Dietary Cholesterol and Coronary Artery Disease: A Systematic Review

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Coronary heart disease (CHD) remains one of the leading causes of death in the United States and other industrialized nations. A better understanding of modifiable risk factors for CHD is critical in order to effectively prevent this disease. Dietary factors known to influence the risk of CHD include saturated fats, *trans*-fats, and polyunsaturated fatty acids. Although higher plasma levels of low-density lipoprotein cholesterol are associated with an increased risk of coronary disease and lipid-lowering therapy has been shown to reduce the risk of cardiovascular disease, the relation between dietary cholesterol and the risk of CHD is not clearly understood. This article reviews the current evidence on the association between dietary cholesterol and the risk of CHD.

Introduction

Despite a decline in the death rate from coronary heart disease (CHD) from its peak in 1968, CHD remains a major public health issue in the United States and other industrialized nations. In 2005, CHD was the cause of one of every five deaths in the United States, and in 2009 it is estimated that nearly 800,000 Americans will suffer a first heart attack and about half that number will experience a recurrent attack [1]. Although 47% of the decline in CHD deaths has been attributable to treatment (ie, revascularization, secondary prevention after myocardial infarction, treatment of dyslipidemia or hypertension), about 44% of the reduction in CHD deaths has been accounted for by changes in risk factors, such as lower prevalence of smoking, increased physical activity, and lower cholesterol [2].

Contrary to a Mediterranean-type diet, a Western-type diet, which is rich in cholesterol and other atherogenic factors, is positively associated with CHD risk. Plasma low-density lipoprotein (LDL) cholesterol, low levels of high-density lipoprotein (HDL) cholesterol, and the ratio of total cholesterol or LDL cholesterol to HDL cholesterol have been shown to increase the risk of CHD. In addition, numerous clinical trials have demonstrated beneficial effects of lowering plasma LDL on the risk of CHD and on the prognosis in CHD patients. In contrast, data on the association between dietary cholesterol and plasma cholesterol or CHD have been inconsistent. It is important to elucidate the role of dietary cholesterol on the diet–heart hypothesis. In this article, we review current evidence on the association between dietary cholesterol and CHD risk. We first describe common sources of dietary cholesterol, then review data on the relation between dietary cholesterol and hard CHD end points as well as subclinical disease, and lastly discuss possible physiologic mechanisms that might support a causal inference and the role of genetic factors on the dietary cholesterol–CHD hypothesis.

Sources of Dietary Cholesterol and Current Recommendations

Cholesterol is a component of cell membranes and is used to synthesize steroids, including vitamin D. Because of the endogenous production of cholesterol by the liver, dietary cholesterol is not essential to meet the daily demand in adults and children aged 2 years and older. Major sources of dietary cholesterol among adults in the United States include egg yolk, beef and other red meat, organ meat, shellfish, poultry, whole milk, whole-fat dairy products, and mixed dishes that contain cheese, butter, or fatty meat [3]. Similarly, among children in the United States ages 2 through 5 years, dietary cholesterol is mainly provided by eggs (30%), whole milk (11%), sweet grain products (7.9%), beef (6.7%), and poultry (5.6%) [4]. Of note, for younger children, breast milk is an important source of dietary cholesterol (containing about 10–15 mg of cholesterol per deciliter). The 2005 dietary guideline for adults in the United States [5] and The National Cholesterol Education Program Adult Treatment Panel III [6] recommend daily intake of less than 300 mg/d of cholesterol for healthy adults and less than 200 mg/d of cholesterol for people with elevated LDL cholesterol. For translation into foods, an average egg yolk provides about 200 mg of cholesterol, and 3 ounces of cooked beef liver contains about 300 mg of cholesterol.

Dietary Cholesterol and CHD

Following the demonstration by the Framingham Heart Study during the early 1960s that elevated plasma total and LDL cholesterol levels are associated with an increased risk of CHD, subsequent investigations confirmed those findings along with a CHD risk reduction associated with LDL cholesterol lowering. In contrast, findings on the relation between dietary cholesterol and CHD have been inconsistent, raising the question of whether a higher intake of dietary cholesterol translates into higher plasma levels of cholesterol with subsequent increased risk of CHD events. Positive studies relating dietary cholesterol with CHD include the Seven Countries Study [7], which showed a positive correlation between dietary cholesterol and 25-year CHD mortality ($r = 0.55$; $P < 0.05$). Specifically, the lowest CHD death rate was observed in Greece and Japan, with a dietary cholesterol intake of 141 to 170 mg/d, whereas eastern Finland had the highest mortality rate (28.8%) and was one of the top four sites with the highest dietary cholesterol intake (537 mg/d). The interpretation of these findings is limited by the ecological design, which precludes the assessment of individual risk and adequate control for confounding factors. In particular, it is unclear whether such observation is independent of saturated and *trans*-fatty acid intakes, which are highly correlated with dietary cholesterol and are known to increase CHD risk. Other investigators have reported a positive association between average cholesterol intake and CHD rate [8]. In the Honolulu Heart program [9], dietary cholesterol was positively associated with the risk of CHD and myocardial infarction or CHD death after 10 years of follow-up after adjustment for age, blood pressure, exercise, serum cholesterol, smoking, and weight (cases had on average an excess of 15 mg of dietary cholesterol per 1000 calories compared with non-cases). In the Western Electric Study, the adjusted hazard ratio for CHD death was 38% higher in the highest category of dietary cholesterol (289–590 mg of cholesterol per 1000 kcal) compared with the lowest-intake group (81–186 mg of cholesterol per 1000 kcal; relative risk of 1.38; 95% CI, 1.00–1.90) [10].

In contrast, other reports did not find an association between dietary cholesterol and CHD. Neither the Framingham Heart Study [11] nor the Lipid Research Clinics Study [12] found a statistically significant association between dietary cholesterol and incident CHD or mortality in men and women. Among more than 80,000 nurses [13] and 43,000 male health professionals [14], dietary cholesterol was not associated with CHD after adjustment for confounders including energy, polyunsaturated fats, *trans*-fats, and saturated fats (all factors that are related to cholesterol levels). This inconsistency across studies examining the relation between dietary cholesterol and CHD extends to investigations of egg intake, which provides about 30% of dietary cholesterol in the American diet [15].

In a case-control study, egg consumption was not associated with nonfatal myocardial infarction among Italian women (odds ratio of 0.8 comparing highest vs lowest tertile; $P > 0.05$) [16]. Likewise, other studies did not find an association between eggs and CHD [17,18]. In the Nurses' Health study and Health Professionals Follow-up study, egg consumption was not associated with CHD among nondiabetic individuals; however, egg intake was related to an increased risk of CHD among diabetic women (50% increased risk) and men (100% increased risk) [19]. In the Oxford Vegetarian Health Study, consumption of six or more eggs per week was associated with a nearly threefold increased risk of CHD death compared with intake of less than one egg per week (relative risk of 2.7; 95% CI, 1.2–6.0) [20]. Among male physicians, no association between egg consumption and myocardial infarction was reported [21•]; however, when restricted to men with type 2 diabetes, there was a nonsignificant relation between eggs and CHD and a strong and positive relation between egg consumption and all-cause mortality (twofold increased risk with intake of five or more eggs per week). The higher susceptibility of diabetic individuals may be partly explained by a positive association between eggs or dietary cholesterol and incident diabetes, as demonstrated in two large cohorts of men and women [22••]. However, additional studies to elucidate the underlying mechanisms are needed. A summary of prospective studies on dietary cholesterol or egg consumption and CHD with available data on adjusted relative risks is presented in Table 1.

Dietary Cholesterol and Subclinical Disease

To date, little attention has been devoted to the association between dietary cholesterol and subclinical atherosclerosis (including intima-media thickness, coronary artery calcium, or ankle-brachial index). In a crossover trial of 49 healthy adults, a 6-week intervention with two eggs per day was not associated with a statistically significant change in endothelial function measured by flow-mediated dilation [23]. It is unclear whether a long-term intervention with eggs would yield similar results. It is not known if there are pathophysiologic mechanisms that could support a causal relation between dietary cholesterol and CHD.

Dietary Cholesterol, Physiologic Mechanisms, and CHD

The diet–heart-hypothesis postulates that a diet that is low in polyunsaturated fat but high in saturated fat and cholesterol may lead to elevated plasma cholesterol with subsequent development of atherosclerosis and CHD as the end point. Does current evidence lend support to an increase in plasma cholesterol following an intervention with dietary cholesterol?

Based on many well-designed feeding studies, it is estimated that every 100 mg/d of dietary cholesterol would result on average in an increase of total plasma cholesterol of 2.2 to 2.5 mg/dL [24–26]. Both LDL and HDL cholesterol appear to be influenced by dietary cholesterol

Table 1. Prospective studies of dietary cholesterol or egg consumption and coronary heart disease

Study	Patients, *n* (age range)	Follow-up	Outcome	Multivariable adjusted RR (95% CI)
Shekelle and Stamler [10]	1824 men (40–55 y)	25 y	CHD death	1.38 (1.00–1.90) for ≥ 289 mg of cholesterol/1000 kcal vs < 186 mg of cholesterol/1000 kcal (RR adjusted for age only)
Hu et al. [13]	80,082 women (34–59 y)	14 y	CHD	1.17 (0.92–1.50) for 5th vs 1st quintile of dietary cholesterol
Ascherio et al. [14]	43,757 men (40–75 y)	6 y	Total CHD	1.03 (0.81–1.32) for 422 mg/d vs 189 mg/d of dietary cholesterol
Hu et al. [19]	37,851 men (40–75 y)	8 y	Nonfatal and fatal CHD	Men: 1.08 (0.79–1.48) for ≥ 7 eggs/wk vs < 1 egg/wk
	80,082 women (30–55 y)	14 y		Women: 0.82 (0.60–1.13) for ≥ 7 eggs/wk vs < 1 egg/wk
Mann et al. [20]	10,802 men and women (16–79 y)	13.3 y	CHD death	2.7 (1.2–6.0) for ≥ 6 eggs/wk vs < 1 egg/wk
Djousse and Gaziano [21•]	21,327 men (40–86 y)	20 y	Myocardial infarction	0.90 (0.72–1.14) for ≥ 7 eggs/wk vs < 1 egg/wk

CHD—coronary heart disease; RR—relative risk.

(increase of 1.9–2.1 mg/dL of LDL and 0.40–0.44 mg/dL of HDL per 100 mg/d of dietary cholesterol [24,26], so that the ratio of LDL to HDL is not altered [24,27–29]. Because the ratio of LDL to HDL is the most important predictor of CHD, it is not surprising that several studies did not find a positive association between dietary cholesterol and incident CHD.

The common limitation across most published studies is the lack of consideration of heterogeneous response to a diet high in cholesterol. It is postulated that about 15% to 25% of the population is sensitive to dietary cholesterol, leaving the majority with a minimal response. Because the difference in plasma cholesterol response to dietary cholesterol between hyper- and hyporesponders is about threefold, it would be important to examine whether dietary cholesterol is associated with CHD among hyperresponders. As reviewed by McNamara [26], the difference appears to affect LDL but not HDL, so 100 mg/d of dietary cholesterol leads to a 2.84-mg/dL increase in LDL in hyperresponders versus a 0.76-mg/dL increase in hyporesponders. It is possible that homeostatic processes may downregulate cholesterol absorption and de novo synthesis in response to an increased dietary cholesterol intake [30,31], especially among hyporesponders. Furthermore, the effects of dietary cholesterol on plasma lipoproteins are influenced by the presence of obesity and insulin resistance [32]. A 4-week intervention with four eggs per day resulted in an increase in non–HDL cholesterol in lean and insulin-sensitive individuals but not in individuals who were lean and insulin resistant or those who were obese and insulin resistant [33]. Obesity is associated with an increased secretion of biliary cholesterol [34], which may inhibit dietary cholesterol absorption [35].

Inflammation plays an important role in the development of atherosclerosis and CHD. However, few studies have examined the relation between dietary cholesterol and markers of inflammation. In a crossover trial of healthy individuals, four eggs per day increased plasma levels of C-reactive protein and serum amyloid A after 4 weeks of intervention. However, this response was limited to participants who were lean and insulin sensitive; in obese or insulin-resistant participants, egg consumption had no effect on inflammatory biomarkers [33]. Limited and inconsistent data have been reported on the association between dietary cholesterol and blood pressure. Consumption of two eggs per day for 12 weeks had no effect on blood pressure in 26 male students [36]. In another study, consumption of one egg per day for 3 weeks had no effects on blood pressure among 17 students [37]. Oh et al. [38] reported no association between eggs (four per day for 4 weeks) and systolic or diastolic blood pressure in 11 participants. Others have also reported no relations between egg consumption and blood pressure [39]. In contrast, data from 418 Seventh-day Adventist volunteers in Australia show a positive relation between egg consumption and blood pressure (10.5 mm Hg and 5.9 mm Hg higher with intake of one or more eggs per day compared with less than one egg per month for systolic and diastolic blood pressure, respectively, adjusting for age, sex, height, and weight) [40]. Unfortunately, these results were not adjusted for energy intake, dietary fiber, saturated fats, *trans*-fats, or polyunsaturated fats, all of which are major confounders for dietary cholesterol association.

It is possible that dietary cholesterol may influence the risk of CHD via glucose metabolism pathway. It is known that people with diabetes have a threefold to fivefold

increased risk of CHD. Dietary cholesterol and egg consumption have been associated with an increased risk of type 2 diabetes [22••,41,42] and gestational diabetes [43]. These data are consistent with animal and human studies, showing a positive relation between dietary cholesterol and inflammation and a reduced risk of incident diabetes after treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors [44], drugs that are known to lower both plasma cholesterol and inflammatory markers [45].

Future Directions in Research

Current evidence indicates that dietary cholesterol has a modest effect on plasma cholesterol (1.9-mg change in LDL and 0.4-mg change in HDL per 100 mg/d of dietary cholesterol) in the general population; more importantly, dietary cholesterol does not appear to influence the ratio of LDL to HDL cholesterol (the most important predictor of CHD) in the general population. However, for 15% to 25% of the population that is sensitive to dietary cholesterol (ie, hyperresponders), dietary cholesterol appears to have an important influence on LDL cholesterol, whereas its effect on HDL is similar between hyporesponders and hyperresponders. The implication of this heterogeneous response is that the true effect of dietary cholesterol on CHD could be biased by unbalanced distribution of individual-response types. In addition, few prior studies have accounted for possible confounding by diabetes status, which has been shown to 1) influence individual response to dietary cholesterol in animal models [46] and 2) modify the relationship between cholesterol and CHD relation [19,21•]. Lastly, several of the previous studies did not collect data on key confounders (ie, energy intake, fiber, saturated fat, polyunsaturated fat, and *trans*-fat, among others) to minimize bias.

Conclusions

It is reasonable to conclude that there is little evidence supporting a major association between dietary cholesterol and CHD risk in the general population. However, dietary cholesterol may have detrimental effects on CHD among hyperresponders and people with type 2 diabetes. Future studies of the relationship between cholesterol and CHD should not only consider individual-response type as an important factor but should also evaluate the role of genetic polymorphisms influencing cholesterol metabolism (eg, absorption, transport, synthesis, and so forth) on such relations. At present, the current guidelines on dietary cholesterol (< 300 mg/d for the general population) remain sound.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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