Media Sensationalism: Meat is Bad for your Heart

TMAO and Carnitine

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Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis.

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Abstract

Intestinal microbiota metabolism of choline and phosphatidylcholine produces trimethylamine (TMA), which is further metabolized to a proatherogenic species, trimethylamine-N-oxide (TMAO). We demonstrate here that metabolism by intestinal microbiota of dietary l-carnitine, a trimethylamine abundant in red meat, also produces TMAO and accelerates atherosclerosis in mice. Omnivorous human subjects produced more TMAO than did vegans or vegetarians following ingestion of l-carnitine through a microbiota-dependent mechanism. The presence of specific bacterial taxa in human feces was associated with both plasma TMAO concentration and dietary status. Plasma l-carnitine levels in subjects undergoing cardiac evaluation (n = 2,595) predicted increased risks for both prevalent cardiovascular disease (CVD) and incident major adverse cardiac events (myocardial infarction, stroke or death), but only among subjects with concurrently high TMAO levels. **Chronic dietary l-carnitine supplementation in mice altered cecal microbial composition, markedly enhanced synthesis of TMA and TMAO, and increased atherosclerosis, but this did not occur if intestinal microbiota was concurrently suppressed.** In mice with an intact intestinal microbiota, dietary supplementation with TMAO or either carnitine or choline reduced in vivo reverse cholesterol transport. Intestinal microbiota may thus contribute to the well-established link between high levels of red meat consumption and CVD risk.

This study was recently published, pushing the hypothesis that L-Carnitine in meats could be a connection between meats and cardiovascular disease risk, via TMAO (Trimethylamine oxide).

TMAO is thought to be atherogenic (plaque causing) because it is associated with cardiovascular disease (i.e., people who get heart attacks tend to have more TMAO in their blood). This study itself established a correlation (n=2595 cohort) between cardiovascular disease and greater blood concentrations of TMAO.

TMAO's molecular structure is common to both carnitine and Choline, and thus it is thought they can bioconvert in the body. TMAO is thought to contribute to atherosclerosis by promoting cholesterol influx into macrophages, which then promotes foam cell formation (and then the foam cells themselves become plaque); this was confirmed in ApoE$^{-/-}$ mice in this study, and appeared to influence macrophages derived from wild-type mice as well. This mechanism is plausible.

The study above noted that following consumption of L-Carnitine (180mg via sirloin and 250mg via radiolabelled capsules), TMAO was confirmed in both the blood and urine. The role of intestinal

microflora was confirmed when participants were put on antibiotics (to suppress the microflora), which abolished diet-induced TMAO increases. Furthermore, this increase was detected in omnivores but not long term (more than 5 years) vegetarians and vegans, and seemed to be related to a higher gut population of *Prevotella* bacteria.

Finally, the researchers conducted a study in APoE$^{-/-}$ mice. The mice fed 1.3% carnitine had roughly double the plaque buildup vs mice that were not fed carnitine. This was again abolished with antibiotic treatment (to destroy the gut:TMAO link). It should be noted that after mouse-to-human body weight conversion, 1.3% carnitine in the diet is not too impractical for a human to consume, especially via supplementation. It should also be noted that APoE$^{-/-}$ mice are genetically modified to exacerbate any bad cholesterol effects (for research purposes).

Overall, what **can** we conclude from this study?

- There is a correlation between higher TMAO in serum and cardiovascular disease risk in humans.
- There appears to be microbial fermentation of dietary carnitine into TMAO in non-vegetarian humans.
- TMAO in serum from dietary carnitine causes atherosclerosis in APoE$^{-/-}$ mice.

What **cannot** be concluded from this study?

- TMAO in humans causes heart disease. ApoE$^{-/-}$ mice are used since it is easy to research pro-atherogenic cholesterol metabolism, but these are mice with a specific genetic fault. This research would have to be replicated in regular mice (and then in humans). Additionally, the human correlational research does suggest there is a link but cannot state that it is a causative link, and past research on Choline does suggest that TMAO is fairly rapidly excreted via the kidneys (suggesting some effects that are differential dependent on species).
- Carnitine causes heart disease, as the link between TMAO and heart disease is not fully established in humans.
- TMAO is bad. To nip this in the bud, most molecules have good and bad associated with them (good example: Cortisol) and it would be improper to conclude that TMAO must be avoided at all cost. To reiterate as well, the correlation between TMAO and cardiovascular disease could very well be a biomarker of some other lifestyle habits.

What can plausibly be concluded, but requires future research to confirm?

- Carnitine **could** contribute to heart disease via pro-inflammatory mechanisms, and this pro-atherogenic effect can likely be negated by other nutraceuticals (including statin drugs such as red yeast extract or other hypocholesterolemic compounds like Berberine).
- Probiotic supplementation could modulate heart disease risk via a TMAO link, but this assumes that the TMAO link is actually relevant in humans.

Fonte: examine.com