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Eggs and beyond: is dietary cholesterol no longer important?

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RECENT GUIDELINES

Within the past 18 mo, 2 sets of nutritional guidelines, the 2013 American College of Cardiology/American Heart Association Lifestyle Guideline for the Reduction of Cardiovascular Disease (1) and the 2015 USDA Dietary Guidelines for Americans (http://www.health.gov/dietaryguidelines/2015.asp), have indicated that the evidence for dietary cholesterol restriction to lower total and LDL cholesterol is insufficient. In fact, the USDA guidelines state that "cholesterol is not considered a nutrient of concern for overconsumption." These statements about dietary cholesterol have provoked considerable reaction.

PUBLIC MESSAGING

Related news coverage has been filled with mixed messages, many of which have been and continue to be misinterpreted. On 10 February 2015, a *Washington Post* headline stated, "The U.S. government is poised to withdraw longstanding warnings about cholesterol" (http://www.washingtonpost.com/blogs/wonkblog/wp/2015/02/10/feds-poised-to-withdraw-longstanding-warnings-about-dietary-cholesterol/). CNN went on to report on 19 February 2015 that "Cholesterol in Food Not a Concern, New Report Says" (http://www.cnn.com/2015/02/19/health/dietary-guidelines/). And although the 10 June 2015 issue of the *Health Hub* from the Cleveland Clinic posed "Do Your Cholesterol Numbers Really Matter?" they went on to say "yes—just because the emphasis on cholesterol in food is less—it does not mean that your blood cholesterol does not matter" (http://health.clevelandclinic.org/2015/06/do-your-cholesterol-numbers-really-matter/). Nevertheless, can the public or even the health care professional distinguish between the relative distinction and importance between dietary cholesterol and saturated or even *trans* fat? In fact, confusion lies in the fact that ~60% of cholesterol intake is from foods that also contain a moderate amount of saturated fat such as beef/beef dishes, burgers, sausage, bacon, and cheese, with the other ~40% mostly from eggs (~25% of total cholesterol intake), chicken and chicken dishes (~12%), and foods such as shellfish, which contain very little or a much smaller percentage of total fat as saturated fat (http://appliedresearch.cancer.gov/diet/foodsources/cholesterol/table1.html).

VARIABLE HISTORICAL SCIENCE IN TERMS OF EXPERIMENTAL DESIGN, QUALITY, AND SUBGROUPS

Studies to document the independent effect of dietary cholesterol on total serum cholesterol and LDL cholesterol have suffered from methodologic flaws, including the absence of data that distinguish the distribution of cholesterol among lipoprotein fractions, the use of extreme ranges of cholesterol intake, and identifying subgroups post hoc that respond differentially (2–4). Yet, a few very well-done studies that support this independent effect of dietary cholesterol are worth noting. In 1982, Schonfeld et al. (5) examined the impact of 750 compared with 1500 mg dietary cholesterol daily consumed in the form of eggs on plasma lipoproteins in 20 young men in the setting of diets with a range of polyunsaturated to saturated fat ratios (P:Ss)[1] of 0.25, 0.4, 0.8, or 2.5. The addition of 750 mg cholesterol/d to the diet with a P:S of 0.25–0.4 increased LDL cholesterol by 16 ± 14 mg/dL, whereas the addition of 1500 mg increased LDL cholesterol by 25 ± 19 mg/dL (both $P < 0.01$). When consumed in the diet with a P:S of 0.8, only 1500 mg cholesterol/d increased LDL cholesterol by17 ± 22 mg/dL ($P < 0.02$), whereas with the diet with a P:S of 2.5, neither amount of cholesterol intake produced significant changes in LDL cholesterol. Thus, both the cholesterol content and P:S of diets were important in determining LDL-cholesterol concentrations. In the mid-1990s, Ginsberg et al. (6) studied healthy young men using a randomized, 4-way crossover design to examine the impact of 0, 1, 2, or 4 eggs/d for 8 wk, with a daily cholesterol intake ranging from 128 to 858 mg, on plasma lipids and lipoproteins, which were consumed while following a step 1 American Heart Association diet. On average, plasma total cholesterol increased by 1.5 mg/dL for every 100 mg dietary cholesterol added to the diet ($P < 0.001$) and LDL cholesterol increased in parallel. A similar study examined the effects of the addition of 0, 1, or 3 eggs/d with dietary cholesterol intakes ranging from 108 to 667 mg/d in healthy young women (7). In the women, LDL cholesterol increased by 2.1 mg/dL per 100 mg dietary cholesterol/d ($P = 0.003$), which accounted for ~75% of the increase in total cholesterol. HDL cholesterol also increased by 0.57 mg/dL per 100 mg dietary cholesterol/d ($P < 0.04$).

NEW META-ANALYSIS

The meta-analysis by Berger et al. (8) published in this issue of the Journal documents the heterogeneous nature of the clinical trials that support a relation between dietary cholesterol and cardiovascular disease (CVD) risk. When extrapolating data shown in their Figure 3,

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[1] Abbreviations used: CAD, coronary artery disease; CVD, cardiovascular disease; P:S, ratio of polyunsaturated to saturated fat.

First published online July 15, 2015; doi: 10.3945/ajcn.115.116905.

wherein subjects showed an increase in cholesterol intake from a mean of 214 to 821 mg, or ~3 eggs daily, the mean increase in LDL cholesterol was 7 mg/dL and in HDL cholesterol was ~3–4 mg/dL. This increase in HDL cholesterol with increases in dietary cholesterol is very similar to the effect of saturated fat on HDL cholesterol and should not be inferred as neutralizing. In general, we live in an age wherein increases in HDL cholesterol should be interpreted cautiously in comparison to changes in LDL cholesterol (9).

REDUCTION IN CORONARY ARTERY DISEASE INCIDENCE FOLLOWING RECOMMENDATIONS FOR <300 OR <200 mg CHOLESTEROL DAILY

Of interest without adequate documentation is the fact that the decrease in coronary artery disease (CAD) incidence began after recommendations for restrictions of total/saturated fat and dietary cholesterol occurred (10) and before reductions in tobacco use and risk factor modifications such as reductions in blood pressure and LDL cholesterol with medications. Although the basis for <300 or <200 mg dietary cholesterol/d may have been questionable at the time, this translated to ~1.5 or 1 egg/d in the absence of any other dietary cholesterol intake. Because eggs remain the most abundant source of dietary cholesterol and could be the most easily assessed change in the low-fat, low-cholesterol diet, the decline in egg consumption since 1945 ensued a bit earlier and paralleled CAD/stroke mortality since ~1950. Although such comparisons can be questioned for many reasons, the association is of interest. Nevertheless, updated data show no consistent relation between egg consumption and CVD (11).

IS DIABETES DIFFERENT?

Despite modest effects of dietary cholesterol on LDL cholesterol, there is some evidence that patients with diabetes may be subject to more harm. Most cholesterol absorption in the intestine is not from the diet but from hepatobiliary sources (12). However, patients with diabetes show increases in Niemann-Pick-like-1 protein, a molecule that facilitates intestinal cholesterol transport, and microsomal transfer protein, which couples triglycerides to apo B-48 during chylomicron assembly; moreover, patients with diabetes show reductions in the *ATP-binding cassette gene (ABCG5G8)* heterodimer that promotes the re-excretion of enterocyte cholesterol back into the intestinal lumen (13). Overall, these alterations support increases in intestinal cholesterol absorption in patients with diabetes. Although some studies indicate that more egg consumption in patients with diabetes results in more CAD events (11, 14, 15), this relation has been questioned (16). Moreover, in a randomized controlled 3-mo trial of 2 eggs/d for 6 d/wk in patients with type 2 diabetes there was no adverse effect on lipid profile when the diet included a higher content of MUFAs and PUFAs (17). Of interest, however, are the results from the recent IMProved Reduction of Outcomes: Vytorin Efficacy International Trial, which showed in patients with diabetes a particularly pronounced beneficial effect of ezetimibe (a drug that inhibits intestinal absorption of cholesterol) + simvastatin compared with simvastatin alone on CVD events (18).

TAKE-HOME MESSAGE

Overall, some reservation is appropriate when claiming that dietary cholesterol is unimportant in modifying LDL cholesterol and the risk of CVD. Yet, the primary emphasis should be placed on dietary patterns wherein the overall diet is heart healthy (1), a setting in which more egg consumption is likely not harmful. Despite >50 y of science, a few better-done crossover studies to address the independent effect of dietary cholesterol in the setting of a heart-healthy lifestyle would be timely, with or without statin therapy on board. Nevertheless, when ordering an omelet, why not order an egg white omelet with plenty of vegetables, lean meat, and spices rather than one with 600 mg cholesterol?

The author had no personal or financial conflicts of interest related to this editorial.

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