

Does dietary cholesterol influence cardiovascular disease risk in people with type 2 diabetes?^{1,2}

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In this issue of the Journal, Fuller et al. (1) showed in a large cohort of 140 people with prediabetes or well-controlled type 2 diabetes that 12 eggs/wk for 3 mo did not elevate LDL cholesterol compared with 2 eggs/wk. Does this completely exonerate eggs and mean no restriction is necessary for people with type 2 diabetes? It would be unwise to base decisions on one trial, especially given the epidemiology linking dietary cholesterol intake and cardiovascular disease (CVD) outcomes in people with type 2 diabetes (2–4) and even in those without type 2 diabetes (5). The participants in this study were overweight or obese with an average BMI (in kg/m²) of 34. More than half were taking hypolipidemic medication, presumably statins. As a group, because of their high BMI they are likely to have 10–15% higher cholesterol synthesis and 20% lower cholesterol absorption than lean individuals without glucose intolerance (6), so they are less likely to respond to increased dietary cholesterol with an increase in either HDL or LDL cholesterol. How statins would influence the response to dietary cholesterol is not clear, but simvastatin has been shown to blunt the HDL and LDL response to dietary fat (7). However, doubling dietary cholesterol will increase the intestinal and lymphatic transit of cholesterol even if absorption is 20% lower, so one would expect to see cholesterol-enriched chylomicron remnants appearing in plasma, especially in hypertriglyceridemic persons, even if fasting variables do not change (8). Taggart et al. (9) performed a fat-feeding study with and without 1 g cholesterol in 10 people with type 2 diabetes and in 10 age-matched controls. Postprandial chylomicron cholesterol and triglycerides increased in both groups with cholesterol feeding but apolipoprotein B-48 concentrations were lower. VLDL apolipoprotein B-48 concentrations increased 10-fold in persons with type 2 diabetes compared with threefold in controls after the cholesterol-rich meals, whereas apolipoprotein B-100 was similar with both meals in the 2 groups. Cholesterol-enriched chylomicron and VLDL remnants are generally regarded as atherogenic (10); and postprandial triglyceride concentrations, which reflect these remnants at 4–6 h, are related to nonobstructive coronary artery disease as assessed by computed tomographic angiography (11).

Where does this study stand in relation to the vast amount of data on cholesterol feeding in humans? Weggemans et al. (12) performed a meta-analysis of 17 feeding studies involving 556 individuals and found that 100 mg dietary cholesterol elevated total cholesterol by 0.056 mmol/L (95% CI: 0.046, 0.065 mmol/L) and HDL

cholesterol by 0.008 mmol/L (95% CI: 0.005, 0.10 mmol/L), whereas in the study by Fuller et al. (1), the equivalent values for a 300-mg increase in dietary cholesterol are 0.03 (95% CI: –0.20, 0.26) mmol/L and 0.024 (95% CI: –0.30, 0.77) mmol/L for total and HDL cholesterol, respectively. So HDL-cholesterol changes are of the same magnitude as in the meta-analysis, whereas total-cholesterol changes appear to be much weaker; however, given the very wide CI, it could contain the true population mean, which might be similar to the mean of the meta-analysis. The cause of the wide variation in response might include differences between individuals in weight, age, or statin usage and none of these factors were examined in this trial. Previous trials generally were in young, lean individuals who might be more consistent in their responses. In addition, this study measured lipids only once before and after the dietary intervention, whereas other studies improved precision by taking at least 2 and frequently 3 fasting lipid samples before and after the intervention.

The primary hypothesis of the study was that dietary cholesterol would elevate HDL cholesterol, and the assumption in the article's Introduction and Discussion is that such an elevation would be beneficial and reduce CVD risk on the basis of the epidemiology of HDL cholesterol and the possibly beneficial effect of fenofibrate on HDL cholesterol and on CVD events. However, saturated fat is the most powerful HDL-cholesterol elevator, and there is little evidence that this is beneficial. Free-living persons with low HDL cholesterol while consuming a high-fat Western diet may have a genetic predisposition to faulty HDL-cholesterol and triglyceride metabolism, and it is this factor that may link HDL cholesterol to CVD risk (13) rather than the HDL cholesterol per se. In the one previous study in type 2 diabetes the combination of weight loss and dietary cholesterol elevated HDL cholesterol compared with weight loss alone, but LDL changes were not different (14).

Shin et al. (2) showed that consumption of >7 eggs/wk was associated with 69% more CVD events in men and women with type 2 diabetes. Rong et al. (3) found the risk of heart attack was 50% higher when comparing the highest with the lowest intakes

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of eggs in 4 studies of populations with diabetes, whereas Djoussé et al. (5) found that the consumption of ≥ 7 eggs/wk was associated with incident heart failure in US physicians. Given these data and the fact that coronary risk is not fully captured by fasting lipids, caution is needed in recommending daily egg consumption in people with type 2 diabetes. Similar caution about making conclusions on the basis of amount and quality of the intervention data has been expressed by others (5).

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REFERENCES

- Fuller NR, Caterson ID, Sainsbury A, Denyer G, Fong M, Gerofi J, Baqleh K, Williams KH, Lau NS, Markovic TP. The effect of a high-egg diet on cardiovascular risk factors in people with type 2 diabetes: the Diabetes and Egg (DIABEGG) study—a 3-mo randomized controlled trial. *Am J Clin Nutr* 2015;101:705–13.
- Shin JY, Xun P, Nakamura Y, He K. Egg consumption in relation to risk of cardiovascular disease and diabetes: a systematic review and meta-analysis. *Am J Clin Nutr* 2013;98:146–59.
- Rong Y, Chen L, Zhu T, Song Y, Yu M, Shan Z, Sands A, Hu FB, Liu L. Egg consumption and risk of coronary heart disease and stroke: dose-response meta-analysis of prospective cohort studies. *BMJ* 2013;346:e8539.
- Tran NL, Barraji LM, Heilman JM, Scrafford CG. Egg consumption and cardiovascular disease among diabetic individuals: a systematic review of the literature. *Diabetes Metab Syndr Obes* 2014;7:121–37.
- Djoussé L, Gaziano JM. Egg consumption and risk of heart failure in the Physicians' Health Study. *Circulation* 2008;117:512–6.
- Gylling H, Hallikainen M, Pihlajamäki J, Simonen P, Kuusisto J, Laakso M, Miettinen MA. Insulin sensitivity regulates cholesterol metabolism to a greater extent than obesity: lessons from the METSIM Study. *J Lipid Res* 2010;51:2422–7.
- Clifton PM, Wight MB, Nestel PJ. Is fat restriction needed with HMGCoA reductase inhibitor treatment? *Atherosclerosis* 1992;93:59–70.
- Clifton PM, Nestel PJ. Influence of dietary cholesterol on postprandial lipoproteins in three phenotypic groups. *Am J Clin Nutr* 1996;64:361–7.
- Taggart C, Gibney J, Owens D, Collins P, Johnson A, Tomkin GH. The role of dietary cholesterol in the regulation of postprandial apolipoprotein B48 levels in diabetes. *Diabet Med* 1997;14:1051–8.
- Masuoka H, Kamei S, Wagayama H, Ozaki M, Kawasaki A, Tanaka T, Kitamura M, Katoh S, Shintani U, Misaki M, et al. Association of remnant-like particle cholesterol with coronary artery disease in patients with normal total cholesterol levels. *Am Heart J* 2000;139:305.
- Staniak HL, Salgado Filho W, Miname MH, Benseñor IM, Lotufo PA, Sharovsky R, Rochitte CE, Bittencourt MS, Santos RD. Association between postprandial triglycerides and coronary artery disease detected by coronary computed tomography angiography. *Atherosclerosis* 2014;233:381–6.
- Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: a meta-analysis. *Am J Clin Nutr* 2001;73:885–91.
- Clifton PM, Noakes M. Impaired HDL response to fat in men with coronary artery disease. *Atherosclerosis* 2000;150:159–65.
- Pearce KL, Clifton PM, Noakes M. Egg consumption as part of an energy-restricted high-protein diet improves blood lipid and blood glucose profiles in individuals with type 2 diabetes. *Br J Nutr* 2011;105:584–92.