Atherothrombotic cardiovascular diseases such as myocardial infarction and stroke are leading causes of death in many countries. Various mechanisms are involved in the development of atherosclerotic lesions: the activation and aggregation of platelets and the generation of an intraarterial thrombus are key events.

The gastrointestinal tract, with its enormous number of microbes, has attracted major interest in the past decade as a potential contributor to systemic disease processes, including the cardiometabolic phenotypes of atherosclerosis, obesity, and type 2 diabetes. Certain dietary nutrients, such as phosphatidylethanolamine, choline, and carnitine, are processed specifically by the gut microbiota to produce trimethylamine (TMA). TMA is absorbed in the gut and converted in the liver to TMA-N-oxide (TMAO) by hepatic flavin-containing monooxygenases (FMOs) (Fig. 1). In humans, foods such as meat and eggs have been associated with increased levels of TMAO, which in turn have been associated with an increased risk of major cardiovascular events in patients with proven coronary heart disease. Plasma levels of TMAO are markedly reduced after the administration of antibiotics and recover after the antibiotics are withdrawn; these observations further support the notion that the gut microbiota is critically involved in the generation of TMAO. Previous work has shown that TMAO exerts proatherosclerotic effects by promoting the accumulation of macrophage-specific cholesterol and the formation of foam cells, both of which contribute to the development of vulnerable plaques.

Zhu et al. recently reported a dissection of the association between dietary components, TMAO levels, and atherothrombotic diseases. The authors observed that plasma levels of TMAO in humans were correlated with the risk of thrombosis. Subsequently, they found that at physiologic concentrations, under shear stress (the tangential force per unit of area exerted by the flowing blood), TMAO increased platelet activation, as assessed by the rate of platelet adhesion to immobilized collagen in whole blood. Physiologically, platelets maintain low levels of intracellular cytosolic calcium (Ca²⁺). However, the direct exposure of platelets to increasing levels of TMAO was associated with release of Ca²⁺ from intracellular stores, which enhanced stimulus-dependent platelet activation by multiple agonists.

When Zhu et al. gave mice an excess of dietary choline, microbe-generated TMAO enhanced platelet responsiveness in vivo, promoting a prothrombotic phenotype, but this effect was not observed when the intervention was preceded by the administration of oral antibiotics or when the choline was administered to germ-free mice. The authors identified 9 taxa of bacteria, each of which was significantly associated with plasma levels of TMAO; 15 taxa were significantly correlated with risk of thrombosis in the mice. Finally, the authors showed that fecal microbial transplantation performed in germ-free mice “transferred” an elevated risk of thrombosis, showing that the risk of thrombosis is a transmissible trait in mice (Fig. 1). A receptor for TMAO in eukaryotes has yet to been identified.

In sum, the study reveals unexpected links among diet, the gut microbiota, platelet activation, and the risk of thrombosis, opening a door to new experimental approaches to treatment. In this context, it is noteworthy that 3,3-dimethyl-1-butanol inhibits the formation of TMA by gut microbes, thereby reducing plasma TMAO levels.
Figure 1. A Model of the Diet, Gut Microbiota, Atherosclerosis, and the Risk of Thrombosis.

Choline is hydrolyzed from dietary phosphatidylcholine and then converted to trimethylamine (TMA) by microbial lyases in the colon. Hepatic flavine monoxygenases (FMOs), such as FMO3, which is overexpressed in persons with insulin resistance, catalyze the conversion of trimethylamine (TMA) to TMA-N-oxide (TMAO). FMO3 also regulates hepatic cholesterol metabolism. A phosphatidylcholine-rich diet modulates the intestinal microbiota in part by altering the composition of bile acid, which augments systemic TMAO levels by inducing FMO3 expression. In studies in mice, high systemic levels of TMAO enhance the development of atherosclerosis by increasing the accumulation of macrophage-specific cholesterol and the formation of foam cells and reducing net reverse cholesterol transport. In addition, TMAO promotes thrombotic events by increasing the release of intracellular calcium in platelets, thereby enhancing the sub-maximal stimulus-dependent activation of platelets. Elevated TMAO levels predict increased risks of cardiovascular disease and major cardiac events such as myocardial infarction and stroke in humans. Thus, TMAO adds an important mechanistic link to the relationships among specific dietary nutrients, the gut microbiota, atherosclerosis, and the risk of thrombosis.
and attenuating the development of choline-diet-enhanced atherosclerosis. Other factors contribute to plasma TMAO levels: Miao et al. observed that levels of FMO3 are elevated in insulin-resistant, obese humans and in insulin-resistant, obese male mice. FMO3 knockdown prevented hyperglycemia, hyperlipidemia, and atherosclerosis in these mice. FMO3 appears to be a central regulator of hepatic cholesterol metabolism; targeting FMO3 and thereby reducing TMAO levels represents another potential approach to the treatment of atherosclerosis and related disorders.

It is unclear whether the data that are currently available provide sufficient evidence to justify clinical application of a TMAO-reducing strategy. It remains to be established whether there exist factors other than diet and microbiota that influence systemic TMAO levels. Moreover, choline is critical to many cellular functions. Clinical studies would be required to determine whether reducing dietary choline would be beneficial. Nonetheless, it appears that the systemic physiological effects of the gut microbiota give new meaning to the dictum, “You are what you eat.”

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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