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The Importance of Dietary Cholesterol

Näringsforskning, Årg 34, 47—50, 1990

By A. C. Beynen and M. B. Katan

Abstract

The amount of cholesterol in the diet influences serum cholesterol concentrations in man. An increase in dietary cholesterol causes an increment in serum total cholesterol, the excess cholesterol being located in both the low (LDL) and high density lipoproteins (HDL). Serum triglyceride concentrations are not systematically influenced by dietary cholesterol. Epidemiological observations are limited but are in agreement with the results of short-term, controlled dietary trials. Thus the effects of dietary cholesterol on serum lipoproteins appear to be permanent. Apparent inter-individual differences in responsiveness are largely due to chance fluctuations in lipoprotein levels; true differences do exist but are small.

Introduction

There is abundant evidence that high concentrations of low density lipoproteins (LDL), which carry 60 to 70% of total cholesterol in serum, cause atherosclerosis. Dietary intervention should thus aim at lowering of LDL cholesterol. High levels of high density lipoproteins (HDL), on the other hand, might protect against atherosclerosis, and it therefore seems reasonable to aim at the formulation of diets that do not cause an undue decrease in HDL cholesterol. We shall largely focus this communication on the effects of dietary cholesterol on serum total cholesterol, LDL cholesterol and HDL cholesterol. We will refer mainly to appropriately controlled studies in humans. Here, appropriately implies amongst others that the test diets differed only with regard to the amount of dietary cholesterol.

There is a persistent controversy about the effect of dietary cholesterol on the concentration of serum cholesterol in man (1). The conflicting results are partly due to poor design of the studies (2), but individual differences in the sensitivity of serum cholesterol to dietary cholesterol have also been invoked (1, 3). In dietary trials cholesterol feeding is usually equivalent to whole egg or egg yolk feeding. One egg yolk contains about 200 mg of cholesterol and 5 g of fat, which is mainly monounsaturated. An increased consumption of eggs or egg yolks will replace some of the energy in the form of carbohydrates by an equivalent amount of fat and protein (4). In order to detect the effect of cholesterol *per se*, the control diet has to be balanced for the fat and protein in the eggs or egg yolks. In order to widen the theoretical base, effects of egg yolk cholesterol should be corroborated by studies using other sources of cholesterol.

From Department of Human Nutrition, Agricultural University, Wageningen and Department of Laboratory Animal Science, State University, Utrecht, The Netherlands.

Dietary cholesterol and serum total cholesterol

The effect of dietary cholesterol on mean serum total cholesterol of groups of subjects can be predicted by the equation $\Delta Chol = 1.5\ (Z_2\text{-}Z_1)$, where $\Delta Chol$ is the change in serum cholesterol in mg/dl (1 mg/dl = 0.0259 mmol/l); Z_2 is the square root of the new cholesterol intake in mg/1000 kcal, and Z_1 the previous cholesterol intake (5, 6). This equation was based on 19 low- and high-cholesterol diet comparisons, the diets containing various amounts and degrees of saturation of fat. Both crystalline cholesterol and egg yolk served as sources of cholesterol. The cholesterolaemic responses to the various levels of cholesterol intake were determined in five different studies (5, 7—10).

In 1984, Keys re-evaluated the formula for the quantification of the change in serum cholesterol induced by dietary cholesterol. For this purpose he used data concerning the serum cholesterol responses to dietary cholesterol in 20 controlled experiments in 10 different laboratories which had been reported after the first publication of the formula (11). Figure 1 illustrates the predicted and observed values for serum cholesterol changes produced by changing the cholesterol content of the diet. The observed values include both those on which the formula was based, and those reported after the formula had been established. It is clear that by using the equation one can predict fairly well the group mean change in serum cholesterol concentration caused by a change in cholesterol intake. The square-root form of the formula indicates that the responsiveness of serum cholesterol to a given increase in dietary cholesterol is less pronounced at higher intakes than at lower basal intakes. However, there is no plateau at which dietary cholesterol no longer influences serum cholesterol.

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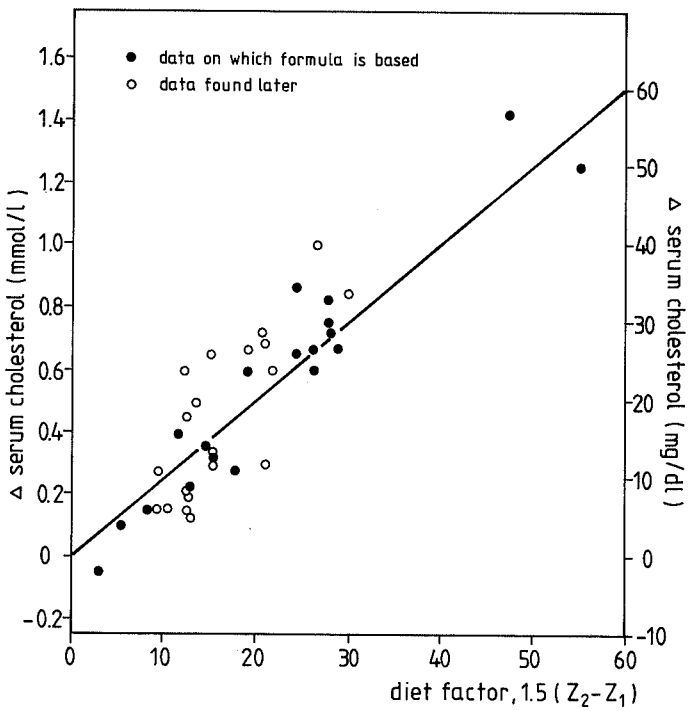
Figure 1. Observed difference in serum cholesterol concentration after changes in cholesterol intake, and plotted against the diet factor 1.5 (Z_2—Z_1). Z is the square root of cholesterol intake, expressed as mg/1000 kcal. The figure is based on Grande *et al.* (5), Keys *et al.* (6) and Keys (11).



Time course of serum cholesterol changes

The full effect on serum cholesterol of increased intakes of cholesterol is probably expressed within two to three weeks (4, 5, 9, 12). Cholesterol loading studies in which subjects were challenged with 750 to 1500 mg of cholesterol per day, provided in the form of egg yolk, have demonstrated that after 1 day serum total cholesterol was not yet changed (13, 14). After two days the mean increase in the concentration of serum cholesterol was 5%, and after 10 days it was 11% (14). Thus serum cholesterol is influenced by the cumulative cholesterol content of the diet in the previous two weeks and not by that of the previous meal. A high serum cholesterol is never due to a single dietary indiscretion on the day preceding the measurement.

Hypo- and hyperresponders

In many studies on the effect of dietary cholesterol on serum cholesterol in man a striking variability in the cholesterolemic response between subjects has been noted (1, 15). Although the concept of hypo- and hyperresponders became widely accepted, the reproducibility of individual differences in response in man has only recently been established. In repeated trials we have demonstrated that modest, stable differences in responsiveness of serum cholesterol to dietary cholesterol do exist in man (3). From these experiments it is also clear that one will always find subjects who appear hyperresponsive in one experiment and hyporesponsive in another (3, 16). The wide scatter of individual responses seen in single experiments and in dietary treatment of patients is largely due to irreproducible chance fluctuations (3). After correction for intraindividual fluctuations of serum cholesterol, the true width of the distribution of the responsiveness to an increase in cholesterol intake from about 100 to 750 mg/day was found to be rather small. Assuming that the distribution is Gaussian, then 16 percent of the subjects would have a cholesterolaemic response of either less than half of the mean response or more than 150 per cent of the mean. Only about 2 per cent would show no increase at all (3). A lack of responsiveness of cholesterol to dietary change in a patient should be ascribed to poor adherence or to chance fluctuations in his cholesterol level obscuring the effect of the diet, rather than to his being a "hyporesponder".

Table 1. Effect of dietary cholesterol as the only variable on serum total, LDL and HDL cholesterol, and triglyceride concentrations in controlled experiments in man employing diets low and high in cholesterol.

	Dietary cholesterol (mg/1000 kcal)			Change in serum cholesterol (%)			Change in serum triglycerides
Reference	n	Low	High	Total	LDL	HDL	%
3	94	49	234	+10		+ 4	
17	6	86	600	+ 9		+21	
18	7	109	889	+29	+41	+18	-18
19	5	150	500	- 1	+ 1	- 8	+18
20	9	53	400	+ 6	+10	- 0	+ 3
21	17	55	218	+ 4	+11	- 5	+ 4
22	6	79	392	+ 5	+ 4	+ 6	+18
23	11	120	300	+11	+15	+ 6	- 7
24	9	0	400	+ 6	+ 7	-10	+23
25	9	74	495	+16	+22	+28	- 2

Dietary cholesterol and LDL and HDL cholesterol in controlled studies

Table 1 summarizes the effect of dietary cholesterol on LDL and HDL cholesterol in various studies. Apart from one study (19), all these studies have shown an increase in serum total cholesterol, which was invariably associated with an increment in LDL cholesterol. As a rough guide, it can be concluded that about 85% of the absolute increase in cholesterol found in serum after cholesterol feeding will be due to an increase in the LDL fraction.

In most studies dietary cholesterol also caused an increase in the concentration of HDL cholesterol. In vegetarians however, Sacks et al (21) found that the ingestion of 1 egg per day reduced HDL cholesterol by 5%. Fisher et al (24) observed a decrease in HDL cholesterol after feeding crystalline cholesterol in a liquid formula diet containing coconut fat as fat source (Table 1). No change in HDL cholesterol was seen when the liquid diet contained corn oil (24). Zanni et al (25) found an increase in HDL cholesterol with diets containing cholesterol and 31% of calories as corn oil (Table 1), but not with lard containing diets.

Egg yolk is a convenient source of cholesterol for dietary trials. However, if one does not correct for the relatively large amount of fat that comes with it, the observed effects may be confounded by changes in fatty acid intake. From the practical point of view the effects of egg yolk feeding as such are relevant because the general public deals with food items rather than with nutrients. The addition of 3 to 6 whole eggs or egg yolks to the diet of healthy subjects has repeatedly been shown to increase both LDL and HDL cholesterol concentrations (4, 12, 26—32). In a study with 34 subjects who habitually ate at least 1 egg/day, we observed that cessation of egg consumption, which reduced dietary cholesterol intake from 323 to 110 mg/1000 kcal, resulted in a decrease of serum total by 5 and HDL cholesterol by 3% (16). These effects could have been anticipated on the basis of the controlled (Table 1) and non-controlled cholesterol feeding studies performed in the laboratories and metabolic wards.

Dietary cholesterol and serum triglycerides

Table 1 shows that increased intakes of cholesterol have no systematic effect on serum triglyceride concentrations. In egg feeding studies a decrease in fasting triglyceride and VLDL concentrations has been observed (4, 27, 33). However, it cannot be excluded that these effects had been caused by the fat in the egg yolks displacing carbohydrates in the diet. Lowering carbohydrate intake is known to lower serum triglyceride levels.

Induction of β-VLDL and HDL_c

Cholesterol feeding causes the appearance in animals of lipoproteins that are not detected normally (34). These particles are β-VLDL, a β-migrating lipoprotein enriched with apoprotein E that floats in the VLDL region, and HDL_c, an HDL particle that is rich in cholesteryl esters and apoliprotein E, and that, unlike normal HDL, is precipitated by heparin-manganese reagent. However, the experimental evidence for induction of such particles by dietary cholesterol in humans is meagre.

Nestel et al (17) reported that in 3 out of 6 subjects tested, cholesterol feeding caused an increase in the number of VLDL particles that bound to heparin on heparin-Sepharose columns. This was taken as evidence for the induction of β-VLDL, because such particles bind heparin. Mistry et al (27) observed β-migrating VLDL on agarose gel electrophoresis in 7 out of 14 subjects after egg yolk consumption. However, VLDL apo E levels have been shown to be unaffected by dietary cholesterol (24).

The idea that cholesterol feeding induces the formation of HDL_c in humans is based on a study of Mahley et al (26), who showed that egg feeding resulted in the appearance of HDL particles with increased ability to displace LDL from the apo B, E receptor in normal human fibroblasts in culture. These data have been interpreted as evidence for the induction of HDL_c. However, apo E concentrations in the HDL density region are not altered by cholesterol feeding (4, 24). Likewise, dietary cholesterol does not influence whole serum concentrations of apo E (17, 22, 23, 25).

Epidemiological data on dietary cholesterol and serum cholesterol

Apart from one study with a limited number of subjects (35) we are not aware of controlled, long-term diet studies where cholesterol was the only variable. Thus the possibility of long-term adaptive effects not detected in short-term experiments cannot be fully discarded. Epidemiological studies may provide information on this point. Comparison of different populations entails a considerable risk that observed associations between dietary cholesterol intake and serum cholesterol levels reflect the effect of other dietary factors, notably saturated fat intake, because a number of foodstuffs, especially high-fat dairy products, are rich in both saturated fatty acids and cholesterol.

In several studies significant within-population correlations were found between cholesterol intake and serum cholesterol independent of other nutrients. In 6-year old children (n=84), Crawford et al (36) found positive correlations for consumption of eggs (r=0.54) and dietary cholesterol (r=0.45). Similar correlations were reported by Knuiman et al (37) for young boys in Finland and in the Netherlands. Within a population of Tarahumara Indians (n=103) Connor et al (38) observed a very strong relationship between dietary and serum cholesterol (r=0.898). These studies suggest that the effect of dietary cholesterol seen in controlled studies is not transient. Perhaps the most convincing data are those of Vorster et al (39). Workers on an egg farm with long-term high intakes of cholesterol (about 1200 mg/day) had higher levels of serum cholesterol than control subjects with low intakes of cholesterol (about 140 mg/day) but otherwise similar diet; the difference agreed quite well with that predicted from short-term experiments using Keys' formula.

Interaction of dietary fatty acids with dietary cholesterol

The type of dietary fat has a major impact on serum cholesterol concentrations (40). This section aims to determine whether the amount of cholesterol present in the diet interacts with the effect on serum cholesterol induced by the type of dietary fat. In order to solve this question only experiments should be considered which used four different diets, varying both in the amount of cholesterol and in fatty acid composition. Preferably, these experiments should be designed as a 4×4 Latin square. The beautiful National Diet-Heart Study (41) specifically addressed this question. The size, duration, design and level of control of this trial as well as the care with which it was executed and reported are such that this study essentially settles the matter; no other experiment even comes close. The dietary-cholesterol-induced increase in serum cholesterol was found to be somewhat smaller against a background diet high in polyunsaturated fatty acids than on a diet high in saturated fatty acids. Thus there is an interaction of dietary fat type with dietary cholesterol. The effect of saturated fatty acids and cholesterol eaten simultaneously is larger than the sum of the effects of these food components when eaten separately.

Underlying mechanisms

The increase in serum total cholesterol after cholesterol feeding of humans is due mostly to an increase in LDL cholesterol concentration. In addition, there may be an increase in HDL cholesterol that is small in absolute terms.

In man an increase in the amount of cholesterol ingested is usually followed by a diminished synthesis of cholesterol in the body and an enhanced excretion of cholesterol metabolites in the form of neutral steroids in the faeces (42). However, the inhibition of cholesterol synthesis is apparently insufficient to prevent the genesis of a new steady state in which serum LDL cholesterol is increased. Upon an increase in cholesterol consumption more dietary cholesterol carried by the chylomicron remnants enters the liver. The liver is probably very efficient at taking in chylomicron remnants from the plasma. Increased intake of cholesterol with the diet thus tends to cause an increase in liver cholesterol pools. The expanded cholesterol pools may theoretically trigger various compensatory mechanisms, namely an increased transport of cholesterol into the bile, an enhanced conversion of cholesterol into bile acids which also enter the bile, an inhibition of hepatic cholesterol synthesis, a down-regulation of the LDL (apo B,E) receptor, and an increased output of apoprotein B-containing lipoprotein particles. Of these, only the latter

two metabolic responses will lead to elevation of serum cholesterol concentrations.

Which of these theoretical responses do actually occur in man? There is some evidence that increased rates of transport of hepatic cholesterol into bile do occur after cholesterol feeding, but this endogenous cholesterol is probably reabsorbed in the intestine (43). Thus this effect cannot be regarded as an effective compensatory mechanism. It has been well documented that humans do not respond to cholesterol loading by increasing bile acid production and excretion (44). Thus enhanced conversion of cholesterol to bile acids does not play a role.

The human liver does appear to respond to excessive uptake of cholesterol by suppression of cholesterol synthesis and also by increased secretion of cholesterol into the blood. The increased output of cholesterol by the liver would explain the observed increase in LDL production after cholesterol feeding (18). LDL may be secreted as such into the plasma from the liver, but most of it appears initially as its precursors VLDL and intermediate density (IDL) lipoproteins. Nestel and Billington (45) have indeed shown that in man cholesterol feeding causes an increase in IDL-apoprotein B production. This may also explain the dietary-cholesterol-induced increase in HDL cholesterol, because precursors of HDL are formed from excess surface material of VLDL and IDL during catabolism of these triglyceride-rich particles. As the triglyceride core of chylomicrons and VLDL becomes depleted, these particles shrink, and surface material, primarily phospholipids and free cholesterol, is transferred to HDL.

Any increase in the plasma level of LDL will lead to a decrease in the number of LDL receptors through down-regulation (46), as shown in blood mononuclear cells (20, 27). In fact, the reduction in the number of LDL receptors on peripheral cells from fasting blood in subjects on high-egg diets is remarkably large, and cannot be accounted for by the quite modest changes in LDL. As a result of the decrease in the number of LDL receptors, the receptor-mediated fractional clearance rate of LDL decreases (18) but the absolute amount of LDL cholesterol delivered to the cells by the receptor pathway increases somewhat because the concentration of substrate (LDL) is increased. The rise in LDL production will also result in increased clearance of LDL by the receptor-independent scavenger pathway (18). In this way a new equilibrium is reached in which LDL production again equals LDL catabolism. □

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The Effect of Fat Quality on Intestinal Steroid Excretion

By Ingvar Bosaeus and Henrik Andersson

Abstract

The interest in dietary modifications to lower blood cholesterol levels has increased the need to know more about the mechanisms underlying the relation between dietary fat and blood cholesterol levels. Studies of steroid excretion and balance have produced conflicting results. This may in part be due to methodological problems. In the ileostomy model, several of these problems can be overcome. Using this model, we have studied short-term effects of increased polyunsaturates, low-fat diets, increased monounsaturates and effects of moderate reductions in saturated fat with or without increases in dietary fibre. Our results show that several modifications of dietary fat are accompanied by rapid changes in small bowel sterol excretion, suggesting excretion changes as one mechanism of action of lipid-lowering diets. Our data also indicate an interaction of dietary fat, cholesterol and fibre on sterol excretion. To further clarify the physiological effects of dietary changes, excretion studies could be combined with studies of other aspects of lipid metabolism.

Introduction

For a long time diet has been known to influence serum cholesterol levels (1), but the mechanisms by which dietary factors influence blood lipid levels are incompletely known (2, 3, 4, 5). The renewed interest in elevated blood lipid levels as risk factors for coronary heart disease has increased the need to know more about the possibilities and limitations of dietary treatment of hyperlipidemia. In spite of the great interest in and the huge efforts spent on various aspects of the lipid hypothesis, the mechanisms underlying the interaction between dietary fat and blood lipid levels are still poorly understood.

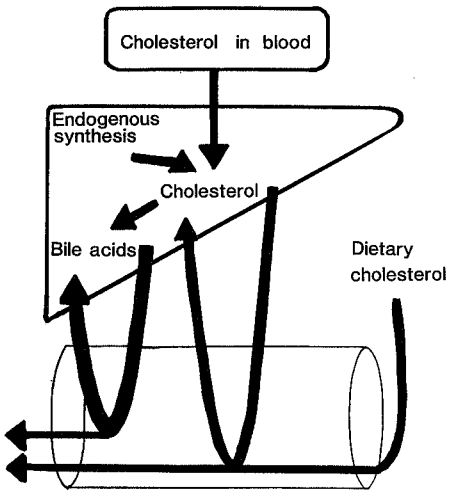
At present the prevailing hypothesis relates to the regulation of the LDL receptor (5). Receptor activity is thought to be down-regulated by dietary saturated fat and cholesterol, thus causing a decreased removal of LDL from plasma. This view has some experimental support (6) although much knowledge is still lacking. However, the mechanisms by which this is brought about are unknown.

As only minor amounts of cholesterol are metabolized to steroid hormones, excreted in urine or lost by skin desquamation, excretion of bile acids and cholesterol in the faeces together with cholesterol intake will determine the steroid balance of the body (7). Thus, a decreased plasma cholesterol pool could be explained by (Figure 1):

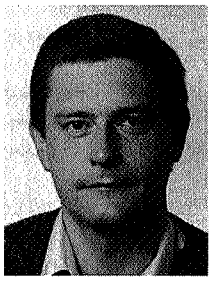
1. decreased absorption of cholesterol,
2. reduction of cholesterol synthesis,
3. increased faecal excretion of cholesterol and/or bile acids or
4. transfer of cholesterol from plasma to other tissues, or a combination of these mechanisms (2, 3, 4).

Many years ago, it was hypothesized that changes in dietary fat induced alterations in the faecal excretion of bile acids and neutral steroids. Early studies seemed to support this concept, but the analytical methods used for faecal steroid determinations were unspecific and probably inaccurate (8). Elaborative techniques for sterol balance studies were developed,

Figure 1. Cholesterol regulation — possible mechanisms.



Ingvar Bosaeus, M.D., Ph.D., and professor Henrik Andersson, M.D., Ph.D., Department of Clinical Nutrition, Gothenburg University, Sahlgren's Hospital, Gothenburg, Sweden.



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