The red and the white, and the difference it makes

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This editorial refers to ‘Impact of chronic dietary red meat, white meat, or non-meat protein on trimethylamine N-oxide metabolism and renal excretion in healthy men and women’, by Z. Wang et al., doi:10.1093/eurheartj/ehy799.

We are full of bacteria: indeed, has been estimated that ~100 trillion microorganisms inhabit our body. This is about three times as many cells as our organs are made of. Most of the bacteria belong to a limited number of 500–1000 species. They live on our skin and determine how we smell, they inhabit the oral cavity, and they help digestion in the gastrointestinal tract. Thus, most of them are quite useful or at least do not cause infections. However, as has been recently discovered, they eat what we eat. This comes as no surprise, but what has attracted a lot of interest in the past years is that there are potential biological effects of the metabolites they produce and excrete. Of note, most of these molecules are rather small and can be easily absorbed, are in part metabolized in the liver, and do reach the circulation where the biological effects that such products exert is currently under intense investigation.

The metabolite trimethylamine N-oxide (TMAO) is the end-product of the metabolism of phosphatidylcholine, choline, and L-carnitine by commensal microbiota of the gut and the portal–hepatic circulation. Trimethylamine (TMA) is produced by gut microbiota, transported to the liver via the portal circulation, and oxidized by flavin monooxygenase 3 to TMAO. Interestingly, a growing body of evidence has linked elevated plasma TMAO levels to atherosclerotic cardiovascular (CV) disease. Indeed, high TMAO levels in patients presenting with acute coronary syndrome (ACS) are predictive of major adverse cardiac events (MACE) at 30 days and 6 months over and above traditional risk scoring systems.1 Furthermore, in patients with stable coronary artery disease, fasting plasma TMAO levels provided a significant incremental prognostic value for all-cause mortality at a total of 5 years of follow-up.2

Animal studies have demonstrated that supplementation with L-carnitine, a nutrient abundant in red meat, results in accelerated atherosclerosis compared with a non-meat-based diet.3 These changes have occurred in the absence of significant changes in plasma lipids, lipoproteins, glucose, or insulin levels, and are thought to be due to an increased TMAO production. Indeed, carnitine has not proven to be an independent predictor of CV risk in humans when TMAO is also part of a risk model.3

Phosphatidylcholine (or lecithin) is the major source of choline, which is then converted to TMA by the enteral microbiome. Choline is found in many animal and plant products including egg yolk, meats, certain fish, dairy, nuts, and soybeans. Several intestinal bacteria have been implicated in TMAO production from choline, including Bacteroides species. Although initially thought to lead to TMA production in the large intestine, more recent studies have shown that TMA is in fact produced only in the small intestine.4

Phosphatidylcholine appeared to be associated with a higher risk of all-cause and CV mortality in the US Nurses Health Study, even when levels are only estimated from dietary questionnaires.5 Although elevated plasma choline levels have been shown to increase the risk of MACE in patients presenting for diagnostic coronary angiography, once TMAO levels are factored into the model, the association between plasma choline and MACE has not been shown to be significant.6

In this issue of the European Heart Journal, Wang and colleagues report the effects of a red meat diet on plasma TMAO levels in healthy adults and the associated impact of a high saturated fat diet compared with low saturated fats.7 By using an isocaloric dietary intervention study designed originally to assess the effects of saturated fats on lipoprotein markers of CV risk in healthy adults, the authors have shown that a red meat-enriched diet significantly increases plasma and urine TMAO levels. Of note, the increase in plasma TMAO levels was on average three-fold compared with white meat and non-meat diets. There was no difference in TMAO levels in high as compared with low saturated fat diets that had red meat as their protein source. There was substantial variation in TMAO levels among those on a red meat diet. Interestingly, when participants discontinued the red meat diet, moving to either the white meat or non-meat diets, TMAO levels decreased, suggesting that dietary changes may exert beneficial effects by modifying the plasma levels of the metabolite. Secondly, in a small subset of 13 patients, isotope tracer studies...
revealed that a red meat diet appears to increase TMAO levels through increased microbial TMA production from L-carnitine, more so than from choline.

The authors conclude that the study demonstrates that specific dietary manipulations can effectively reduce TMA/TMAO levels. Indeed, the authors should be commended for their use of the iso-caloric study design and direct provisioning of foods compared with other approaches such as food questionnaires. The study proves that a lean red meat-based diet (with either low or high saturated fats) results in substantial increases in plasma TMAO levels.

Several important questions arise from this research. First, in a controlled isocaloric diet, there were wide variations in plasma TMAO levels in patients on the red meat diet. Further investigation to delineate the differences at the level of the microbiome, or genetic differences of the host patients at the extremes of plasma TMAO levels while consuming a red meat diet may provide further insights into this interesting phenomenon.

This leads us to the crucial question: what constitutes a healthy microbiome in terms of TMAO levels? Assessment of the subjects’ microbiome prior to the study did not take place, so more chronic dietary patterns prior to the commencement of the study may have resulted in underlying differences in the individuals’ microbiomes at baseline which then may be responsible for the variation in TMAO levels. Previous studies have indeed suggested that long-term vegetarians and vegans have much lower plasma TMAO levels, along with markedly reduced production of TMAO by the gut microbiota compared with long-term omnivores.

The second question is: where should we go next in the investigation of TMAO and its role in cardiovascular disease? One approach would be further research into the molecular mechanisms of atherosclerotic plaque formation. This pathway appears distinct from the conventional CV risk factors such as LDL-cholesterol, among others. In line with that assumption, in some studies lean red meat diets have not been shown to increase cholesterol levels compared with non-red meat diets in healthy patients. So far, other studies have shown that TMAO increases expression of scavenger receptors (CD36 and SR-A1) on macrophages, with resultant promotion of the formation of foam cells. Furthermore, TMAO inhibits reverse cholesterol transport and has been shown to increase platelet activation.

Finally, should interventions target the products of the microbiome or the microbiome itself? Certainly, a chronic lack of dietary fibre reduces bacterial diversity. The Mediterranean diet, which emphasizes legumes, grains, fruit, and vegetables, with fish as the preferred animal protein source, reduces urinary TMAO levels compared with a more Western diet. Some probiotics have also demonstrated promise in reducing TMA and therefore TMAO plasma levels. A pharmacological approach would be the use of microbial TMA lyase inhibitors such as 3,3-dimethyl-1-butanol. Another strategy would be transplantation of faecal microbiota which can introduce a large population of bacteria and restore dysbiosis caused by a Western diet high in processed carbohydrates and animal products, as has been successfully used in irritable bowel syndrome or Crohn’s disease. However, it remains uncertain whether such an intervention would be sustainable as would be required in a chronic disease such as atherosclerosis and its complications such as ACS and stroke. Certainly, the work presented here by Wang et al. proves that red meat, through L-carnitine, is the major source of elevated TMAO plasma levels in a healthy Western population and sets the stage for further trials in patients with CV disease.

Take home figure Potential therapeutic targets for reducing plasma TMAO levels.
Conflict of interest: none declared.

References


