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RISK FACTORS

Intestinal microbiota: "a new direction in cardiovascular research"

"Microbes in the gut, and both their varied composition between individuals and how they digest certain nutrients, [have been identified] as strong participants in the development of atherosclerosis," announce Stanley Hazen and colleagues from the Cleveland Clinic, OH, USA. An increased plasma level of trimethylamine-*N*-oxide (TMAO), a product of the microbial metabolism of dietary phosphatidylcholine, is associated with an increased rate of major adverse cardiovascular events (MACE).

Intestinal microbial organisms, or 'microbiota', influence the metabolism of their host, but might also contribute to pathological mechanisms in the development of coronary artery disease. Phosphatidylcholine is a semiessential nutrient and the main dietary source of choline, which is essential for lipid metabolism and synthesis of the neurotransmitter acetylcholine. In the cecum and colon, choline is metabolized by microbiota to produce trimethylamine, which is rapidly oxidized to TMAO. Hazen and colleagues have previously shown, in a study published in *Nature Medicine*, that microbial metabolism of L-carnitine from red meat also produces TMAO, which accelerates the progression of atherosclerosis in mice.

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In their latest study, published in the *New England Journal of Medicine,* Hazen *et al*. research the microbiota-dependent metabolism of dietary phosphatidylcholine. Next, they use clinical data to investigate the relationship between the plasma TMAO level and the rate of MACE after elective cardiac catheterization.

In the phosphatidylcholine metabolism study, 40 participants were fed two large, hard-boiled eggs (together containing ~500 mg of choline) and a capsule of 250 mg of deuterium-labelled phosphatidylcholine as a tracer. A time-dependent increase in the plasma levels of both the natural and tracer isotopes of choline and TMAO was clearly detectable. However, administration of oral, broad-spectrum antibiotics for 1 week in six participants to suppress their microbiota abolished the rise in plasma TMAO level after phosphatidylcholine challenge. The rise in plasma choline was unaltered. Withdrawal of antibiotics for ≥1 month resulted in re-establishment of the rise in the plasma TMAO level after phosphatidylcholine challenge.

The clinical outcomes part of the study involved 4,007 participants (mean age 63 years, 64% men) with a high prevalence of cardiovascular risk factors. Over the 3 years of follow-up, the incidence of MACE was associated with conventional risk factors (advanced age, high fasting glucose level, presence of diabetes mellitus or hypertension, or previous myocardial infarction). Furthermore, participants who experienced MACE had a higher baseline level of TMAO than those who did not experience MACE (5.0 μmol/l versus 3.5 μmol/l; $P<0.001$). Individuals with a high level of plasma TMAO had an increased risk of MACE compared with those who had a low plasma TMAO level (HR 2.54, 95% CI 1.96–3.28, $P<0.001$). This relationship remained significant after adjustment for traditional risk factors.

According to the investigators, these data suggest that "excessive consumption of dietary phosphatidylcholine and choline should be avoided". Choline intake can be reduced with a vegetarian or high-fibre diet, but choline is a semiessential nutrient, so should not be entirely eliminated from the diet. Alternatively, probiotic interventions might be used to modulate the composition of the microbiota, or pharmacological approaches might target biochemical pathways. For example, a short course of antibiotics might be used to reduce the quantity of TMAO-producing microbes. Importantly, sustained antibiotic use has been shown to have only a transient inhibitory effect on the plasma TMAO level, which is consistent with the flourishing of antibiotic-resistant microbiota.

These data have been heralded as an exciting breakthrough in understanding the pathophysiology of atherosclerosis. In an independent editorial that accompanied the article, Joseph Loscalzo comments that the studies "point to a truly novel and potentially modifiable risk factor for atherothrombotic vascular disease". Frederic Bushman, who was not involved in the research, believes that the study "clarifies an unanticipated biochemical pathway involved in cardiovascular risk [and] launches a new direction in cardiovascular research". Another independent investigator, Max Nieuwdorp, hopes that "TMAO inhibition [will become] a novel treatment target for cardiovascular disease. The next step would be to identify which intestinal bacterial strains are involved in TMAO metabolism, which would then open the gates for probiotic-based, targeted therapies."

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Original article Wilson Tang, W. H. *et al*. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N. Engl. J. Med.* **368**, 1575–1584 (2013)

Further reading Koeth, R. A. *et al*. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat. Med.* doi:10.1038/nm.3145 | Loscalzo, J. Gut microbiota, the genome, and diet in atherogenesis. *N. Engl. J. Med.* **368**, 1647–1649 (2013)