The Gut Microbiome and Trimethylamine N-Oxide: Implications for Chronic Disease Risk and Dietary Regulation

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The leading causes of death in the United States include many chronic diseases with modifiable risk factors including ischemic heart diseases. Gut microbiota-dependent trimethylamine N-oxide (TMAO) synthesis has been implicated in cardiovascular disease risk in recent years. New evidence may also implicate TMAO involvement in other chronic diseases including diabetes mellitus and chronic kidney disease. The role of diet in TMAO synthesis has also been of considerable interest, as certain dietary precursors are known to modulate circulating TMAO. The gut microbiome is indeed susceptible to diet-induced change which may modulate the risk for chronic disease. Plant-based diets are considered by many to be beneficial for gut health and may play a protective role by reducing TMAO synthesis. This review discusses the purported role of TMAO and the mechanisms by which TMAO may contribute to atherosclerosis and chronic disease risk. The role of diet in chronic disease is also discussed with emphasis on utilizing clinical nutrition to reduce the burden of disease.

Introduction

The leading causes of death in the United States include ischemic heart diseases, diabetes mellitus and chronic kidney disease (CKD), among others[1]. While these chronic diseases are multifactorial, the development of many diseases and the risk for all-cause mortality are derived in part from lifestyle factors including diet[2–4]. Considerable attention has recently been given to the role of gut microbiota in chronic disease, as well as how diet modulates the human enterotype[5–7]. Over the last decade, research on mechanisms of chronic disease have revealed an obligate role for gut microbiota in production of pro-atherogenic species including trimethylamine N-oxide (TMAO)[5,8]. TMAO is produced after phosphatidylcholine and related metabolites are converted by host microbiota to trimethylamine, which undergoes further oxidation in the liver by flavin monooxygenase enzymes (FMOs)[9–11]. This article reviews the proposed mechanisms by which TMAO may contribute to atherosclerosis and chronic disease risk. Special attention is given to the role of diet in modulating the human enterotype as well as the therapeutic viability of dietary regulation in modifying chronic disease risk.

TMAO Synthesis

A study published in 2011 by Wang et al. identified a molecular pathway by which phosphatidylcholine is converted to choline and metabolized by gut microbiota to trimethylamine (TMA)[9]. After absorption of TMA into host circulation, hepatic enzymes further oxidize this species, producing TMAO[9]. Specifically, flavin monooxygenase 3 (FMO3) carries out this oxidation and displays the greatest specificity towards TMA[12]. Further characterization of this purported mechanism has revealed that other phosphatidylcholine-related species such as L-carnitine and betaine also result in the production of TMAO via conversion to TMA as an intermediate[10,13]. This mechanism of TMA production has recently been revised for L-carnitine, as the intermediate gamma-butyrobetaine (GBB) is generated before conversion to TMA in humans[11].

Elucidating the interplay between diet and TMAO synthesis is important, as plasma TMAO levels are associated with cardiovascular

disease (CVD) risk and mortality in a dose-dependent manner[14]. Observational studies have also revealed that TMAO levels are predictive of major adverse cardiac events (MACEs) in certain population cohorts; specifically, Li et al. found that, in patients presenting to the emergency department with symptoms of chest pain, plasma TMAO levels were independently predictive of future MACEs[15]. Diet and the human enterotype are intrinsically linked to TMAO synthesis, as choline-containing species are converted to TMAO by gut microbiota[9,11]. Furthermore, animal products are largely implicated in TMAO production, as both choline and L-carnitine are concentrated in foods such as meat, dairy and eggs[9,16]. Interestingly, the choline derivative betaine is found more largely concentrated in plant foods and is associated with CVD risk when there is a concomitant rise in TMAO levels[17,18].

TMAO Mechanism of Action in Atherosclerosis

Rather than serving as a biomarker for a diet high in saturated fat and cholesterol, TMAO has been characterized in many studies as an contributer to atherosclerosis. These studies have implicated TMAO in lipid metabolism dysfunction and inhibition of reverse cholesterol transport (RCT) as well as multiple inflammatory mechanisms[19].

Wang et. al discovered that dietary supplementation of phosphatidylcholine-derived metabolites to atherosclerosis-prone mice resulted in increased expression of the macrophage scavenger receptors CD36 and SR-A19. These macrophage-specific receptors then facilitate creation of foam cells—macrophages which engulf oxidized low density lipoprotein (LDL) and contribute to the formation of atherosclerotic plaques[9,20]. Importantly, high levels of dietary choline induced macrophage foam cell formation in a microbiota-dependent fashion, as mice treated with broad spectrum antibiotics show complete mediation of this phenotype[9]. Additionally, TMAO has also been found to increase risk of thrombosis and modulate platelet hyperreactivity in mouse models[21].

Experimental data suggests that the capacity of gut microbiota to generate TMAO is important in atherosclerosis progression[9,22]. A study published by Gregory et al. demonstrated that mice receiving large-intestine microbial transplants from atherosclerosis-prone donor mice had increased incidence of atherosclerosis compared to those receiving microbial transplants from atherosclerosis-resistant mice[22]. Recently, a CD36-dependent pathway has been identified whereby TMAO stimulates macrophage migration and foam cell formation. SiRNA-mediated knockdown of the cell-surface receptor CD36 subsequently downregulated these processes and inhibited foam cell formation. The action of enzymes including MAPK (mitogen activated protein kinase) and JNK (jun N-terminal kinase) in a downstream signaling pathway were also shown to be necessary for foam cell formation[23]. Several other pathways of inflammation and immune responses to TMAO have also been explored, including activation of atherosclerosis-promoting proteins by nuclear factor-kB[19,24].

Studies suggest that TMAO also modulates gene expression of certain cholesterol transporters and other enzymes regulating bile synthesis in mice, leading to a reduction in the total bile acid pool and inhibition of reverse cholesterol transport (RCT)[10,19,25]. Koeth et al found that cholesterol transporter expression was reduced in enterocytes after dietary TMAO supplementation. Furthermore, dietary TMAO supplementation altered gene expression (mRNA levels) of cholesterol transporters in enterocytes, hepatocytes and macrophages[10]. These findings reveal how TMAO might affect cholesterol elimination at multiple levels, as well as how TMAO can lead to inhibition of RCT10. Interestingly, FMO3 also plays an important and independent role in lipid metabolism, as targeted knockdown of FMO3 results in increased non-biliary macrophage RCT and restoration of cholesterol equilibrium[26]. Taken together, these results suggest that TMAO may increase cholesterol deposition in peripheral tissues due to

decreased elimination and RCT, resulting in injury to the arterial endothelium and atherosclerotic plaque formation. Upregulation of macrophage scavenger receptor expression may increase engulfment of LDL cholesterol and foam cell formation, further exacerbating this process.

Surprisingly, one study in mice found that TMAO slowed aortic lesion development. Collins et al. purport that TMAO may actually have a protective effect on arterial function, preventing atherosclerosis[27]. Additionally, one review questioned the role of TMAO as a deleterious molecule, as TMAO is used as an osmolyte in marine animals, and fish (TMAO-producing) consumption is associated with health benefits[28]. Observational studies have also found considerable intra-individual differences in TMAO levels independent of diet[28]. While these findings seem to challenge the best available balance of evidence, the role of TMAO in atherosclerosis may need further clarification.

TMAO in Other Chronic Diseases

Recent evidence has implicated TMAO in other chronic disease processes. In 2006, Bain et al. discovered TMA and TMAO accumulation in the blood of patients with end-stage renal disease prior to hemodialysis treatment[29]. While TMA and TMAO normalized to healthly levels following dialysis, their accumulation continued before subsequent treatment. Years later, a cohort with chronic kidney disease (CKD) was found to have elevated TMAO levels in blood plasma independently associated with increased risk for MACEs[30]. Further studies found increased TMAO-associated risk for all-cause mortality in those with CKD, as TMAO has been identified as an independent predictor of systemic inflammation and mortality in these patients[31,32]. Another study showed that TMAO levels are also inversely correlated with glomerular filtration rate (GFR), an indicator of kidney function[33]. While these results suggest a causal relationship between TMAO and kidney function, interpretation is complicated by renal clearance of TMAO. Elevated TMAO in patients with CKD may simply result from pre-existing kidney dysfunction and subsequent TMAO retention[34]. On the contrary, some animal studies suggest TMAO may promote renal fibrosis and vascular calcification[31,35]. Recent studies in rats identified TMAO-associated vascular calcification via the NLRP3 and nuclear factor-kB signaling pathways, but further investigation in humans is warranted[35].

A number of recent studies have also identified a causal relationship between TMAO and type-2 diabetes (T2D). Li et al. showed that increases in phosphatidylcholine consumption were associated with greater risk of T2D in three large prospective cohorts[36]. Further studies reported up to 10-fold increases in blood plasma TMAO levels in diabetic mice compared to wild-type littermate controls. Additionally, these mice displayed an increased body mass index (BMI), and TMAO levels increased with age in both diabetic mice and controls[37]. This study also identified a trend between TMAO levels and diabetes status in human patients: individuals with prediabetes had higher TMAO levels than those with normal glucose tolerance, and those with frank T2D had the highest circulating TMAO, though this data was not statistically significant.

Subsequent research in younger cohorts has found no association between TMAO levels and increased T2D risk, and only a modest increase in prediabetes prevalence in a non-linear fashion for men and women 20-55 years old[38,39]. These results may suggest that a decline in renal function is key to linking TMAO and conditions including T2D. As T2D is a risk factor for kidney disease, progressive renal dysfunction may reduce TMAO clearance and signal adverse metabolic events already underway[38]. Associations between increasing age and TMAO levels may support this conclusion, as declining kidney function and increased insulin resistance may happen independently of TMAO action. General gut dysbiosis is indeed implicated in T2D, but the role of TMAO as an effector of these processes is not currently evident[40]. While the role of TMAO in atherosclerosis and CVD is better characterized, further interventional studies

are needed to characterize a potential causal relationship between TMAO and other chronic diseases.

Diet and TMAO Synthesis

Diet plays an important role in TMA/TMAO production, as the precursors for TMA synthesis are derived from food[9,10]. Both choline and L-carnitine are concentrated in animal products; however, the contribution of these foods to chronic disease risk through TMAO production has remained controversial.

Koeth et al. first identified a decreased capacity for vegans and vegetarians to generate TMAO in their 2013 study[10]. Postprandial ("post-meal") TMAO production after an L-carnitine supplement was significantly reduced for both vegans and vegetarians when compared to omnivores. Fasting TMAO levels were also lower in this cohort. One subject who followed a vegan diet for more than five years undertook an L-carnitine challenge and had almost no capacity to generate TMAO as well as nominal fasting plasma and urine TMAO levels[10]. Recent evidence suggests this phenomenon may be due to diet-dependent conversion of the intermediate GBB to TMA[11]. This study identified that both omnivores and vegans/vegetarians rapidly convert L-carnitine to GBB, but omnivores have a much greater capacity to subsequently metabolize GBB to TMA. These results suggest that omnivores and vegans cultivate enterotypes with varying capacities to metabolize GBB to TMA. Wu et al. independently reported similar results: after an oral carnitine challenge test (OCCT), omnivores had a much greater capacity to generate TMAO than the vegetarian subjects in the study[41]. Interestingly, some long-term vegetarians still demonstrated a remarkable ability to generate TMAO after the OCCT, which may be due to continued consumption of eggs and dairy[41].

Recently, diet-dependent taxonomic shifts in microbiome composition have been investigated for those on plant-based versus animal product-based diets[7]. David et al. found that switching between plant-based and animal product-based diets can rapidly alter the gut microbiome in as little as one day. One vegetarian subject in the study transitioned from a *Prevotella*-rich microbiome to a predominantly *Bacteroides*-rich microbiome after just four days on an animal product-based diet[7]. Interestingly, a *Prevotella*-rich microbiome has been associated with increased synthesis of short-chain fatty acids (SCFA) implicated in suppression of inflammation and cancer[42]. A *Prevotella*-rich gut microbiome across vegetarians and vegans has indeed been corroborated by other studies and may stem from a higher intake of dietary fiber[41,43,44].

Many researchers have investigated the effects of Mediterranean diets (MDs) on TMAO synthesis, as MDs are often associated with reduced risk for chronic disease[45]. Some studies suggest MDs may lower TMAO production, but results have varied. Griffin et al. found that a 6-month MD intervention did not significantly alter plasma TMAO levels in a cohort of healthy adult males[46]. Other studies have also suggested this dietary intervention may not significantly alter fasting TMAO levels, but that postprandial TMAO levels may be more sensitive to dietary intake. Conversely, one study showed that MDs lower TMAO levels when compared to a high-fat Atkins diet, but both were outperformed by an Ornish-style plant-based diet[47]. Indeed, a landmark 1990 study by Ornish et al. showed that a plant-based diet and other healthy lifestyle behaviors were sufficient to reverse atherosclerotic lesion size in those with coronary artery disease[48]. The efficacy of a MD could depend on the relative consumption of fruits, vegetables and plant foods to animal products implicated in TMAO production.

Together, these studies may suggest that a low-fat, plant-based diet provides the best therapeutic dietary intervention to reduce TMAO production. Indeed, patients suffering from trimethylaminuria (caused by mutations in FMO3 which disrupt TMA metabolism[49,50]) often become vegans to reduce circulating TMA and find relief from the disorder[9]. Utilization of a plant-based diet to modulate the gut enterotype and reduce TMAO production may be the safest and most cost-effective therapy

currently available to patients with elevated TMAO and at risk for CVD and other cardiometabolic disorders. It is currently unclear how veganism and ovo-lacto-vegetarianism compare to one another as effective therapies, but a more strict plant-based diet may be preferable, as choline is concentrated in eggs and other dairy products[41,47]. While choline is an essential nutrient for human health, some plant sources high in dietary choline have not been shown to exert the same deleterious effect seen from choline-rich animal products. This may stem from their effects on the liver enzyme FMO3, as the choline-rich brussel sprouts were shown to downregulate FMO3 activity and TMAO production[51]. One study also found that choline-rich pistachios lowered TMAO levels for those on pistachio-supplemented diets[52]. An Ornish-style plant-based diet was also found to increase plasma betaine levels, but the association between betaine and CVD risk was lost without a concomitant rise in TMAO[47]. On the contrary, one study showed a diet high in resistant starch elevated TMAO levels in the short term[53].

Conclusion

Taken together, diet-dependent conversion of phosphatidylcholine-related metabolites to TMAO is largely implicated in atherosclerosis and the progression of cardiovascular disease. TMAO is purported to exert a deleterious effect on the arterial endothelium via increased foam cell formation, inhibited reverse cholesterol transport and promotion of systemic inflammation. Clarification of the exact role of TMAO in these processes as well as investigation of the causal relationship between TMAO and chronic diseases like CKD and T2D are warranted. Limiting the consumption of animal products rich in choline and L-carnitine while transitioning to a plant-based diet may be the safest and most cost-effective dietary intervention currently available to those with elevated TMAO levels. Further randomized controlled trials are needed to elucidate the long-term impact of a plant-based diet on gut health and one's capacity to produce TMAO.

Competing Interests

The author declares no competing interests.

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