Eggs and Heart Disease: A Failed Hypothesis

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Abstract

The hypothesis that dietary cholesterol raises blood cholesterol levels and thereby heart disease risk has been tried and tested for over forty years, and consistently shown to be null. Evidence from epidemiological surveys, prospective studies, and clinical trials time and again indicate that eggs and dietary cholesterol have no significant relationship to hypercholesterolemia or cardiovascular disease risk. Recent studies have even shown that components within eggs, choline and lutein, actually help lower cardiovascular disease risk as well as making important contributions to the nutritional well-being of the public. In contrast to the United States, many countries have no dietary cholesterol restrictions and inclusion of eggs is advocated by health promotion organizations for their many contributions to health promotion and disease prevention. The eggs and heart disease hypothesis has failed the test of time and should be considered null and void.

History of a Hypothesis

In 1968 the American Heart Association added to its dietary recommendations for those at high risk for heart disease a restriction in dietary cholesterol to less than 300 mg per day,c and a specific restriction on egg consumption to no more than 3 whole eggs per week. Two points are of interest in that there was no scientific justification for selecting 300 mg per day as the limit (other than the average intake was 580 mg per day) and this was the only food specific restriction in the set of recommendations. Understandably it was difficult in 1968 to discuss total and saturated fat since consumers had little knowledge on this issue and the much simpler expressed relationship of cholesterol in food equals cholesterol in the blood would involve animal products in the diet which were the sources of dietary saturated fat. Except for the egg which, while high in cholesterol, contains a relatively modest 1.5 grams of saturated fat per 50 gram egg. One of the consequences of this focus on dietary cholesterol and eggs was that the egg became the icon for both high dietary cholesterol and high blood cholesterol and, even if the evidence was weak for a relationship, the message was simple and easily conveyed by health professionals not only to their high risk patients but to the public at large.

The justification for the focus on dietary cholesterol came from three lines of research evidence – animal studies, epidemiological surveys, and clinical investigations. All of these have their strengths and weaknesses and interpretation plays a major role in how the evidence is used to set recommendations. For example, feeding cholesterol to a herbivore species like the rabbit results in pronounced hypercholesterolemia and development of atherosclerosis. In contrast, feeding

cholesterol to an omnivore or carnivore species, like the dog or rat, has little effect on any of these end points. There is also the question of dosage in that feeding pharmacological levels of cholesterol to a primate species can result in hypercholesterolemia simply due to the animal's inability to metabolically compensate for such massive doses (a human equivalent of 3,500 mg/day). Similar complications are seen in the early cholesterol feeding studies where subjects are fed 1,000 to 3,000 mg per day to induce a change in plasma cholesterol levels even though the body's endogenous cholesterol production is only 850 mg per day for a 70 kg adult. The body's metabolic regulatory systems were simply overwhelmed by the excess dose. And much of the epidemiological evidence was based on simple correlations between dietary cholesterol intakes and heart disease incidence with no correction for the fact that dietary cholesterol and saturated fat, also found by simple correlation analysis to be related to heart disease risk, were correlated with each other. Even though these various arguments were raised during the discussions of recommending dietary cholesterol restrictions, it was judged that no harm would be done and some benefit might accrue. A best guess became a recommendation and today is viewed as recommendation based on sound scientific evidence. As once noted by H.L. Menckin: "For every problem, there is a solution that is simple, neat, and wrong."

The Great Tragedy of Science - The Slaying of A Beautiful Hypothesis By An Ugly Fact. (T.H. Buxley)

Once the dietary cholesterol and egg restrictions became part of the "Prudent Diet" approach to heart disease prevention there was little scientific or research room for argument or questioning of the policy. There were a number of outspoken critics of the dietary cholesterol and egg guidelines but for the most part the naysayers were marginalized and discounted (for a complete history of the diet-heart disease battles read Good Calories, Bad Calories by Gary Taubes (Taubes, 2007). For many skeptics in the scientific community the application of reverse onus (now it needed to be proven that eggs did not cause heart disease) was an insurmountable obstacle and was set aside in favor of more achievable objectives. It has taken forty years of research to begin to undo the effects of those early condemnations and the cholesterol-phobia much of the world suffered from.

The undoing of this hypothesis came about from both advances in our understanding of the intricacies involved in the diet-heart disease relationship and progress in research defining more precisely lipoprotein risk factors for heart disease and how they were affected by dietary factors. As in all studies of the relationships between diet and health, three lines of evidence were used to test the dietary cholesterol-heart disease relationship: animal model studies, analysis of epidemiological survey data, and clinical interventions. All three lines of evidence, used initially to formulate the hypothesis, failed to validate the hypothesis over time.

A Hypothesis Based on a Best Guess

Animal Model Studies: Feeding cholesterol to rabbitts results in pronounced dyslipidemia and the development of atherosclerosis(Anitschkow and Chalatow, 1913). Feeding cholesterol to a dog or rat has little if any effect on plasma cholesterol levels. To develop hypercholesterolemia in some primate species it is necessary to feed the human dietary cholesterol equivalent of 3,000 mg per day. The majority of animal species, when fed a physiological amount of cholesterol in

the diet, have little change in their plasma cholesterol profile due to appropriate metabolic feedback mechanisms. When cholesterol is fed, endogenous cholesterol synthesis is suppressed and bile acid synthesis and excretion is increased (Dietschy, 1984). These compensatory mechanisms are sufficient to maintain a steady state level of plasma cholesterol with no change in atherosclerotic risk. The quandary becomes which animal model best mimics the human condition. Many investigators would contend that probably no animal model best mimics the human response to dietary cholesterol for a number of reasons: differences in the plasma lipoprotein profile and the factors involved in lipoprotein remodeling, and differences in the tissue distribution of endogenous cholesterol synthesis and sterol excretion patterns being two major considerations, as well as species differences in the response to dietary factors (Fernandez, 2001; Fernandez et al., 1999).

Analysis of Epidemiological Survey Data: In 1968 the use of simple correlation analyses showd that both dietary cholesterol and dietary saturated fat were related to elevated plasma cholesterol levels and heart disease risk. Unfortunately, since both are found in animal products, they are significantly related to each other. Analysis of epidemiological survey data using multivariant analysis indicated that while saturated fat was independently related to heart disease risk, the significant relationship for dietary cholesterol was lost once the covariance with saturated fat was accounted for (Hegsted and Ausman, 1988; Kromhout et al., 1995). As noted by Ravnskov (Ravnskov, 1995), in eleven reports from prospective and retrospective epidemiological studies there was no differences in dietary cholesterol intakes between cases and controls. And when applied to eggs, which have a high cholesterol content but are relatively low in saturated fat, there was no significant relationship between egg intake and heart disease risk. Across cultures there is no significant relationship between per capita egg intake and cardiovascular disease mortality rates (Lee and Griffin, 2006; McNamara, 2000a).

A number of studies have looked specifically at the relationship between egg consumption and either plasma cholesterol levels or heart disease risk (Dawber et al., 1982; Hu et al., 1999; Nakamura et al., 2006; Qureshi et al., 2007; Song and Kerver, 2000; Tillotson et al., 1997). These studies have consistently shown that egg intake is unrelated to either plasma cholesterol levels or to heart disease risk (Kritchevsky, 2004; Kritchevsky and Kritchevsky, 2000). In these studies, the relative risk for coronary heart disease was the same whether one ate one egg a week or one egg a day. These findings are consistent with the body of epidemiological analysis reporting that dietary cholesterol is unrelated to heart disease risk within populations (Lee and Griffin, 2006; McNamara, 2000a, 1999). Recent studies investigating the effects of dietary lipids on subclincal atherosclerosis have also reported the absence of a relationship between dietary cholesterol intakes and mean carotid intimal medial thickness (Merchant et al., 2008).

Clinical Interventions: In the early days of metabolic ward studies on the effects of dietary factors on plasma cholesterol levels, patients were often fed liquid formula diets to have precise control over the composition of the dietary fat and the amount of dietary cholesterol. Unfortunately, in many cases this led to dietary cholesterol challenges not with physiological levels but with pharmacological levels of 1,000 to 4,000 mg per day added to liquid diets with 40% of calories as coconut oil. Once the endogenous cholesterol metabolic capacity was overwhelmed, there was obviously an increase in plasma cholesterol levels as the body attempted to excrete the excess (McNamara, 1987; McNamara, 1990). In addition, virtually all of the

earlier studies used to justify the dietary cholesterol restriction used total plasma cholesterol levels as the surrogate marker for assumed changes in heart disease risk.

As the pattern of research studies shifted from formula feeding to solid foods and more rational cholesterol intakes, and the variables shifted from total to lipoprotein cholesterol levels, the evidence supporting the atherogenicity of dietary cholesterol began to progressively weaken. However, a consistent finding from study after study was the high degree of variability of the plasma cholesterol responses to a dietary cholesterol challenge between patients. In order to explain this variability it is necessary to consider the inter-individual differences in cholesterol metabolism.

Cholesterol synthesis is a function of body weight, approximately 12 mg/kg-day. Therefore, changes in plasma cholesterol with the same dietary cholesterol challenge will differ for individuals having different body weights. Studies also indicate that the fractional absorption rate for cholesterol is highly variable, ranging from 20 to 80%, with an average of 55% (McNamara, 1987). Based on these considerations, it is easy to understand why feeding an additional 500 mg per of cholesterol to a 100 kg male with a fractional absorption rate of 20% will have a very different effect on plasma cholesterol levels as compared to the same dietary cholesterol challenge to a 50 kg female with an absorption rate of 80%. Only a limited number of cholesterol feeding studies have adjusted for differences in body weights and fractional absorption rates between patients (McNamara et al., 1987). Numerous analyses have shown that the average weight adjusted plasma cholesterol response to a 100 mg/day increase in dietary cholesterol in a 70 kg individual is an increase in plasma total cholesterol of 2.4 mg/dl (0.062 mmol/L) with increases in both the LDL cholesterol (1.9 mg/dl, 0.049 mmol/L) and HDL cholesterol (0.4 mg/dl, 0.010 mmol/L) (Clarke et al., 1997; Howell, 1998; McNamara, 2000b; McNamara, 1990; Weggemans et al., 2001). These studies indicate that, while adding cholesterol does have a small effect on plasma cholesterol levels, there is little if any change in the LDL:HDL cholesterol ratio, an important determinant of cardiovascular disease risk (Fernandez and Webb, 2008; Herron et al., 2002; Herron et al., 2003). Data also indicate that changes in LDL cholesterol levels are not due to changes in the number of LDL particles but rather due to changes in the cholesterol content of the LDL particles resulting in less atherogenic large, buoyant LDLs (Herron et al., 2004) rather than the more atherogenic small, dense LDL particles (Williams et al., 2003). With little effect on the LDL:HDL cholesterol ratio (Fernandez, 2006; Herron and Fernandez, 2004) or on LDL particle number (Hsia et al., 2008), dietary cholesterol has little effect on cardiovascular disease risk, as documented by the various epidemiological survey analyses (Kritchevsky, 2004; Kritchevsky and Kritchevsky, 2000).

Do No Harm

Restrictions of high quality, nutrient rich foods like eggs from the diet because of their cholesterol content is not risk free. An affordable source of high quality animal protein in the diet, especially a source that is widely available and easy to cook, chew and digest is of significant importance for growth and development as well as maintaining lean muscle tissue mass in the elderly (Houston et al., 2008). Eggs are also an excellent source of the essential nutrient choline (Zeisel, 2006) which has been shown to be inadequate in the diets of 9 out of 10 individuals. Choline plays an important role in fetal and neonatal brain development (Zeisel and

Niculescu, 2006) and inadequate choline intake during pregnancy increases the risk for neural tube defects such as spina bifida (Shaw et al., 2004). Choline is also related to decreased levels of plasma inflammatory factors and homocysteine which are related to increase cardiovascular disease risk (Detopoulou et al., 2008; Konstantinova et al., 2007). Eggs also provide highly bioavailable forms of the xanthophylls lutein and zeaxanthin which are related to lower risks for age-related macular degeneration and cataracts (Chung et al., 2004; Goodrow et al., 2006; Ribaya-Mercado and Blumberg, 2004; Wenzel et al., 2006) as well as some types of cancer (Huang et al., 2007; Mannisto et al., 2007; Slattery et al., 2000) and carotid artery atherosclerosis (Dwyer et al., 2001). Restricting eggs in the diet can have negative consequences and, based on the available data, little benefit in terms of cardiovascular disease risk reduction. It is essential that any food's value to health promotion – disease prevention be based on its totality of nutrients and not just a single component.

Summary

For over forty years the scientific community has debated the dietary cholesterol – blood cholesterol relationship and the rationale for restricting high cholesterol foods, like eggs, in the diet. What the epidemiological surveys show is that there is no relationship between dietary cholesterol intakes and either blood cholesterol levels or cardiovascular disease risk between or within populations. The only group found to have an increased cardiovascular disease risk with increased egg intake are those with type II diabetes (Hu et al., 1999; Qureshi et al., 2007); however, this may relate to the degree of diabetic control in the study population. Until this question is resolved there is justification in recommending that patients with type II diabetes limit their egg intake to less than 6 per week based on the available data.

Clinical studies form the basis of continued dietary cholesterol restrictions in some populations based on dietary cholesterol induced changes in total cholesterol levels. This change does not reflect change in cardiovascular disease risk when considered in light of the lack of effect of dietary cholesterol on the LDL:HDL cholesterol ratio (Fernandez and Webb, 2008) or on the number of LDL particles (Hsia et al., 2008). There is no conflict between the observed lack of effect of dietary cholesterol on cardiovascular disease risk observed in epidemiological surveys and the small change in plasma cholesterol levels observed in clinical feeding studies when the specific effects of dietary cholesterol on the atherogenicity of the plasma lipids is fully analyzed.

The lack of evidence for a relationship between dietary cholesterol and heart disease risk is why most countries of the world do not specifically recommend dietary cholesterol restrictions. In fact, in Canada and Australia eggs carry the approval marking of their respective heart associations. Given the available evidence, it would seem that the only health risk associated with egg consumption is that associated with unnecessary restrictions on egg intake.

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Effects of dietary cholesterol on plasma lipoprotein cholesterol levels[1].

	Δ plasma cholesterol per 100 mg/day increase in dietary cholesterol		
Diet[2]	Mean	P:S < 0.7	P:S > 0.7
Total cholesterol	2.2	2.7	1.7
LDL cholesterol	1.9	2.4	1.4
HDL cholesterol	0.3	0.3	0.3

[1]Data from (Weggemans et al., 2001)

[2]P:S = ratio of polyunsaturated to saturated fat in the test diet.