BRIEF REPORT

NORMAL PLASMA CHOLESTEROL IN AN 88-YEAR-OLD MAN WHO EATS 25 EGGS A DAY

Mechanisms of Adaptation

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DIETARY cholesterol increases the plasma level of total and low-density lipoprotein (LDL) cholesterol and accelerates the development of atherosclerosis and its complications, but individual responses to a given change in the dietary cholesterol level vary widely.[1-7] Such responses are reproducible to some extent, suggesting genetic as well as physiologic determinants.[8,9] Several genetic determinants have been identified in nonhuman primates.[10-13] The homeostatic and regulatory mechanisms that maintain a relatively constant level of plasma cholesterol despite changes in dietary cholesterol intake include alterations in the efficiency of intestinal absorption and in the rates of cholesterol biosynthesis, LDL-receptor activity, secretion of cholesterol into bile, and hepatic conversion of cholesterol into bile acids, the chief metabolic product of cholesterol.[5,7,14,15]

In humans, these responses to increases in the dietary intake of cholesterol have been investigated for 25 years, primarily by metabolic-balance studies. Balance studies are time consuming and costly, require unusual levels of patient compliance, and are therefore usually limited to small numbers of subjects. In recent years new procedures have been developed that allow almost complete assessment of the regulation of cholesterol metabolism in subjects who are not hospitalized, with a minimum of inconvenience and discomfort. These techniques have not yet been extensively employed.

My colleagues and I have used many of these procedures in studies of the relation of cholesterol-mechanisms to several risk factors for cholesterol gallstones, primarily female sex-steroid hormones and dietary cholesterol levels.[16-18] When we recently learned of an 88-year-old man who ate 25 eggs a day and who maintained a normal plasma cholesterol level, we took advantage of the opportunity to study him in order to learn more about the control of cholesterol metabolism in response to an unusually excessive intake of cholesterol.

CASE REPORT

An 88-year-old man who lived in a retirement community complained only of loneliness since his wife's death. He was an articulate, well-educated elderly man, healthy except for an extremely poor memory without other specific neurologic deficits. He had been given a diagnosis of Alzheimer's disease and was intermittently depressed. His general health had been excellent, without notable symptoms. He had mild constipation. His weight had been constant at 82 to 86 kg (height, 1.87 m). He had no history (according to the patient and his personal physician of 15 years) of heart disease, stroke, or kidney disease except for an episode of mild chest pain three years earlier. The only objective change at that time was transient depression of the ST segments and T waves in the lateral leads on his electrocardiogram. The patient had been treated for angina and had had no recurrence. There was no history of gallstones or of symptoms of biliary tract disease, but no cholecystography or ultrasound examination had been done recently. His physician's records showed numerous serum cholesterol measurements that ranged from 3.88 to 5.18 mmol per liter (150 to 200 mg per deciliter).

The patient had never smoked and never drank excessively. His father died of unknown causes at the age of 40, and his mother died at 76. One sister died at the age of 82, and another was alive at 86; their plasma lipid values were not available.

The patient's poor memory impaired the accuracy of the dietary history, but his consumption of 20 to 30 eggs a day was verified. Although he could not remember the duration of this eating pattern, his physician attested to its presence for 15 years; a friend, for even longer. He always soft-boiled the eggs and ate them throughout the day. He kept a careful record, egg by egg, of the number ingested each day. The nurse at the retirement home confirmed the daily delivery to him of approximately two dozen eggs. A psychiatrist and a clinical psychologist had characterized this unusual eating habit as compulsive behavior, based on complex psychological factors. Efforts to modify the behavior had been unsuccessful. The patient stated, "Eating these eggs ruins my life, but I can't help it."

METHODS

The studies were approved by the human subjects committee of the University of Colorado School of Medicine. The patient gave written informed consent.

Plasma total, LDL, and high-density lipoprotein (HDL) cholesterol; triglyceride; and apolipoproteins A-I and B were measured by standard clinical laboratory techniques. The absorption of cholesterol was determined by the isotope-ratio method,[16-18] which requires the simultaneous administration of 2 μCi of [^{14}C]cholesterol orally and 2 μCi of [^{3}H]cholesterol intravenously. Blood samples are taken 24 and 48 hours later for the measurement of isotope ratios. Sterol synthesis was quantified by measuring the [^{14}C]acetate incorporated into sterols by mononuclear cells freshly isolated from 30 ml of blood.[16-18] Bile-acid kinetics were determined by a stable-isotope method[19] that employs plasma bile acids. [^{13}C]cholic acid and [^{13}C]chenodeoxycholic acid, the two primary bile acids, were given by mouth, and blood was drawn daily for five days for the measurement of molar ratios of labeled to unlabeled bile acids by gas chromatography–mass spectroscopy. The fractional turnover rate, pool size, and rate of synthesis of each bile acid were calculated.[19]

The data obtained were compared with those obtained in a study currently in progress. Eleven volunteers, 10 women and 1 man, ranging in age from 30 to 60 years, were studied similarly while following their usual diet and again after 16 to 18 days during which their diets were supplemented with five eggs a day, representing approximately 2590 μmol (1000 mg) of additional cholesterol. The mean daily dietary cholesterol intake was 567 μmol (219 mg) during the low-cholesterol period and 2995 μmol (1156 mg) during the high-cholesterol period. All the subjects were healthy, except that eight had asymptomatic radiolucent gallstones.

RESULTS

The patient's plasma lipid levels were normal: total cholesterol, 5.18 mmol per liter (200 mg per deciliter); LDL, 3.68 mmol per liter (142 mg per deciliter); and

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HDL, 1.17 mmol per liter (45 mg per deciliter). The ratio of LDL to HDL cholesterol was 3.15.

The mean amount of cholesterol absorbed was 54.6 percent in the subjects on the low-cholesterol diet (300 of the 567 μmol of cholesterol ingested per day) and 46.4 percent on the high-cholesterol diet (1390 of the 2995 μmol in the daily diet) ($P<0.001$ by paired t-test). The patient absorbed only 18 percent. Thus, although he ingested approximately 12,953 μmol of cholesterol per day, he absorbed only 2331 μmol, or 941 μmol per day more than the subjects on the high-cholesterol diet (Fig. 1). The subjects' rate of cholesterol synthesis during the high-cholesterol diet was 16 percent lower than the rate during the low-cholesterol diet (53.1 vs. 63.2 pmol per 10^7 cells per hour; $P<0.001$ by paired t-test). It was 52.1 pmol per 10^7 cells per hour in the patient, the same as in the subjects on the high-cholesterol diet.

In the patient, 967 μmol of cholic acid and 546 μmol of chenodeoxycholic acid were synthesized daily, for a total rate of bile-acid synthesis of 1513 μmol per day — approximately twice the mean rate of synthesis in the normal volunteers (766 μmol per day on the low-cholesterol diet and 812 μmol per day on the high-cholesterol diet). Thus, he disposed of 701 μmol more cholesterol per day as bile acids than the normal subjects on the high-cholesterol diet. The patient's fractional turnover rate was diminished somewhat (cholic acid, 0.22 per day, as compared with 0.29 for the subjects on each of the two diets; chenodeoxycholic acid, 0.186 per day, as compared with 0.27 and 0.26 per day in the low- and high-cholesterol periods, respectively). The bile-acid pool was greatly increased in the patient and was at least twice that of the normal subjects during the low- and high-cholesterol diets (cholic acid, 4352 vs. 2070 and 2302 μmol; chenodeoxycholic acid, 2934 vs. 1162 and 1076 μmol; deoxycholic acid, 3465 vs. 911 and 1360 μmol). The patient's total bile-acid pool was 10,751 μmol as compared with 4143 and 4738 μmol in the normal subjects during the low- and high-cholesterol diets, respectively (Fig. 2).

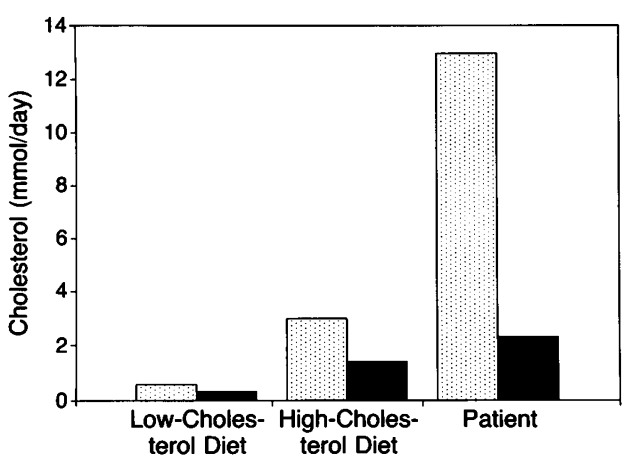

Figure 1. Levels of Dietary Cholesterol (Stippled Bars) and Absorbed Cholesterol (Solid Bars) in the Normal Subjects Following the Low-Cholesterol and High-Cholesterol Diets and in the Patient Studied.

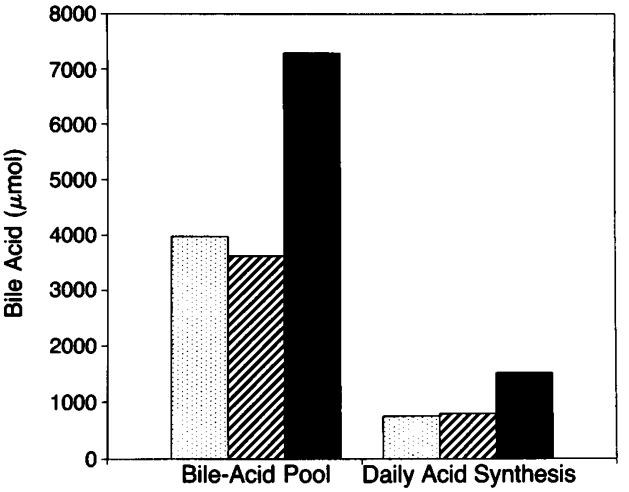

Figure 2. Size of the Bile-Acid Pool and Amount of Bile Acids Synthesized Daily in the Normal Subjects Following the Low-Cholesterol (Stippled Bars) and High-Cholesterol (Hatched Bars) Diets and in the Patient (Solid Bars).

Discussion

Although it would have been desirable to study this patient on a low-cholesterol diet as well as on his customary diet of 25 eggs per day, it was impossible to do so. Therefore, we compared his cholesterol metabolism with that of our other subjects who were being studied by the same techniques. The results explain in dramatic fashion the apparent paradox of an enormous dietary cholesterol intake and longevity to the age of 88 without clinically important atherosclerosis. The patient had extremely efficient compensatory mechanisms — namely, a marked reduction in the efficiency of cholesterol absorption, greatly increased synthesis of bile acids, and apparently reduced cholesterol synthesis relative to his cholesterol absorption.

The decrease in the efficiency of cholesterol absorption to only 18 percent of the unusually large intake played an important part in maintaining a normal plasma cholesterol level. Approximately 10,622 of the 12,953 μmol of cholesterol ingested each day passed through the patient's gastrointestinal tract to be excreted in the feces. Although he still absorbed 2331 μmol of cholesterol per day (2032 and 941 μmol per day more than the mean amount absorbed by the normal subjects during the low- and high-cholesterol diets, respectively), he compensated further, primarily by doubling the usual rate of bile-acid synthesis.

Cholesterol absorption is a complex process involving a number of steps. Although the rate-limiting step is not known with certainty, it is currently believed to be the transport of micellar free cholesterol from the intestinal lumen through the unstirred water layer[20] and, in molecular form, across the cell membrane of the enterocyte. This has classically been thought to occur by passive diffusion, but several studies[21,22] suggest a role for an as yet unidentified brush-border pro-

tein. The other processes — luminal hydrolysis of dietary cholesterol esters, reesterification in the enterocyte, incorporation into chylomicrons and intestinal very-low-density lipoprotein cholesterol, and transport in the lymph — are not normally rate-limiting. The efficiency of cholesterol absorption in animal species ranges from 35 to 85 percent[23] and is usually 50 to 60 percent in humans over a wide range of dietary intake.[4] Decreased absorption in the presence of increased dietary cholesterol serves as a major control mechanism in cholesterol homeostasis,[15] but there is a great individual heterogeneity.[3] In this patient it was extraordinarily effective. Since it is likely that much of the reduction in the efficiency of absorption is simply due to the physical barrier to diffusion of micelles, reduced absorption cannot be considered a regulatory process. On the other hand, the additional down-regulation of a putative brush-border transport protein by excess cholesterol cannot be excluded.

The rate of sterol synthesis by peripheral-blood mononuclear leukocytes (primarily monocytes) accurately reflects hepatic and whole-body synthesis of cholesterol.[5,24-26] Physiologic and metabolic perturbations that increase or decrease hepatic cholesterol synthesis have similar effects on the synthesis of sterols by these cells. Cholesterol biosynthesis by the liver and other cells is down-regulated by the uptake of both chylomicron remnants and LDL cholesterol, probably mediated at least in part by endogenous synthesis of hydroxylated sterols, such as 25-hydroxy cholesterol, which are byproducts of cholesterol biosynthesis that inhibit the activity of hydroxymethylglutaryl-CoA reductase,[27] the rate-limiting enzyme of cholesterol synthesis. The finding of a rate of cholesterol synthesis in this patient that was equal to the mean synthesis rate in the normal subjects ingesting the high-cholesterol diet is surprising, since other studies suggest that inhibition of synthesis can have a more prominent regulatory role in response to dietary cholesterol.[28,29] It may, however, reflect the fact that the patient absorbed only 941 μmol of cholesterol more than the normal subjects did during the period of high cholesterol intake and converted about 750 μmol of that to bile acids.

The rate of bile-acid synthesis in the patient was greater than in any of the 200 subjects we have studied during the past 13 years, and it was a major compensatory response. An increase in the excretion of bile acids in some subjects on a high-cholesterol diet has been well documented in balance studies,[28] but bile-acid synthesis itself has not often been measured. It is of interest that persons with the same apolipoprotein E phenotype ($E_{2/2}$, $E_{2/3}$, $E_{2/4}$) have diminished cholesterol absorption and increased synthesis of bile acids.[30] In rats, some studies suggest that the availability of substrate, microsomal cholesterol, is a major regulator of the rate-limiting enzyme cholesterol 7α-hydroxylase.[31] Since the conversion of cholesterol to bile acids accounts for approximately 70 percent of the cholesterol disposed of daily,[32] increased bile-acid synthesis is clearly a major means of maintaining cholesterol homeostasis.

It was not possible in our patient to measure biliary cholesterol secretion, a procedure requiring 8 to 10 hours of nasoduodenal intubation, but in view of the greatly expanded bile-acid pool circulating through the patient's liver and the known regulation of biliary cholesterol secretion by the secretion of bile acids, it is very likely that biliary cholesterol secretion was similarly increased. As we found in a recent study, however, when the secretion of bile acids is increased by increasing dietary cholesterol, cholesterol secretion often increases proportionately, and supersaturated bile, a precursor of cholesterol gallstones, is not secreted.[18]

In summary, most of the physiologic processes involved in cholesterol balance and in maintaining a normal plasma cholesterol level were studied in an unusual patient, an 88-year-old man who for psychological reasons had eaten about 25 eggs per day, in addition to regular meals, for many years. His almost complete freedom from clinically important atherosclerosis and its complications may be explained in part by a great reduction in the efficiency of cholesterol absorption from the intestine and by a marked increase in the conversion of cholesterol to bile acids. In addition, his cholesterol synthesis was probably reduced moderately, and his biliary cholesterol secretion may have been increased. These physiologic adaptations would leave little if any of the dietary cholesterol to elevate plasma cholesterol levels and be deposited in arterial walls.

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