

EDITORIAL COMMENT

Can Fishy Odor Be a Risk Factor for Coronary Artery Disease?*



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There is interest in describing more definitive risk factors for coronary artery disease that mechanistically link to the actual disease process, as opposed to indirect measures of disease, such as age, sex, hypertension, dyslipidemia, smoking, and diabetes, all of which are used in the Framingham risk score. Toward that end, Senthong et al. (1) propose in this issue of the *Journal* that the organic compound trimethylamine *N*-oxide (TMAO) may serve just such a purpose. On the basis of their own pioneering work (2,3), the team identified a correlation between patients' TMAO levels (of the order of micromoles in ethylenediaminetetraacetic acid plasma, as determined by mass spectrometry) and the anatomic spread of atherosclerotic lesion sites over the coronary artery trees, as detected by computed tomography for assessing lesion extent and complexity via SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) scores.

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The investigators also report significant associations in plasma between TMAO levels and soluble cardiac troponin values, used as a measure for myocyte necrosis, even when adjusted for other risk factors, although once adjusted for C-reactive protein levels, body mass index, estimated glomerular filtration rate, and patient medications, the TMAO-troponin association was no longer significant. The take-home message is that patients with diffuse

compared with focal lesions have higher TMAO plasma values. Prediction of atherosclerotic lesion spread and complexity in the coronary artery tree as determined by SYNTAX scores may be enhanced by adding TMAO values to traditional risk factors.

In explaining the influence of TMAO, it should be remembered that dietary choline and phosphatidylcholine in red meat are associated with enhanced trimethylamine levels. TMAO can be derived from trimethylamine by reactive oxygen species. The gut microbiota plays an obligatory role in appearance of TMAO in plasma following placement of carnitine (which has the trimethylamine structure) into the stomach (2). TMAO has a fishy odor and can appear in various body fluids and in the breath, in line with the idea that it is a member of a chain of reactions associated with tissue decomposition. Thus, identification of the exact mechanism(s) for the generation of TMAO and the mode of its action that ultimately causes atherosclerosis serves as a lead into the actual tissue breakdown mechanism. As such, TMAO is an interesting molecule that can serve as point of departure into the pathogenesis of atherosclerosis and at the same time function as a potentially useful clinical marker.

To further bring to light the significance of the association between anatomic locations of atherosclerotic lesions and plasma levels of TMAO, we need to understand details about where TMAO is generated. Is it in lesions, in the plasma, or perhaps in other organs, such as the intestine? Senthong et al. (1) argue in favor of the intestine as the host of the microbiome. But if the intestine is involved, then there are other potential sources that may directly or indirectly generate decay products, such as powerful digestive enzymes or partially degraded food products.

If TMAO is generated by the microbiota in the intestine, the microbial source and the TMAO plasma levels should be closely linked in the same

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individuals. Patients with more dispersed atherosclerotic lesions should have higher microbial counts. Besides lowering TMAO levels, interventions (e.g., antibiotics) should be effective at reducing lesion size, including SYNTAX scores, and experimental studies argue in favor of this possibility (4). However, to gain full confidence in this hypothesis, quantitative analysis should confirm that the number of bacteria in the gut (although large in number, these only amount to a modest total biomass) have sufficient total enzyme activity to explain the concentrations of TMAO seen in patients, especially considering that TMAO, as a small molecule, is readily transported out of the intestine and the cardiovascular system. TMAO plasma values in mice models and in humans correlate with lesion size but, in mice, are about an order of magnitude higher than in human patients (2). This discrepancy between mice and humans requires an explanation that has a quantitative basis. If gut bacteria are considered to dominate TMAO generation, other degrading mechanisms that could generate TMAO need to be excluded on the basis of a conclusive analysis.

Because TMAO has a direct effect on cell activity, as suggested by L-carnitine feeding studies (2,4), there is an opportunity to identify 1 or more mechanisms that lead to cell dysfunction by the use of culture studies. One should be able to determine the mechanisms by which TMAO produces early forms of endothelial dysfunction. How does TMAO affect the mechanotransduction mechanisms by fluid shear stress, recognized for its involvement in localization

of atherosclerotic lesions (5,6)? An indirect pathway of action by impairment of cholesterol elimination, suggested by Koeth et al. (4), needs to be scrutinized. What binding and signaling pathways does a degradation product such as TMAO affect and how? TMAO-mediated impairment of cholesterol transport should affect other cell types that depend on cholesterol metabolism, including endothelial cells in venules or capillaries. Also, correlations between plasma TMAO levels and cell dysfunctions or lesions in segments of the circulation, other than just the arteries, should be detectable if a cholesterol pathway is involved.

As a clinical index and also a marker for tissue decay, TMAO is an attractive candidate and an alternative to traditional risk factors whose biochemical and biophysical relationship with the actual disease process remains uncertain. As a small molecule, TMAO has the advantage that it is rapidly transported from its site of generation into the plasma and may even be detected in the breath by noninvasive methods. Last but not least, for TMAO to become a widely usable risk factor, a new technology needs to be introduced to detect TMAO levels at the point of care with a new biosensor, perhaps even designed along the line of our own sensors in the olfactory epithelium.

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