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Egg consumption and endothelial function: a randomized controlled crossover trial

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Abstract

Background: Because of egg cholesterol content, reduction in egg consumption is generally recommended to reduce risk of cardiovascular disease. Recently, however, evidence has been accumulating to suggest that dietary cholesterol is less relevant to cardiovascular risk than dietary saturated fat. This randomized controlled crossover trial was conducted to determine the effects of egg ingestion on endothelial function, a reliable index of cardiovascular risk. *Methods:* Forty-nine healthy adults (mean age 56 years, 40% females) underwent a baseline brachial artery reactivity study (BARS), and were assigned to two eggs or oats daily for 6 weeks in random sequence with a 4-week washout. A BARS was done at the end of each treatment phase, measuring flow-mediated vasodilation (FMD) in the brachial artery using a high-frequency ultrasound. *Results:* FMD was stable in both egg and oat groups, and between-treatment differences were not significant (egg −0.96%, oatmeal −0.79%; p value >0.05). Six weeks of egg ingestion had no effect on total cholesterol (baseline: 203.8 mg/dl; post-treatment: 205.3) or LDL (baseline: 124.8 mg/dl; post-treatment: 129.1). In contrast, 6 weeks of oats lowered total cholesterol (to 194 mg/dl; $p=0.0017$) and LDL (to 116.6 mg/dl; $p=0.012$). There were no differences in body mass index (BMI), triglyceride, HDL or SBP levels between egg and oat treatment assignments. *Conclusion:* Short-term egg consumption does not adversely affect endothelial function in healthy adults, supporting the view that dietary cholesterol may be less detrimental to cardiovascular health than previously thought.

Keywords: Egg consumption; Endothelial function; Randomized controlled crossover trial

1. Introduction

Restricted egg consumption is widely recommended in efforts to lower blood cholesterol and mitigate risk of heart disease. However, there has been little if any evidence that egg consumption is directly related to cardiovascular risk [1,2]. On the contrary, large epidemiological studies have found that consumption of one egg per day is unlikely to have any substantial effect on cardiovascular disease risk in healthy subjects [3,4]. Moreover, there has been a lack of consistent literature to support the notion that regular or near-regular egg ingestion leads to substantial elevation in serum lipids and total cholesterol levels [1,5].

Because there are many serum moieties used to gauge cardiac risk, a physiologic measure that captures their aggregate influence is desirable. Endothelial function, which refers to arterial vasomotor responses mediated through release of chemical mediators including nitric oxide (vasodilating) and endothelin (vasoconstricting) from the vascular endothelium [6], is generally viewed as such a measure. Impaired release of nitric oxide results in endothelial dysfunction which can be detected non-invasively by use of ultrasound as the propensity of vessels to constrict and impede flow in response to stimuli that should lead to dilatation and flow augmentation [7]. One method of assessing endothelial function non-invasively is by the induction of hyperemic flow and sheer stress to stimulate nitric oxide release [8]. Due to the strong correspondence between peripheral and coronary endothelial responses [9], measurement of flow-mediated dilatation (FMD) of the brachial artery using high-resolution ultrasound is a standard assessment method [10].

Endothelial dysfunction anticipates the development of anatomically overt coronary artery disease [9], correlates

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strongly with both coronary disease and its risk factors [11] and reverses in response to risk modification efforts [12]. While a definitive association between endothelial function and clinical events awaits the results of an on-going multicenter trial, endothelial dysfunction has increasingly been viewed as an indicator of coronary risk [9], and its amelioration as an indicator of risk reduction [12,13].

Endothelial function testing has been used extensively to evaluate the acute and chronic effects of foods and nutrients on cardiac risk [14–17]. In previous studies, oat ingestion has produced favorable effects on endothelial function in healthy adults challenged with a high-fat test meal [18,19], and in adults with features of insulin resistance [20]. We therefore used oat ingestion as a positive control and conducted a randomized controlled crossover trial of short-term (6 weeks) daily ingestion of eggs on endothelial function and lipid levels in healthy adults.

2. Materials and methods

2.1. Subjects

A total of 50 healthy adult men ($n=31$) and women ($n=19$) were recruited from the greater Lower Naugatuck Valley, CT, primarily through mass media (newspaper advertisements, press releases) and posters. The sample size was determined to allow for 10% attrition and provide at least 80% power to detect a minimal difference of 4.0% in FMD between treatment groups at a two-tailed alpha level of 0.05. Inclusion criteria were: (1) age greater than 35 for males; (2) post-menopausal and not currently using hormone replacement therapy for females; (3) non-smokers; (4) no known coronary artery or other vascular disease; (5) no vasoactive medication use; (6) no regular use of high dose vitamin E or fiber supplements. Subjects from all ethnic and minority groups were equally eligible for study participation.

Individuals failing to meet inclusion criteria, including those with hypercholesteremia (total cholesterol (T_{chol}) greater than 240, or T_{chol}/HDL ratio greater than 4.5 for women, or 5.5 for men), or anticipated inability to complete the study protocol for any reason were excluded. Those subjects ($n=107$; $m=57$, $f=50$) who responded to recruitment efforts were prescreened using a semi-structured telephone interview. Subjects who met initial prescreening criteria ($n=94$) underwent a clinical screening examination (height, weight, body mass index (BMI), waist, hip and blood pressure measurements) performed by the clinical research specialist, and laboratory testing (fasting total cholesterol, HDL, LDL and triglyceride levels). The 50 eligible subjects enrolled were randomly assigned to six groups. Each group was then randomly assigned to a treatment sequence. Subjects could not be blinded to treatment assignment; however, the ultrasonographer was strictly blinded to treatment assignment. All subjects provided informed consent prior to randomization. Participants were compensated monetarily for their time.

2.2. Methods

Subjects first presented for baseline brachial artery reactivity studies (BARSs), lipid panel and weight measurements following an overnight fast. Subjects then returned for 3 consecutive weeks and underwent BARS following oatmeal ingestion, egg ingestion and ingestion of a sausage and cheese sandwich (comparable to McDonald's Sausage McMuffin™) [15] high in saturated fat, in random sequence. These single acute doses of egg, oats and sausage/cheese sandwich were administered before the start of the sustained intervention to gain some preliminary insight into the direction of effect on FMD of a single dose of each study treatment (eggs and oats) relative to the high-saturated fat breakfast sandwich.

Subject assignment to treatment groups was performed by the data manager using block randomization with one subject per block. Groups were randomly assigned to each of the two treatment assignments (eggs or oatmeal) daily for a period of 6 weeks, followed by BARS and laboratory testing, a 4-week washout period, then crossover to the other treatment, again followed by BARS and laboratory testing. The daily oat treatment during the sustained phase consisted of 60 g uncooked whole oats. The daily egg treatment consisted of two eggs. Subjects were at liberty to prepare the treatment foods according to preference, but were encouraged to consume them as part of the breakfast meal. On the day of testing, BARS, lipid panel, and weight measurement were performed in the morning following an overnight fast. Immediately after the baseline scan, each subject received the assigned treatment; eggs were prepared hard boiled, oatmeal was served plain. BARS testing was repeated exactly 3 h post-prandially for each subject.

Subjects were instructed to return all egg and oatmeal containers to confirm compliance. Subjects also completed a 3-day food diary during each treatment period, including the 4-week washout, as well as a side-effects survey.

Informed consent was obtained from each subject and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Griffin Hospital Institutional Review Board.

2.3. Vascular reactivity testing: brachial artery reactivity studies

Each vascular reactivity test consisted of pre- and post-prandial BARS. Endothelial function was measured non-invasively in the right brachial artery by means of a high frequency ultrasound machine (Phillips Medical Systems; Sonos 4500) in accordance with published guidelines [10]. Subjects were required to lie at rest in the quiet, temperature-controlled, softly lit room for at least 15 min before scanning was initiated. The baseline diameter of the bra-

chial artery was measured from two-dimensional ultrasound images using a high frequency, 10–15 MHz, vascular ultrasound transducer (Phillips Medical Systems 15-6L L7540 linear array transducer). Arterial flow-velocity was measured by means of a pulsed Doppler signal at a 70° angle to the vessel, with the range gate in the center of the artery. Flow is determined by multiplying the arterial cross-sectional area (πr^2) by the Doppler flow velocity. The timing of each image frame with respect to the cardiac cycle is determined with simultaneous ECG gating during image acquisition via the high-quality mainframe ultrasound system. Measurements were taken from the anterior to the posterior "m" line in diastole. The brachial artery was imaged at a location 3–7 cm above the antecubital fossa in the longitudinal plane. A segment with clear anterior and posterior intimal interfaces between the lumen and vessel wall was selected for continuous 2D gray scale imaging. The transmit (focus) zone was set to the depth of the near wall because of difficulty in differentiating the near from the far wall "m" line (the interface between media and adventitia). Images were acquired on videotape and magnetic optical disk for evaluation and analysis. Diameter was obtained from m-line to m-line, over a consistent segment of vessel at least 10–15 mm in length. To create a flow stimulus in the brachial artery, a sphygmomanometer (blood pressure cuff) was placed on the upper arm proximal to the transducer. The cuff was inflated for 5 min. Repeat scans were obtained at 15, 60 and 120 s post-deflation. At each scanning interval, both cross-sectional vessel diameter and flow velocity were recorded. Measures of vessel diameter and flow velocity were obtained by a single dedicated vascular clinical research specialist blinded to subject treatment status. Velocity measures were generated automatically, while the arterial diameter was measured at a fixed distance from an anatomical marker, such as a bifurcation, with ultrasonic calipers recorded on magnetic–optical disk. A random sample of 30 BARS were provided to the clinical research specialist for a blinded second reading. The resultant coefficient of intraobserver reliability was 0.95.

Table 1
Baseline clinical characteristics of study population by gender

Variables (not including one male dropout in acute phase)	Mean ± S.D.	
	Male ($n=30$)	Female ($n=19$)
Age (years)	54.1 ± 9.9	59.2 ± 8.5
BMI (kg/m^2)	28.1 ± 3.5	29.5 ± 10.7
Total cholesterol (mg/dl)	196.2 ± 31.1	215.7 ± 28.4
HDL (mg/dl)	46.1 ± 10.2	63.1 ± 14.7
LDL (mg/dl)	120.8 ± 24.7	131.2 ± 24.2
Triglycerides (mg/dl)	146.2 ± 80.9	118.8 ± 68.7
Reference diameter (cm)	0.40 ± 0.07	0.32 ± 0.05
Diameter change 60 s to baseline (cm)	0.04 ± 0.03	0.03 ± 0.04
% Diameter change 60 s to baseline	11.0 ± 9.4	11.1 ± 12.8
Systolic blood pressure (mm Hg)	129.8 ± 11.7	131.9 ± 16.0
Diastolic blood pressure (mm Hg)	79.2 ± 9.5	79.7 ± 13.1

S.D. = Standard deviation.

Table 2
Flow-mediated dilatation (FMD) after an acute treatment with egg, oatmeal, or sausage and cheese ($n=49$)

Treatment	Pre-prandial*	Post-prandial*	% Change
Egg	13.7 ± 11.0	9.6 ± 11.5†‡	− 4.04‡
Oatmeal	8.3 ± 13.0	8.4 ± 10.3†‡	− 0.14‡
Sausage and cheese	10.9 ± 7.6	10.4 ± 9.9†‡	− 0.50‡

* Mean ± S.D.
† p Value >0.05 adjusting with pre-prandial (paired t test).
‡ p Value >0.05 compared to other treatments (ANOVA).

2.4. Statistical analysis

All data were entered and stored by a dedicated data manager using Microsoft Excel 2000. Data were manually checked for entry accuracy. Flow-mediated dilatation, or FMD, was calculated as the percent change in diameter post-occlusion of brachial artery at 60 s relative to the measurement at baseline before cuff inflation {[(response− baseline)/baseline] × 100}. FMD was calculated during the pre-prandial state and post-prandial state. A difference measure between post-prandial FMD and pre-prandial FMD was calculated to determine the value of post-prandial FMD after adjusting with pre-prandial FMD.

All data analysis was conducted using SAS software (Version 8.1 of the SAS System for Windows; SAS Institute, Cary, NC). A two-tailed p value of <0.05 was considered statistically significant. The change in hyperemic response among the two treatment groups was measured using repeated measures ANOVA. To control for type I comparison-wise error rate, Duncan's Multiple Range Test for treatments was included. In the analysis, treatment and time are considered as the main effects to compare treatment-specific measures while accounting for time differences. Paired t tests were performed to compare pre- and post-prandial vascular responses within treatments. To account for variability in the strength of the stimulus that triggered endothelial reactivity (i.e., the hyperemic flow

Table 3
FMD after 6 weeks of treatment with egg or oatmeal ($n=49$)

Treatment	Pre-prandial*	Post-prandial*	% Change
Egg			
Reference diameter (cm)	0.43 ± 0.08	0.43 ± 0.08	–
Hyperemic diameter at 60 s (cm)	0.47 ± 0.08	0.44 ± 0.07	–
Flow-mediated vasodilation (FMD)	8.66 ± 9.69	8.32 ± 6.33†‡	− 0.96‡
Oatmeal			
Reference diameter (cm)	0.43 ± 0.07	0.43 ± 0.07	–
Hyperemic diameter at 60 s (cm)	0.46 ± 0.08	0.47 ± 0.07	–
Flow-mediated vasodilation (FMD)	6.98 ± 8.45	6.56 ± 7.99†‡	− 0.79‡

* Mean ± S.D.
† p Value >0.05 adjusting with pre-prandial (paired t test).
‡ p Value >0.05 compared to different treatments (ANOVA).

induced to stimulate endothelial response), FMD was divided by flow at 15 s post-cuff deflation to create a stimulus-adjusted response measure. The study was powered at a minimal level of 80% to test the primary hypothesis that egg ingestion differs from oat ingestion with regard to effects on endothelial function.

3. Results

Subjects ranged in age from 36 to 73, with a mean age of 55.7 years. Demographic data for the study population are provided in Table 1. A total of 49 subjects completed the study. One male subject dropped out for unknown reasons.

With acute administration, both egg and the sausage/cheese breakfast sandwich resulted in a non-significant decline in FMD, while oat ingestion produced a non-significant increase (see Table 2). The treatments did not differ significantly from one another, nor were there inter-treatment correlations in FMD response.

With daily ingestion of eggs or oats for 6 weeks, there were no statistically significant differences in endothelial function between treatment groups. FMD following egg treatment did not differ from baseline with regard to the pre-prandial or post-prandial measures. In a paired t test analysis, the mean FMD difference (between pre-and post-prandial responses) for egg treatment was not significant (-0.96; $P>0.05$).

Results following oat treatment were similar, with no differences from baseline in pre-prandial FMD, post-prandial FMD or the difference between pre- and post-prandial measures (see Table 3). These findings persist after controlling for type I comparison-wise error. There was no significant difference between treatment groups for stimulus adjusted response measures.

Ingestion of egg for 6 weeks had no effect on total cholesterol (baseline: 203.8 mg/dl; post-treatment 205.3) or LDL (baseline: 124.8 mg/dl; post-treatment: 129.1). In contrast, ingestion of oat treatment for 6 weeks lowered total cholesterol to 194 mg/dl ($p=0.0017$) and LDL to 116.6 mg/dl ($p=0.012$). Post-treatment total cholesterol ($p=0.0008$) and LDL ($p=0.0006$) were both lower following treatment with oat than with egg. There were no differences in body mass index, triglyceride, HDL or SBP level between the egg and oat assignments (see Table 4).

Table 4
Outcome variables after 6 weeks of treatment with egg or oatmeal

Variables	Mean ± S.D.		
	Baseline	Egg	Oatmeal
BMI (kg/m^2)	28.7 ± 7.2	28.1 ± 5.8	28.5 ± 5.7
Total cholesterol (mg/dl)	203.8 ± 31.5	205.3 ± 35.6	194.0 ± 30.5*
HDL (mg/dl)	52.6 ± 14.6	51.2 ± 15.1	53.3 ± 16.5
LDL (mg/dl)	124.8 ± 25.0	129.1 ± 32.2	116.6 ± 30.8*
Triglycerides (mg/dl)	135.6 ± 77.3	126.6 ± 72.8	122.5 ± 75.7
Reference diameter (cm)	0.37 ± 0.07	0.44 ± 0.07	0.43 ± 0.07
Diameter change 60 s to baseline (cm)	0.04 ± 0.04	0.48 ± 0.07	0.48 ± 0.07
% Diameter change 60 s to baseline	11.0 ± 9.5	8.3 ± 6.3	6.6 ± 8.0
Systolic blood pressure (mm Hg)	129.8 ± 11.7	124.9 ± 10.9	124.1 ± 12.5
Diastolic blood pressure (mm Hg)	79.4 ± 9.1	77.4 ± 7.0	77.5 ± 8.7

*p Value <0.05 compared to baseline value.

4. Discussion

To our knowledge, this is the first study to demonstrate the effect of egg ingestion on endothelial function. Our findings provide evidence that short-term egg consumption (6 weeks) does not adversely affect endothelial function in healthy adults. Moreover, consuming two eggs daily did not alter serum cholesterol or other measures of the lipid profile.

The prevailing view has long been that dietary cholesterol contributes to elevated serum cholesterol, thereby increasing heart disease risk [21–23]. The association between dietary cholesterol and serum cholesterol, independent of dietary fat, is at best controversial, however [24,25]. Concern over egg consumption and potential adverse effects on cardiovascular health stems from the high cholesterol content (approximately 213 mg of cholesterol) of egg yolk. However, there is limited if any epidemiological evidence that egg consumption is directly related to cardiovascular disease or mortality risk [1,3,4]. On the contrary, a recent large epidemiologic study concluded that consumption of one egg per day is unlikely to have any substantial effect on cardiovascular disease risk in healthy subjects [3]. Analysis of Framingham data for 912 subjects revealed no relationship between the incidence of coronary heart disease and tertile of egg intake [4]. Other studies investigating cholesterol effects of egg consumption failed to show significant increase in serum cholesterol levels [26], LDL or triglycerides [27]. However, others report finding mild increases in LDL and total cholesterol [28,29].

Egg ingestion is associated with mild increases in HDL [27,30]. Homeostatic control of cholesterol absorption and elimination may physiologically adapt to increasing dietary cholesterol intake by limiting the amount of cholesterol absorbed at higher dietary intake levels and by down-regulation of cholesterol biosynthesis [31,32]. In the aggregate, the evidence supports an important role for internal metabolic control over serum cholesterol levels, with dietary fat (quality and quantity) influencing plasma cholesterol far more than dietary cholesterol [25].

The relative importance of dietary cholesterol to cardiovascular risk, and the association between dietary and serum cholesterol are both subject to ongoing debate [24,33,34]. The association between dietary cholesterol and coronary events and mortality is generally positive but rather weak, and derived largely from ecological and prospective cohort studies with variable follow-up [33,

35,36]. In most such studies, covariance of dietary fat and cholesterol intakes makes it difficult to un-bundle their effects reliably.

While rich in cholesterol, eggs are also rich in monounsaturated fatty acids, polyunsaturated fatty acids and micronutrients, and provide relatively little total fat and proportionately little saturated fat compared to other sources of animal protein [37,38]. Data from NHANES III reveal that egg consumption is an important nutritional contribution to the average American diet [2], providing a relatively inexpensive source of amino acids and essential fatty acids [39]. Eggs provide arginine, a precursor to nitric oxide, which, in turn, plays a central role in endothelial function [40].

While providing valuable, preliminary data regarding egg ingestion and cardiovascular health, this study naturally has limitations. The sample size was relatively small and derived from the population of one confined geographic area in CT. Dietary intake data, including compliance to the treatment assignment, were tracked by food diaries and suggest no significant unintended changes in dietary pattern during the study. Nonetheless, changes in diet or behavior that were not captured might have contributed to the findings observed. Subjects were not instructed to eliminate either of the two treatment assignments from their normal diets during the study. The duration of egg consumption during this study limits the ability to project long-term effects of egg ingestion. The study cohort was limited to healthy adults; the implications for other groups are uncertain. However, the strong correlation between endothelial function and clinical risk factors for coronary heart disease, coronary atherosclerosis, myocardial infarction and unstable angina [41], suggests that these findings are of considerable potential importance.

In conclusion, short-term, sustained ingestion of two eggs daily did not adversely affect endothelial function or cholesterol levels in healthy adults. Our findings are consistent with the view that dietary cholesterol may be less detrimental to cardiovascular health than previously thought. Investigation of the differences between saturated (and trans) fat and dietary cholesterol effects on diverse measures of cardiac risk is warranted, as is further study of the health effects of habitual egg ingestion in diverse populations. In the interim, there appears to be no clear reason to exclude moderate intake of eggs from the dietary patterns of healthy adults.

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