

The influence of some dietary factors on cholesterol metabolism

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In this review I shall discuss the effects of dietary cholesterol, fat and fibre on cholesterol metabolism, beginning with an introductory outline of the normal physiology of cholesterol.

The physiology of cholesterol

The enterohepatic circulation. About two-thirds of the cholesterol in the body is exchangeable with that in the plasma. This exchangeable mass takes part in an enterohepatic circulation in which cholesterol is excreted into the bile together with conjugated bile acids (the major end-products of the metabolism of cholesterol in the whole body).

The cholesterol entering the duodenum in the bile mixes with dietary cholesterol and is partially reabsorbed from the jejunum. The unabsorbed cholesterol is excreted in the faeces after modification by bacteria. The bile acids entering the duodenum are partially reabsorbed from the ileum and, to a smaller extent, from the large intestine. In the lower ileum and large intestine the bile acids are deconjugated and converted into secondary bile acids, of which deoxycholic acid is the major component, by intestinal micro-organisms. Some secondary bile acids are absorbed from the large intestine. The primary and secondary bile acids that are not reabsorbed are excreted in the faeces.

The continual loss of cholesterol from the exchangeable mass, either as cholesterol itself or as bile acids, is replaced by endogenous synthesis or (in non-herbivorous animals) by absorption of dietary cholesterol.

Synthesis. Almost all animal tissues synthesize cholesterol from acetyl-CoA by a pathway in which the rate-limiting step is the reduction of hydroxymethylglutaryl-CoA (HMG-CoA), a reaction catalysed by HMG-CoA reductase (*EC* 1.1.1.34). The main site of synthesis of the plasma cholesterol of endogenous origin is the liver.

Absorption. Since cholesterol is a constituent of all animal tissues and is present in eggs and milk, it is present in all human diets except those of complete vegetarians.

Dietary cholesterol mixes with the cholesterol excreted in the bile and is partially absorbed from the jejunum, as described above. The ability to absorb dietary cholesterol varies widely from one species to another, but in all species it appears to be incomplete. The efficiency with which cholesterol is absorbed depends partly on the amount of triglyceride in the food. In man, about 50% of the cholesterol

taken in the food is absorbed when the intake varies from 0.1 to 2 g/d. Thus, over this range of intakes, which includes that of most Western diets, the amount of cholesterol absorbed per d is roughly proportional to the amount ingested.

Regulation. In most species of laboratory animals the balance between the intake of cholesterol into the body and its removal by excretion and catabolism is maintained by two regulatory mechanisms. First, increased dietary intake leads to decreased hepatic synthesis of cholesterol by repression of HMG-CoA reductase. Second, increased dietary intake leads to increased conversion of cholesterol into bile acids.

In man, dietary cholesterol represses hepatic HMG-CoA reductase, but the efficiency of this control mechanism varies from one individual to another and, possibly, from one race to another. Man lacks the ability to increase his output of bile acids in response to increased absorption of cholesterol. However, when cholesterol absorption is increased in man, the amount excreted in the bile and subsequently lost in the faeces is also increased.

Bile acids returning to the liver from the intestine inhibit their own synthesis by repression of cholesterol 7α -hydroxylase, the enzyme catalysing the rate-limiting step in the conversion of cholesterol into bile acids. Hence, if the reabsorption of bile acids is interfered with, this enzyme becomes de-repressed and the degradation of cholesterol to bile acids is stimulated. This effect may be exploited in the treatment of hypercholesterolaemia by giving the patient an unabsorbable anion-exchange resin which binds bile acids in the intestinal lumen and so prevents their reabsorption. A daily dose of an anion exchanger such as Questran may increase the output of bile acids tenfold and this usually leads to a substantial fall in plasma cholesterol concentration.

Dietary cholesterol

The effect of dietary cholesterol on the plasma cholesterol concentration shows a marked extent of species variation. Small amounts of dietary cholesterol produce large increases in the plasma cholesterol level in rabbits but it is difficult to produce any change in rats or dogs by giving cholesterol. However, cholesterol feeding may cause an accumulation of cholesterol in the livers of rats without changing the plasma cholesterol level (Morris & Chaikoff, 1959). Recent work suggests that within a given species there is a wide variation in the response of different individuals to dietary cholesterol, and that this variability is due partly to differences in the efficiency of the regulatory mechanisms mentioned above (Ho, Taylor, Biss & Mikkelsen, 1968; Lofland, Clarkson, St Clair & Lehner, 1972). There is evidence to suggest that in squirrel monkeys (*Saimiri sciurea*) individual variations in the response to increased dietary cholesterol are due to differences in cholesterol absorption and to differences in the extent to which different monkeys can increase bile acid output (Lofland *et al.* 1972).

Until fairly recently, it was generally held that dietary cholesterol has little or no influence on the plasma cholesterol concentration in man. But this view seems to be mistaken. Provided that fat is present in the diet, it is always possible to raise the plasma cholesterol level in normal human subjects by giving large amounts of

cholesterol in the diet. In the experiment shown in Fig. 1, 2.4 g cholesterol/d, given as egg yolk, led to a sustained and reproducible rise in plasma cholesterol concentration. This suggests that differences in the dietary intake of cholesterol could explain in part the geographical variations in plasma cholesterol level.

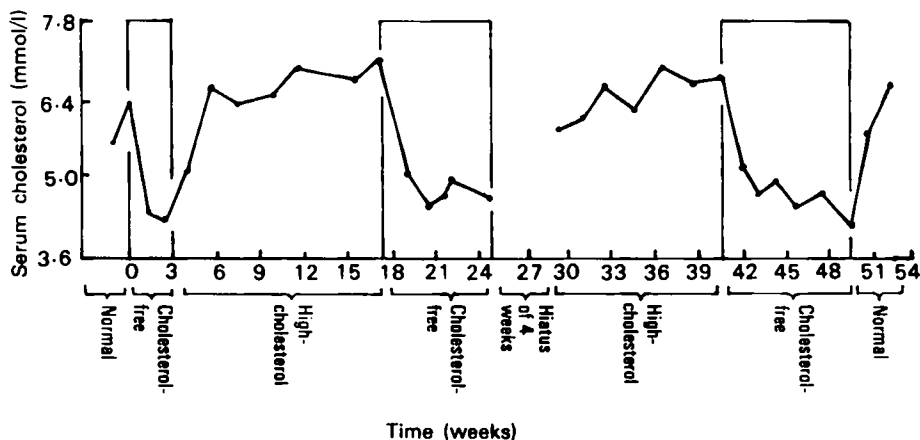


Fig. 1. Effect of dietary cholesterol (2.4 g/d as egg yolk) on serum cholesterol concentration in a normal man. Periods of cholesterol feeding alternated with periods of cholesterol-free diet. The whole experiment lasted 1 year. (From Connor & Connor, 1972.)

Dietary fat

It has been known for more than 20 years that saturated fat in the diet raises the plasma cholesterol concentration, and that when saturated fat is replaced by polyunsaturated fat the plasma cholesterol level falls. However, there is disagreement as to which saturated fatty acids (FA) are responsible for raising the plasma cholesterol level and as to whether polyunsaturated FA have an intrinsic 'cholesterol-lowering' effect or whether they act simply by replacing saturated fat. Keys, Anderson & Grande (1965) have drawn the following conclusions from the study of the effects of different fats on cholesterol metabolism of human subjects kept under carefully controlled conditions: (1) saturated FA with more than twelve, but less than eighteen, carbon atoms raise the plasma cholesterol concentration; (2) polyunsaturated FA have an opposite, but weaker, effect to that of saturated fat, 2 g polyunsaturated fat being required to counteract the effect of 1 g saturated fat; (3) mono-unsaturated FA (e.g. oleic acid) have no effect on the plasma cholesterol level.

There is a good deal of controversy as to how dietary fat influences the plasma cholesterol level. Some workers have observed an increase in the faecal output of bile acids and neutral steroids in human subjects given polyunsaturated fats in the diet, the increased removal and degradation of cholesterol being more than sufficient to explain the observed loss of cholesterol from the plasma (Wood, Shioda & Kinsell, 1966; Connor, Witiak, Stone & Armstrong, 1969). Others, however, have failed to find a significant increase in steroid excretion in response to these diets and have concluded that the cholesterol-lowering effect of

polyunsaturated fat is due to a shift of cholesterol from the plasma into the tissues (Avigan & Steinberg, 1965; Spritz, Ahrens & Grundy, 1965). It is known that when animals are given polyunsaturated fats the ratio, polyunsaturated:saturated FA in the plasma lipoproteins increases and there is some evidence to suggest that this change leads to a decrease in the capacity of lipoprotein molecules to carry cholesterol.

Diet and regional differences in plasma cholesterol concentration

Much of the present interest in dietary fat in relation to cholesterol metabolism arises from attempts to explain regional differences in the prevalence of ischaemic heart disease in terms of regional differences in the intake of saturated fat. According to the 'dietary-fat hypothesis', populations consuming large amounts of saturated fat have high death rates from heart disease because their mean plasma cholesterol concentration is high. Regional differences in plasma cholesterol level are therefore of considerable interest.

In populations living under conditions of Western affluence, the mean plasma cholesterol concentration in adults (about 5.70 mmol/l, or higher) is greater than that in communities living under conditions of primitive agriculture; in some of the latter populations the mean plasma cholesterol level in adults may be less than 4.40 mmol/l and values above 5.2 mmol/l are rare (Myant & Slack, 1973) (see Fig. 2). Most, if not all, of this inter-population difference is environmental, since people who emigrate from a population in which the mean plasma cholesterol level is low to one in which it is high acquire the high plasma level characteristic of the host population within a few years of their emigration (Stamler, 1973). The idealized distributions shown in Fig. 2 raise two important questions: first, what are the

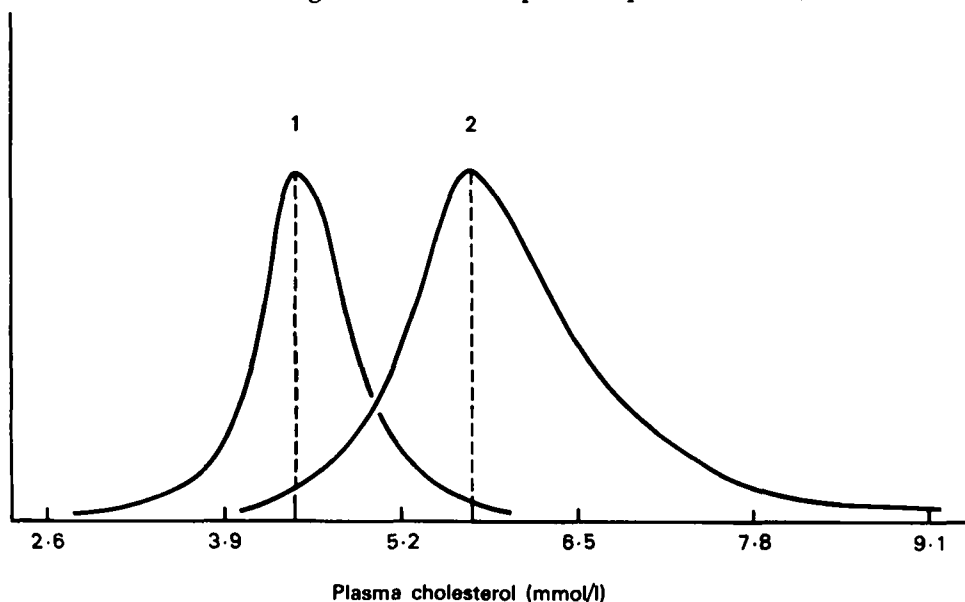


Fig. 2. Idealized distributions for plasma cholesterol concentration in two human adult populations: 1, under conditions of primitive agriculture; 2, under conditions of Western affluence.

environmental causes of inter-population differences in plasma cholesterol level?; second, what are the causes of the differences in plasma cholesterol level from one individual to another within a given population (intra-population variability)?

As regards differences between populations, many studies have shown a close correlation between the mean plasma cholesterol level and the mean intake of saturated fat, expressed as a percentage of the total energy intake, in different populations (Keys, 1970) (Fig. 3). In view of what is known about the effect of saturated fat on human cholesterol metabolism under experimental conditions, it is reasonable to assume that this association between fat intake and plasma cholesterol level is one of cause and effect. However, the difference between fat intake in different populations is usually too small to explain the whole of the observed difference in mean plasma cholesterol level. This suggests that other environmental factors, in addition to saturated fat intake, contribute to inter-population differences in plasma cholesterol level. One of these factors may be the intake of dietary cholesterol, but there may be other factors, not all of them necessarily related to diet.

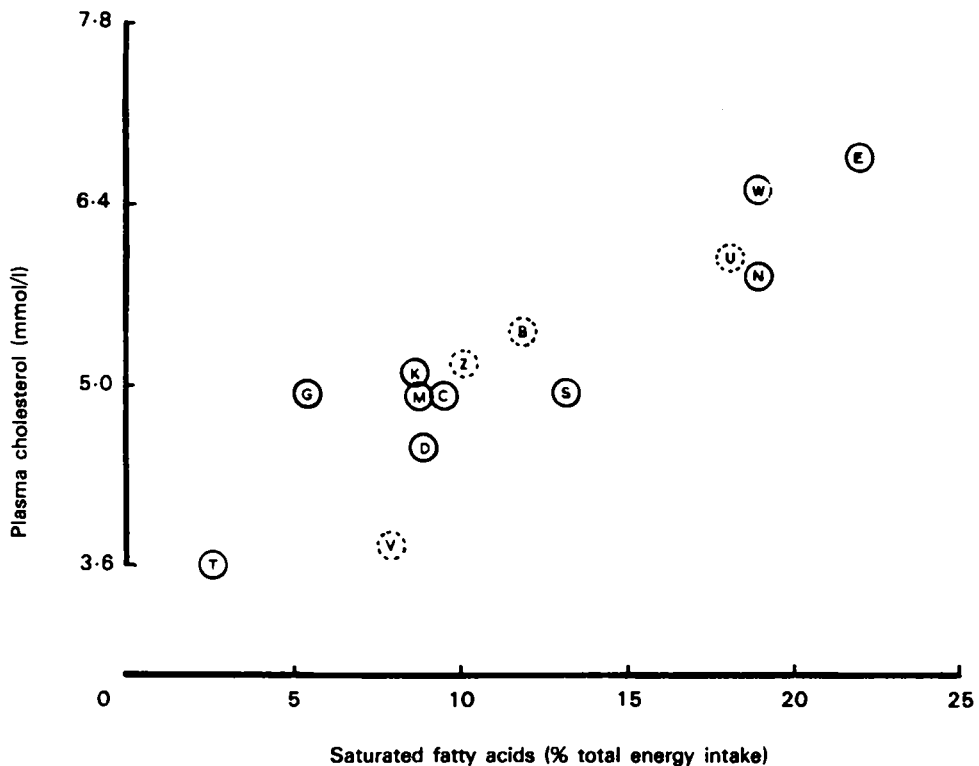


Fig. 3. Plasma cholesterol concentration in relation to saturated fat consumption (as % total energy intake) in fourteen communities ($r = 0.89$). B, Belgrade; C, Crevalcore; D, Dalmatia; E, east Finland; G, Corfu; K, Crete; M, Montegiorgio; N, Zutphen; S, Slavonia; T, Tanushimaru; U, US railroad; V, Velika Krsna; W, west Finland; Z, Zrenjanin. (From Keys, 1970.)

There are several known exceptions to the general rule that mean plasma cholesterol level is correlated with mean saturated fat intake in different populations. For example, some communities in the South Pacific have a high intake of saturated fat (mainly as coconut oil) but have low mean plasma cholesterol levels (Prior & Evans, 1970). Exceptions such as this would be expected, since environmental factors other than dietary fat and cholesterol are known to influence the plasma cholesterol level in man.

Intra-population variation in plasma cholesterol level is much more difficult to explain. Until recently, there was no convincing evidence for a correlation between plasma cholesterol level and any dietary constituent (except for a possible negative correlation with bread consumption (Morris, Marr, Heady & Mills, 1963)) within any population. Keys (1970) has suggested that the reason for this lack of correlation is that in most populations the day-to-day variation in fat consumption in a given individual is as great as the variation in mean fat consumption between individuals. Another possibility, suggested by Connor & Connor (1972), is that in communities in which a correlation has been sought, the consumption of saturated fat and cholesterol is so high that it exceeds the threshold above which variations in consumption could produce variations in plasma cholesterol level. If this explanation is valid, it should be possible to demonstrate a positive correlation between the consumption of cholesterol or saturated fat and plasma cholesterol level in a population in whom the intake of these dietary constituents is very low. In support of this, Connor and his colleagues have shown that in the Tarahumara Indians of northern Mexico, whose diet consists largely of maize and pinto beans with an occasional egg, there is a close correlation between the mean daily consumption of eggs and the plasma cholesterol concentration in different individuals (W. E. Connor, personal communication).

Dietary fibre

During the 1950's, high-fat diets lacking indigestible residue ('fibre') were found to be more atherogenic for experimental animals than high-fat diets containing a normal amount of fibre. It was also noted that animals given fibre-free diets tended to have high plasma cholesterol concentrations. Subsequent work, particularly by Portman (1960) and by Gustafsson & Norman (1969), indicated that dietary fibre stimulates the output of bile acids in the faeces of animals and that this effect is due partly to a change in the microbial flora of the intestinal lumen. Portman (1960), for example, showed that cholic acid output was markedly diminished in rats given semi-purified diets, that the diminished output could be restored almost to the normal level by adding cellulose to the diet, and that the effect of cellulose was largely prevented by sterilizing the intestinal contents with an unabsorbable sulphonamide.

There is no simple explanation for these findings, which have been confirmed in all essentials by many groups of workers, but it seems likely that fibre influences cholesterol metabolism by interacting in a complex way with bile acids and micro-organisms in the intestine. Fibre may also directly influence the absorption of cholesterol from the intestine.

Binding of bile acids. Bile acids are bound in vitro by several types of dietary fibre, including fibre derived from fruits and vegetables, wheat bran, lucerne and lignin (Kritchevsky & Story, 1974). Some of these fibres have also been shown to increase the output of faecal bile acids in animals in vivo. Binding of bile acids in the intestinal lumen would interfere with their reabsorption and would thus diminish feed-back inhibition of bile-acid synthesis in the liver, so leading to increased catabolism of cholesterol. The mechanism of binding probably differs with different types of fibre. Some fibres may possibly act as anion-exchangers, binding bile acids in a manner similar to that shown for drugs like Questran. However, most dietary fibres, including cellulose and lignin, cannot bind in this way because they have no ionizable groups. These fibres may act either as non-ionic adsorbers or by imbibing water in which bile acids, and perhaps neutral sterols, are trapped. On the other hand, they may act in a non-specific manner by shortening the time of transit down the intestine and thus reducing the time available for reabsorption of bile acids.

The intestinal flora. The fact that sterilization of the intestinal lumen diminishes the effect of dietary fibre on bile-acid output suggests that fibre exerts part of its effect by modifying the nature or quantity of the micro-organisms in the intestine. Possibly, the presence of fibre favours the growth of bacteria which produce secondary bile acids that are reabsorbed less efficiently than primary bile acids or that have a smaller inhibitory effect on bile-acid synthesis in the liver. It is also possible that micro-organisms themselves adsorb bile salts and thus diminish their reabsorption from the lower ileum and the large intestine.

Fibre and human cholesterol metabolism. Although there does seem to be a negative correlation between plasma cholesterol concentration and the amount of fibre in human diets, experimental evidence for an effect of specific fibres on plasma cholesterol concentration or bile-acid metabolism in man is confusing and contradictory (Eastwood, 1975). There is some evidence that pectin lowers the plasma cholesterol level and increases bile-acid output in man, but several groups of workers have failed to find either of these effects when bran is added to the diet. It is, of course, possible that the effects of fibre in free-living populations are the result of dietary habits maintained over many years. If so, short-term experiments on human subjects may not tell us how dietary fibre acts under natural conditions.

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