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Are eggs good again? A precision nutrition perspective on the effects of eggs on cardiovascular risk, taking into account plasma lipid profiles and TMAO ☆

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Abstract

Although eggs are a nutrient dense food delivering high quality protein and micronutrients, given that eggs are also rich in cholesterol and choline, whether egg intake is contraindicated for individuals at risk for cardiovascular disease (CVD) remains controversial. In this mini review, we provide a Precision Nutrition perspective, highlighting the importance of two factors: the effect of egg cholesterol on plasma cholesterol concentrations in most people and in cholesterol hyper-absorbers, and the effect of egg choline on plasma concentrations of trimethylamine-N-oxide (TMAO), a microbe-host co-metabolite independently associated with increased CVD risk. We discuss recent evidence from intervention studies showing that in most individuals egg intake does not have a deleterious effect on plasma lipid profiles, but also highlight that some individuals are cholesterol hyper-absorbers or individuals who are not able to maintain cholesterol homeostasis by suppressing endogenous cholesterol synthesis, and that for these individuals the intake of eggs and other dietary sources of cholesterol would be contraindicated. We also discuss the complex relationship between dietary sources of choline vs. phosphatidylcholine, the gut microbiome, and plasma TMAO concentrations, highlighting the high inter-individual variability in TMAO production and gut microbiome profiles among healthy individuals and those with metabolic conditions. Precision Nutrition approaches that allow the clinician to stratify risk and improve dietary recommendations for individual patients are desirable for improving patient compliance and health outcomes. More clinical studies are needed to determine how to identify individuals at risk for CVD for whom egg intake is contraindicated vs. those for whom egg intake is not associated with negative effects on plasma lipid profiles nor plasma TMAO concentrations.

Keywords: Egg; CVD; Cholesterol; TMAO; Gut microbiome; Choline.

1. Introduction

Eggs are a complete and convenient food packed with macro- and micronutrients, providing 7 g of complete protein, minerals such as Zn, bioactive antioxidant and anti-inflammatory components such as lutein and zeaxanthin, phospholipids, and a host of other nutrients, per 80-Calorie egg [1]. However, eggs are also enriched with cholesterol and choline, which have the potential to have deleterious rather than beneficial effects on cardiovascular disease (CVD) risk in certain population groups. In order to make Precision Health-based dietary recommendations to individuals it is critical to examine the appropriateness of any individual food or dietary component in the context of the risk and benefit profile of consuming that food at the individual level. In this mini review we evaluate recent evidence from dietary intervention studies on the effects of egg intake on cardiometabolic risk factors, including plasma lipid profiles and the novel gut microbiome-derived metabolite trimethylamine-N-oxide (TMAO). We also outline a strategy to clinically evaluate the appropriateness of egg intake for individuals at risk for CVD.

2. Do eggs raise plasma cholesterol?

Dietary cholesterol intake was at first thought to be associated with increasing plasma cholesterol concentrations [2], but it was later discovered that in most cases dietary cholesterol does not in fact raise plasma cholesterol, except in individuals with genetic polymorphisms in the ABCG5 and ABCG8 genes, which result in cholesterol hyperabsorption at the level of the intestinal tract [3]. Gut bacteria may also play a role in cholesterol absorption as individuals with microbes forming coprostanol have lower levels of fecal and serum cholesterol [4]. Interestingly, the decision has been made to remove the dietary cholesterol restriction of 300 mg/d from the US Dietary Guidelines [5], given recent evidence that dietary cholesterol, when not accompanied by high saturated fat content as with eggs, does not tend to raise plasma cholesterol in most individuals in both observational and intervention trials [6], and recent meta-analyses of large prospective US cohort

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studies showing that consumption of 1 egg per day is not associated with overall CVD risk factors [7].

The assumption of course, is that the dietary guidelines are meant for the "average" American and not individuals who may have the underlying genetic predisposition to hyper-absorb cholesterol. Because one egg contains approximately 200 mg cholesterol, it is important to understand whether for a given individual egg intake is appropriate due to low/normal dietary cholesterol absorption or inappropriate because of underlying genetic factors that increase cholesterol absorption and thus raise plasma cholesterol. Hyper-responders and hypo-responders to dietary cholesterol are classified as individuals whose total cholesterol concentrations increase (>2.2 mg/dL) or decrease (< 2.0 mg/dL) for every 100 mg/d of dietary cholesterol consumed, respectively [8]. The prevalence of sitosterolemia is at least 1 in 2.6 million and 1 in 360,000 for the *ABCG5* and *ABCG8* gene mutations, respectively, suggesting that a very small percentage of the population is affected by the known mutations [9]. There are tests available to clinicians that measure markers of cholesterol absorption (concentrations of phytosterols, campesterol and sitosterol) [10] that may be useful in helping to identify individuals who are likely to be responders to dietary cholesterol, and for whom eggs and other sources of dietary cholesterol should be minimized to reduce plasma cholesterol and CVD risk. For the remainder of individuals, it appears that egg intake is not associated with deleterious changes in lipoprotein profiles. In fact, recent studies have shown that although consuming 2-3 whole eggs per day did not change total cholesterol or LDL-cholesterol concentrations, it did increase paraoxonase-1 (PON1) activity, in healthy individuals [11] and the cholesterol efflux capacity of HDL particles in overweight postmenopausal women [12], as well as in individuals with metabolic syndrome who were consuming eggs in the context of carbohydrate restriction [13], suggesting that in some individuals there may even be a beneficial effect of egg intake on CVD risk profiles.

Thus, whether eggs raise plasma cholesterol depends on the individual. In most cases, dietary cholesterol intake in the form of eggs, since it is not accompanied also by an increased saturated fat intake as would be the case with meat, does not raise plasma LDL or total cholesterol, and may even improve HDL cholesterol efflux capacity. In a clinical practice where patients at risk for CVD or with a family history of CVD are being treated, and where there is therefore a higher likelihood of finding individuals who may have one of the ABCG5 or ABCG8 mutations that contribute to cholesterol hyperabsorption in the intestinal tract, it may be beneficial to do further testing, such as measurement of plasma phytosterol concentrations to determine whether egg intake is appropriate for the individual patient.

3. Do eggs raise plasma TMAO?

Fasting plasma concentration of TMAO is a risk factor for CVD even after adjustment for other CVD risk factors [14]. However, whereas there is a clear positive association between fasting plasma TMAO concentrations and CVD risk [15], and increased production of TMAO in many individuals in the hours immediately following the intake of eggs [14,16], studies have not shown a consistent link between the dietary intake of eggs and long-term fasting TMAO concentrations. Controlled intervention studies feeding 2-3 eggs per day have not shown increases in TMAO concentrations [17,18]. In comparison, observational studies show links between higher intakes of fish, and less so eggs, and circulating TMAO concentrations [19]. Thus, it is likely that the production of TMAO related to egg intake is highly individual, and dependent on a number of factors, including the individual's gut microbiome profile. It is important to note that since the conversion of choline to TMA by gut microbes is the first step, while the further conversion of the absorbed TMA to TMAO in the liver is the second step in the synthesis of circulating TMAO, the rate of TMAO production is also affected by the individual patient's liver flavin-containing monooxygenase 3 (FMO3) activity [20]. Several factors are known to modulate FMO3 expression and activity including estradiol [21], and bile acids [20] via the farnesoid x receptor [20]. Moreover, TMAO can also be absorbed directly from dietary sources particularly fish [19], and its concentrations are also dependent on the rate of clearance from plasma and thus kidney function [22].

Egg lipids as a source of choline in the form of phosphatidylcholine have been shown to result in increased concentrations of TMAO in the hours after consumption of 2 or more eggs [16]. Sphingomyelin is an additional source of choline from eggs, however, dietary sphingomyelin has been shown to have only modest effects on increasing circulating TMAO concentrations in mice [23]. There is high inter-individual variability in TMAO production following egg consumption, with the observation that individuals who follow a vegan diet do not produce TMAO whereas omnivores do [16]. Strikingly, although vegans do not produce TMAO at all after ingesting eggs and other sources of choline, omnivores are highly variable in their TMAO production ranging from near 0 μM, just as in the vegans, to as high as 30 μM [16]. It has now been shown that variation in the gut microbiome contributes to differences in TMAO production [24] and the gut microbes involved in this relationship include those belonging to the phyla *Firmicutes* and *Proteobacteria* [25,26], however the relationship between diet, the gut microbiome, and circulating TMAO concentrations is complex.

Although it is now clear that shifts in gut microbiome composition can be seen as quickly as within 4 days of a major shift in diet (e.g., from a low-fiber, high fat "fast food" diet of burgers and fries, to a high-fiber Mediterranean diet), TMAO concentrations did not change at this time scale [27]. On the other hand, in a crossover intervention study between a plant-based (Plant) and animal-based (Animal) diet for 8 weeks each in healthy adults, in the group randomized to consuming the Animal diet first and Plant diet second, TMAO concentrations decreased without significant changes in gut microbiome composition [28]. It was recently shown that fecal microbiota transplantation from vegan donors to patients with metabolic syndrome changed the composition of the gut microbiome, however, these changes were not associated with reduced TMAO concentrations, and in fact, the relative proportion of TMA-generating species *Alcaligenes faecalis* increased after the fecal microbiota transplantation [29]. Whether a particular bacterial species within a family, genus, or phylum produces TMA from choline or other sources like carnitine, is dependent on whether that species carries the metabolic machinery required for the conversion steps. Metagenomic sequencing combined with bioinformatic approaches have recently revealed that the microbial enzymes necessary for the conversion of choline and carnitine to TMA include the *cut* gene cluster, which has been identified in 89 bacterial genomes including known choline degraders (*Desulfovibrio*, *Clostridia*, *Streptococcus*, *Klebsiella*, and *Proteus*) [30,31].

In addition to the importance of the composition of the gut microbiome, including specifically whether the microbes present in the gut have the necessary genetic machinery to convert choline and carnitine to TMA, the availability of the substrate to the microbes is also a factor. Since egg choline is present mostly in the form of phosphatidylcholine, which is known to be readily absorbed in the upper gastrointestinal tract [32], there may be less choline available to the gut microbes, which are concentrated in the lower intestinal tract, than when choline is consumed in other forms. Sources of free choline such as choline bitartrate may be

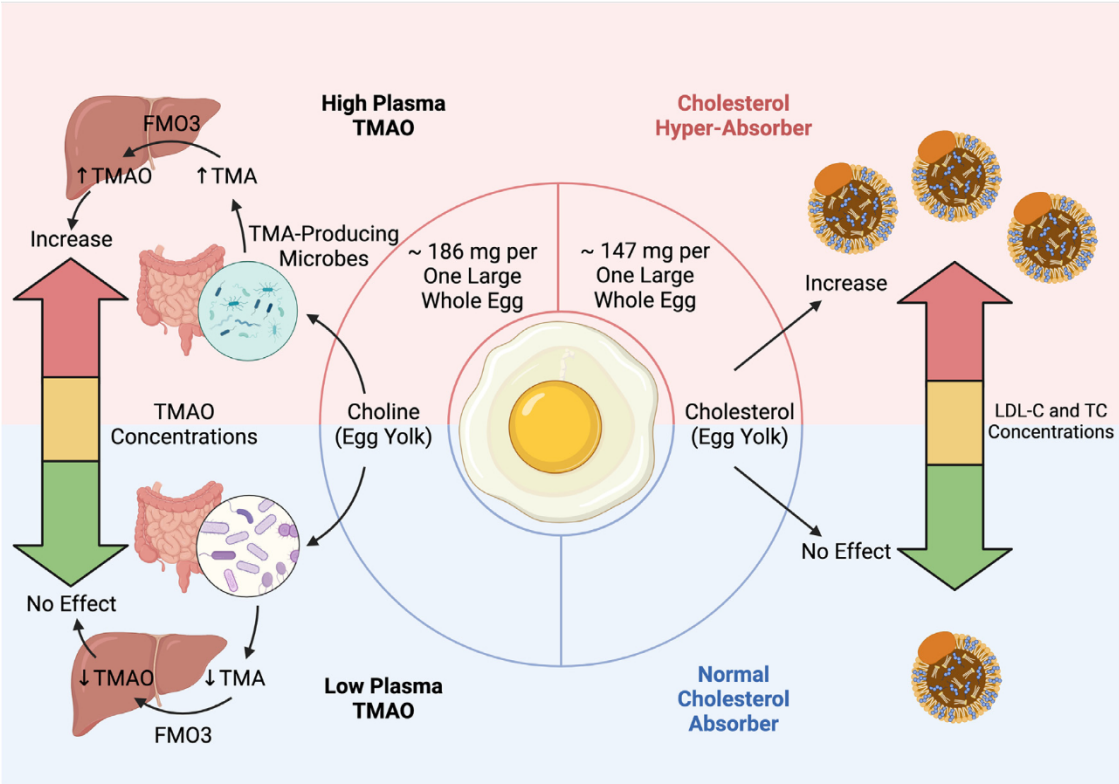

Fig. 1.

more easily accessible to gut microbes because their absorption is not as efficient as that of choline in the phosphatidylcholine form [33]. These differences in the absorption of free choline vs. choline in the form of phosphatidylcholine may affect its metabolism by gut microbes, and thus also the rate of TMAO production and appearance in the bloodstream. When choline (600 mg) in the form of choline bitartrate was given to healthy men it induced higher plasma and urinary TMAO changes from baseline compared to equal amounts of choline in the form of phosphatidylcholine [34]. In the same study it was found that choline bitartrate feeding resulted in increased concentrations of *Clostridium* from *Ruminococcaceae* and *Lachnospiraceae* in the phylum *Firmicutes* in high-TMAO producers compared to low-TMAO producers [34]. These observations are in agreement with a prospective cohort study showing an association between fecal levels of *Ruminococcaceae* and *Lachnospiraceae* and plasma TMAO concentrations [35].

Thus, the gut microbiome is an important determinant of whether an individual's TMAO concentrations are likely to increase in response to egg intake. Many companies and laboratories now offer fast, and ever less expensive metagenomic sequencing services, and machine learning approaches are being widely deployed to develop algorithms to process the sequencing data. However, the evaluation of an individual's gut microbiome composition to predict the extent of TMA production in response to choline intake is currently still in the research realm and has not yet been translated into a clinical diagnostic. Instead, the direct measurement of TMAO in plasma is an available approach to evaluate an individual patient's TMAO status. Some states have already approved the measurement of TMAO in plasma for prognostic purposes, and some clinical labs already offer routine TMAO analysis for clinicians who want to order this test for their patients. In individuals who already have high TMAO concentrations, it would be inappropriate to recommend increases in the intake of choline and carnitine, and in fact, decreased intakes of food sources, and especially supplements, of these molecules would be prudent. On the other hand, in individuals for whom eggs are already an important and regular source of protein and other nutrients in the diet, and whose TMAO concentrations are low, it would be beneficial to recommend keeping eggs in their diet. It is important to consider an individual's overall diet and to keep track of total protein intake and protein source. In the case of an individual in whom plasma TMAO concentrations are high, if the overall diet includes high amounts of choline, carnitine, or TMA-containing foods (i.e., meats and fish) and these foods are the primary sources of protein, it may take some time, effort, and education to transition to alternative protein sources. Based on the current evidence, which is primarily from observational studies, a focus on reducing meat (particularly processed meat products) and fish rather than eggs would be a reasonable approach for reducing plasma TMAO concentrations. Interventional studies using precision nutrition-based approaches are needed to better understand how substituting choline, carnitine, and TMA-containing foods with specific protein alternatives affects the gut microbiome and plasma TMAO concentrations in individuals.

It is important to note that most of the studies on egg and choline intake and TMAO production have been performed in healthy individuals with normal gastrointestinal function, thus it is important to consider that individuals with decreased absorption capacity due to a number of possible underlying lipid malabsorption conditions including disorders of bile acid metabolism, liver, pancreatic and gall bladder disease, inflammatory bowel disease, and other gastrointestinal disorders may in fact produce higher levels of TMAO in response to egg consumption due to a failure to absorb the phosphatidylcholine in the upper gastrointestinal tract, and thus greater availability of this precursor to TMA-producing gut microbes in the colon Fig. 1.

4. Conclusions

In this mini review, we evaluated the current evidence on the effects of egg intake on cardiometabolic risk factors including plasma cholesterol and TMAO levels, with a specific focus on individuals at risk for CVD. In those patients at risk for CVD, whose plasma cholesterol concentrations are unaffected by dietary cholesterol intake, and whose diet and microbiome are not associated with increased TMAO concentrations, eggs are beneficial to incorporate or keep in the diet. This has not been evaluated in clinical studies directly, thus it is critical that clinicians carefully evaluate the individual needs of their patients based on their individual status and risk. Some clinical tools, including the measurement of phytosterols to assess the extent of dietary cholesterol absorption, and the measurement of TMAO to assess the extent of TMAO production in the context of diet, are already available. It is likely that these measures are more informative and can better aid the clinician in determining the appropriateness of egg intake in the context of careful evaluation of the patient's diet in the weeks prior to the blood draw, since both the microbiome and plasma metabolites change depending on recent diet [11,12,17,18,27,28]. Given that eggs are a convenient and excellent source of both macro- and micronutrients, they may be an important dietary tool to achieve adequate nutrient status in some individuals, even those at risk for CVD. However, many factors including personal genetic background, absorption and bioavailability differences, the integrity of the patient's gastrointestinal tract and associated digestive organs, and the individual's microbiome should all be considered in patients at risk for CVD to prevent high plasma cholesterol and TMAO levels due to egg intake. Further studies are needed to develop Precision Nutrition approaches that can identify patients at risk for CVD for whom egg intake is contraindicated and others for whom egg intake is not associated with increased plasma cholesterol or TMAO.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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