Title

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

Short title: A Risk Factor for Coronary Artery Disease
Cover title: Can Fishy Odor be a CAD Risk Factor?

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Conflicts: GWS-S owns equity in InflammaGen, a company by Leading Bioscience Inc, San Diego CA, which develops therapy for shock patients.

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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. Towards that end, Senthong et al. propose in this issue of the *Journal* that the organic compound trimethylamine *N*-oxide (TMAO) may serve just such a purpose (1). Based on their own pioneering work (2,3), the team identified a correlation between patient TMAO levels (of the order of micromoles in ethylenediaminetetraacetic acid [EDTA] plasma as determined by mass spectrometry) and the anatomical spread of atherosclerotic lesion sites over the coronary artery trees, as detected by computed tomography (CT) for assessing lesion extent and complexity via SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) scores.

The authors 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 as compared to 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 member of a chain of reactions associated with tissue decomposition. Thus, identification of the exact mechanism(s) for 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 anatomical 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? The Senthong team (1) argues in favor of the intestine as 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 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 numbers, these only amount to a modest total biomass) have sufficient total enzyme activity to explain the concentrations of TMAO seen in the patients, especially since TMAO as a small molecule is readily transported out of the intestine and the

cardiovascular system. TMAO plasma values in mice models and in man correlate with lesion size but, in mice, are about an order of magnitude higher than in human patients (2). This discrepancy between mice and man 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 based on a conclusive analysis.

Since TMAO has a direct effect on cell activity, as suggested by l-carnitine feeding studies (2,4), there is an opportunity to identify one or more mechanisms that lead to cell dysfunction by use of culture studies. One should be able to determine the mechanisms by which TMAO produces early forms of endothelial dysfunctions. 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 and coworkers (4), needs to be scrutinized. What binding and signaling pathways does a degradation product like 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 marker for tissue decay, TMAO is an attractive candidate and an alternative to traditional risk factors whose biochemical/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 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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