

Editorial

Is the Gut Microbiome the Next Target for Atherosclerosis?

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EDITORIAL

Atherosclerotic vascular disease remains the leading cause of disease burden and mortality in the developed world. The complex interplay of genetics, nutrition, and environmental factors leading to atherosclerosis continues to attract great investigation. Role of triglyceride and cholesterol rich diets in the development of atherosclerosis is well established. This has led to preventative approaches to atherosclerosis with emphasis on dietary modification. Low fat and cholesterol content along with caloric restriction is advocated to reduce incidence of atherosclerotic cardiovascular disease. Now, there is increasing awareness of a third class of lipids, dietary phospholipids and their role in atherogenesis. Animal models indicate a link between phospholipid metabolism by gut flora and risk of developing obesity and insulin resistance [1]. The role of vascular inflammation and infectious agents in the pathobiology of atherosclerosis is still evolving. There is a growing body of literature recently that has implicated intestinal microbiota or 'gut flora' and its metabolism of dietary phospholipids in the multifaceted mechanism leading to atherosclerosis [2]. Comprehension of this relationship has the potential of modifying current preventative and treatment strategies for atherosclerosis.

The intestinal microbiome includes numerous non-pathogenic commensal organisms that aid in digestion and absorption of various nutrients. Metabolomic studies in patients with atherosclerotic disease by Wang *et al.* identified three distinct phospholipid metabolites - choline, betaine and Trimethylamine-N-Oxide (TMAO), which are independent predictors for clinical cardiovascular risk. Choline is an essential nutrient and component of dietary phosphatidylcholine (PC), which is the predominant phospholipid found in cell membranes. It is also a precursor for the neurotransmitter acetylcholine and participates in DNA methylation. Choline rich foods include eggs, liver, red meat, and fish. Animals obtain choline from diet or from conversion of phosphatidylethanolamine (PE) to PC which is further metabolized to choline by phospholipase D. Betaine is a byproduct of choline oxidation in the kidney and liver. Choline and betaine are metabolized by intestinal microbiota to form gaseous Trimethylamine (TMA) [2,3]. Carnitine is also another source of dietary source of TMA. TMA quickly is reabsorbed

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from the gut lumen into the host plasma and rapidly oxidized to TMAO in the liver by at least one of the member of hepatic flavin monooxygenases, particularly FM03 (Figure 1) [2].

Recent animal model and human clinical studies have identified that TMAO is directly involved in atherosclerosis. In atherosclerosis prone apoE $-/-$ mice, atherosclerotic plaque area positively correlated with TMAO plasma levels with choline or TMAO supplemented diets. Also, dietary choline or TMAO supplementation also enhances macrophage accumulation of cholesterol and formation of foam cells in atherogenic plaques[2]. TMAO also modulates cholesterol and sterol metabolism by stimulating scavenger receptors involved in the uptake of modified lipoproteins, CD36 and SRA1, which promote the development of atherosclerosis by accelerating accumulation of cholesterol within macrophages. Systemic levels of TMAO are independently associated in large clinical cohorts with risk of myocardial infarction, stroke and cardiovascular death. Tang *et al.* performed a clinical outcomes study involving 4007 patients undergoing elective diagnostic cardiac catheterization. Baseline TMAO levels were measured for all participants and were followed for 3 years to track incidence of myocardial infarction, stroke and death. TMAO levels in patients with clinical events were significantly elevated compared to those without events, even after adjusting for traditional risk factors [4]. The prognostic value of TMAO remained significant even in relatively low risk subgroups of patients as well. While elevated choline and betaine plasma levels are associated with poor cardiovascular prognosis, however this is only in the presence of coexisting increased TMAO levels[5]. Therefore, TMAO synthesis by gut microbiome is likely the major factor in development of cardiovascular events rather than its precursors [5].

This article highlights the importance of gut flora as a potential therapeutic target for cardiovascular disease. Many bacterial species are involved in producing TMA including *Clostridia*, *Proteus*, *Shigella*, and *Aerobacter* [6]. The composition of intestinal microbiota is likely to be of greater importance as there are numerous factors including diet and environmental factors which contribute to a unique intestinal microbiome. Suppression of intestinal gut flora through antibiotic therapy has been postulated as a method to reduce TMAO levels and by extension, cardiovascular risk. In mouse studies, broad spectrum antibiotics administered with high choline diet did not result

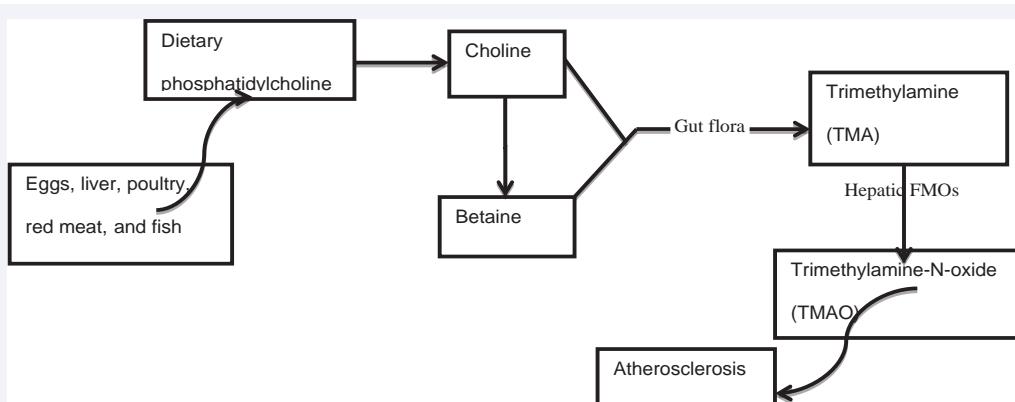


Figure 1 Steps involved in conversion of dietary phosphatidylcholine into trimethylamine-N-oxide which stimulates scavenger receptors involved in the uptake of modified lipoproteins, CD36 and SRA1, which promote the development of atherosclerosis in part by triggering accumulation of cholesterol within macrophages.

in elevated TMAO plasma levels or increase in atherosclerotic plaque burden. Suppression of TMAO in murine model by broad spectrum antibiotic therapy highlights the obligate role of intestinal microbiome in the production of TMAO [2]. Short courses of broad spectrum antibiotic therapy have been used in humans to confirm the role of microbiome on TMAO, however there are no prospective studies for long term antibiotic therapy for gut flora modification to reduce cardiovascular events [7]. Also, the administration of chronic antibiotic therapy carries the risk of colonization and proliferation of antibiotic resistant gut flora and pathogens. Alternatively, probiotics have garnered interest as a pharmacological intervention to target gut flora composition. Further studies are needed to determine whether the use of probiotics can alter cardiovascular risk [7].

Another therapeutic approach relies on genomic targeting of the metabolic pathway leading to TMAO synthesis. There is limited data on underlying genetic markers which predispose individuals to elevated TMAO levels. Recent genomic wide association study in combined mice/human model indicated *Slc30a7* as a novel gene which affects TMAO levels in mice via FMOs. However, FMO3 is currently the only genetic factor known to affect plasma TMAO levels in humans [8]. As such, FMO3 is another potential target for inhibition of TMAO synthesis and potentially reducing cardiovascular risk. Current data suggests the importance of avoiding choline rich diet and correspondingly increasing vegetable and fruit intake relative to red meat and eggs.

Pathogenesis of atherosclerotic cardiovascular disease in humans is intricate and the complex relationship of multiple factors still remains to be elucidated. The role of gut microbiome in synthesis of proatherogenic molecule of TMAO is intriguing. The role of TMAO as promoter of atherosclerosis and prognostic

molecular biomarker for CVD needs to be further investigated on a mechanistic scale. Additional work is needed to assess the role of gut microbiota composition in cardiovascular disease as a gateway to developing novel diagnostic and therapeutic strategies for prevention and treatment of cardiovascular disease.

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