL remnants accumulate in some subjects homozygous for apolipoprotein E_2. This major isoform of apolipoprotein E differs by one cysteine–arginine substitution for apolipoprotein E_3, but has a greatly reduced affinity for the apoprotein E receptor. These patients, who are susceptible to premature macrovascular disease, have characteristic xanthomata which will disappear on therapy, with diet, weight loss and, if necessary, with a fibric acid derivative.

Diabetes mellitus is a common cause of secondary hyperlipidaemia. An early study of dietary manipulation in diabetes was that of Stone & Connor (1963). They reduced cholesterol from 900 mg/d to 100 mg/d and total fat from 42 to 20% of total energy intake. Saturated fat was reduced from 22 to 4%, while polyunsaturates were increased from 3 to 6%. Carbohydrate intake was increased from 41 to 64%, probably without much emphasis on fibre intake. In twenty-five controls there was no significant change in serum lipids, but over 1 year thirty-one experimental subjects maintained significant falls in cholesterol and triglycerides of 20 and 15% respectively.

Anderson & Ward (1978) studied ten male diabetics and were able to reduce their hypoglycaemic drug therapy on a high-carbohydrate, high-fibre diet. Blood glucose levels fell, but so did mean weights. Cholesterol and triglyceride levels fell during the initial acute 18 d ward treatment, and the triglyceride but not the cholesterol reductions were well maintained subsequently.

In a 1-year study, diabetics of stable weight showed improvement in lipid levels with diet and insulin treatment. Serum lipid levels fell, but levels of cholesterol in HDL and in HDL_2 rose. These improvements in lipid levels were maintained over 1 year (Reckless, 1984).

Dietary effects on ischaemic heart disease risk

Keys (1967, 1970) not only demonstrated a relation between saturated fat intake and serum cholesterol, but also showed that levels of serum cholesterol in populations were related to the risk of coronary death.

Because of the high prevalence of ischaemic heart disease in North Karelia, Finland, a programme to reduce this was instituted. Over 10 years from 1969 to 1979 heart disease rates fell by 24 and 51% in males and females respectively, twice as fast as overall rates of fall of heart disease in Finland. Changes in the risk factors of smoking, cholesterol and hypertension were seen, although only accounting for some of the improvement.

In observational longitudinal studies such as at Framingham, USA, subsequent coronary risk can be related to initial cholesterol levels, and it is possible to calculate a predicted fall in cholesterol that might be expected for a given population fall in serum cholesterol. On this basis a reduction of 1 mmol/l in serum cholesterol might be associated with a reduction of 32% in coronary risk.

Not all primary and secondary intervention studies have shown significant falls in coronary risk. However, for a decrease of 1 mmol/l in serum cholesterol, a 22% reduction in coronary risk would be expected. Other studies with pharmacological intervention show similar potential reduction in coronary risk, a 1% fall in serum cholesterol perhaps related to a 2% reduction in coronary risk.

Conclusion

It should be clear that dietary manipulation can affect markedly concentrations of serum lipids. If nutrition is taken to mean only 'beneficial' dietary choices then 'nutrition can favourably affect serum lipids'.

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