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Trimethylamine-N-Oxide (TMAO): Potential Benefits, and Therapeutic Targets Conceivable as a Mitigation Strategy for Cardio-Metabolic Diseases

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Abstract

Trimethylamine-N-oxide (TMAO) is the gut microbiome derived metabolite synthesized from a volatile amine-containing organic compound called Trimethylamine (TMA) by the action of the hepatic Flavin Monooxygenase enzyme (FMO) isoform 1 and 3. TMA is largely synthesized from choline, betaine and L-carnitine by gut microbial enzymes. TMAO has been speculated to be independently associated with various cardiometabolic and chronic diseases in humans such as atherosclerosis, type 2 diabetes mellitus, cancers, Chronic Kidney Disease (CKD), heart failure and dyslipidemia. In marine animals, TMAO has been purported to be useful in counteracting the effect of osmotic stress and hydrostatic pressure emanating from their surrounding environment. In this review, the potential benefits and comparable deleterious effect of TMAO in animals and human has been elucidated. The interventions targeting TMAO in mitigating diseases have also been reviewed and concluded that based on the current stance of available literature on the effect of TMAO, the development of a validated non-lethal antagonist would confer protection and extend the life of patients with cardiometabolic and other chronic diseases.

Keywords: Cardiometabolic • Gut microbiome • Herbal products •Therapeutic targets • Trimethylamine • Trimethylamine-N-oxide

Abbreviations: TMA: Trimethylamine Oxide; ALS: Amyotrophic Lateral Sclerosis; AXOS: Arabinoxylan Oligosaccharides; ApoEKO: Apolipoprotein E-Gene Knocked Out Mice; TMAO:Trimethylamine-N-Oxide; FMO: Flavin Monooxygenase Enzyme; CKD: Chronic Kidney Disease; GBB: γ-Butyrobetaine; DMB: 3,3 Dimethyl Butanol; TNBC: Triple Negative Breast Cancer; PERK: Protein kinase RNA-like endoplasmic reticulum kinase; PrP(C): Cellular Prion Protein; MJD/SCA-3: Machado-Joseph Disease/Spinocerebellar Ataxia-3; HFHC: High-Fat High Cholesterol Diet; HFD: High Fat Diet; BMI: Body Mass Index; Cyp7a1: cholesterol 7 alpha-hydroxylase; PAD: Peripheral Arterial Diseases; IL-6: Interleukin-6; CRP: C-reactive protein; TNFα: Tumour Necrosis Factor alpha; ROS: Reactive Oxygen Species; RCT: Reverse Cholesterol Transport; PCS: P-Cresyl Sulfate; LcS: *Lactobacillus casei* Shirota; C57BL/6J: Black 6 Jackson Laboratory strain mice; NF-κB/MAPK: Nuclear factor kappa B/mitogen-activated protein kinase; HUVEC: Human Umbilical Vein Endothelial Cells

Introduction

Trimethylamine-N-Oxide (TMAO) is the gut microbiome derived metabolite synthesized from a volatile amine-containing organic compound called Trimethylamine (TMA) by the action of the hepatic Flavin Monooxygenase Enzyme (FMO) isoform 1 and 3 [1]. TMA is synthesized by the action of the gut microbial enzymes from the precursor molecules choline, betaine, L-carnitine and to a lesser extent ergothioneine, lecithin and γ-butyrobetaine (GBB) [2]. Different types of microbial enzymes catalyze these precursor molecules to produce TMA. For instance, choline is converted into TMA by the action of TMA lyase and L-carnitine is converted into TMA by the action of carnitine oxidoreductase and betaine by betaine reductase. The precursor molecules for TMA can be obtained from food materials consumed from the diet. Choline and betaine are vastly found in red meat, poultry, milk, fish, and eggs (arranged in order of decreasing concentration) [3].

TMAO was initially regarded as the waste product from choline metabolism and L-carnitine that is excreted in urine and has nothing to do with the body's physiology. Recently, a growing awareness speculates that TMAO is independently associated with various cardiometabolic and chronic diseases in humans. For instance, studies have found an association of TMAO with atherosclerosis, type 2 diabetes mellitus, cancers, Chronic Kidney Disease (CKD), heart failure, and dyslipidemia. Nevertheless, for marine animals' large amount of TMAO is produced and get accumulated by their body cells and it has been purported to be useful in counteracting the effect of osmotic stress and hydrostatic pressure emanating from their environment. The high concentration of TMAO in body fluids of sea foods poses the risk for cardiovascular diseases and other metabolic diseases once consumed. Also, several types of studies have explored the effect of TMAO on the pathophysiology of various cardio metabolic diseases [4].

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In this narrative review, the potential benefits and comparable deleterious effect of TMAO in animals and human has been elucidated. It is anticipated that the gathered information will help other researchers to look at the molecules on both sides as previous studies have kept focus on the deleterious effect alone underrating its potential benefits [5].

Benefits of TMAO

Many studies have been conducted to highlight the potential associations of TMAO with various cardiometabolic diseases. Here in this section, we have focused on the potential benefits of the molecules that have been revealed in various studies conducted in animal and human models. Earlier studies on TMAO showed that it is responsible for oxidative phosphorylation in bacteria by being the electron acceptor in the last step of anaerobic respiration in some of the anaerobic bacteria belonging to Enterobacteriaceae. It also showed that TMAO can inhibit the growth of staphylococcus aureus bacteria by inhibiting the electron transport chain reaction. Studies have also found that TMA and TMAO can be used as supplementary energy sources for marine heterotrophic bacteria, particularly during starvation and hence implied in marine carbon and nitrogen cycling mechanism [6].

Among mammals living in marine environments such as elasmobranchs, TMAO is crucial molecule in subduing the effect of osmotic stress emanating from the large quantities of urea produced by their cellular metabolism. Albeit these species of marine mammals produce a vast amount of urea which would have impacted the functioning of macromolecules such as protein, this effect is not experienced in elasmobranchs because of the enormous amount of TMAO produced in their body [7]. It was studied that in marine mammals the TMAO levels increase in a linear pattern with increasing the sea depth. Another experimental study explained the possible involvement of TMAO in counteracting the effect of hydrostatic pressure on denaturing macromolecules that are expected to be observed among marine invertebrates and teleost. Recently it has been studied intensively in animal, human and experimental models the potential benefits of TMAO molecules in urea-rich cells acting as an adaptive mechanism in counteracting the effect of urea in osmotic stress. It has shown that cells in the human kidney that are subjected to a large amount of urea during the production of concentrated urine are not affected by such large urea concentrations because of the effect of TMAO in subduing the effect of urea. Along with characteristic smelling, earlier studies have explored the potential uses of TMAO as pheromones in dogs and coyotes, scent marking in mice and courtship attractants in some insects [8].

Interestingly TMAO in synergism with urea also participates in stabilizing the cell membrane bilayer disturbances caused by osmotic stress in marine mammals. One could speculate that the same thing would happen if human cells were subjected to osmotic stress conditions, as in type II diabetes and chronic kidney disease. It has also been proposed that TMAO promotes microtubule assembly by inducing tau protein-associated tubulin polymerization into microtubules [9]. It does so by changing the tau protein from a non-functional unstructured form to a functional secondary or tertiary dimensional structure thereby making it functional in promoting microtubule assembly and aggregation. Surprisingly TMAO has been implicated as among the causal culprits in the pathophysiology of central nervous systems degenerative tauopathies such as Alzheimer's disease [10].

Literature Review

TMAO has also been speculated to be involved in cancer amelioration through intricate mechanisms. Recently it has been investigated that TMAO plays a great role in activating $CD8^+$ T cell-mediated anticancer immunity and therefore caught the attention of its roles in tumor therapy. A comprehensive clinical cohort study by Wang et among patients having Triple Negative Breast Cancer (TNBC), found that TMAO, a microbial-derived metabolite activates $CD8^+$ T lymphocytes cells by activating endoplasmic reticulum stress kinase PERK and hence inducing pyroptosis [11]. The findings accrue to the insights about the possible uses of TMAO as a therapeutic strategy in immunotherapy for patients having deadly diseases like TNBC. Another study in the mice model found that TMAO abrogates the conversion of alpha-helices of the Cellular Prion Protein (PrP(C)) into beta-sheets during the formation of the pathogenic isoform (PrP(Sc)) during the pathogenesis of a neurodegenerative disease called transmissible spongiform encephalopathy caused by a prion. Comparable benefits of TMAO in ameliorating diseases through preventing conformational changes of proteins involved in pathogenesis have been studied in Machado-Joseph disease/spinocerebellar ataxia-3 (MJD/SCA-3) and Amyotrophic Lateral Sclerosis (ALS)s [12].

TMAO in cardio-metabolic diseases

Cardiometabolic disorders are conditions that start with insulin resistance, progress to the metabolic syndrome, pre-diabetes, and ultimately more serious conditions including heart, vascular diseases, and type 2 diabetes. Despite the aforementioned benefits of TMAO in bacteria, marine mammals and to a lesser extent in humans, TMAO has been extensively studied for its involvement in the pathogenesis of various cardiometabolic diseases. In this section, we have explored the involvement of TMAO in escalating cardiometabolic diseases. Dambova et al. found that TMAO, a gut microbiome derived metabolite was associated with diabetes in db/db mice and human samples [13]. They observed that age, diabetes and Body Mass Index (BMI) are linked with spiraling TMAO concentrations independently of L-carnitine. It has also been studied that dietary TMAO in mice fed with a High-Fat Diet (HFD) aggravates impaired glucose tolerance and causes perturbations in the hepatic insulin signaling pathway and initiates adipose tissue inflammation [14]. A similar effect of TMAO on impaired glucose tolerance and abnormal lipid metabolism was observed in Macaca Mulatta fed with a High-Fat High Cholesterol Diet (HFHC).

Several researches have been done to explore how TMAO predicts Peripheral Arterial Diseases (PAD) and coronary artery diseases. Elko et al found that elevated serum TMAO levels is associated with the increased size of the intima of the carotid artery and the lifestyle modification intended in mitigating atherosclerosis is associated with diminishing levels of TMAO in serum. Similarly, a study done in apoE/mice suggested that TMAO aggravates atherosclerosis by impairing normal bile acid metabolism through inhibition of Cyp7a1 expression. A recent ground-breaking *in vitro* study has shown TMAO when treated in endothelial progenitor cells is associated with up-regulation of interleukin-6 (IL-6), CRP, TNFα and Reactive Oxygen Species (ROS) providing evidence of the possible effect of TMAO in endothelial nitric oxide disturbances [15]. TMAO recently has been enormously studied for possible mechanisms in atherosclerosis pathogenesis including activation of the inflammasome, causing endothelial cell pyroptosis, enhancing monocyte adhesion and impairing endothelial cells repair and altering the Reverse Cholesterol Transport (RCT) mechanism, and it increases vasoconstriction activity of angiotensin II in hypertension.

In recent years, there has been growing evidence that suggests the possible involvement of TMAO in the pathophysiology of CKD and a number of cancers [16]. For instance, a meta-analysis study showed there was a strong association between serum TMAO levels and cancer incidence, and kidney function. Also, Xiamoi et al observed that elevated TMAO levels in an independent prognostic biomarker in colorectal cancer and its association with a low chance of survival among patients [17]. Furthermore, it has been proposed that the mechanism driving kidney function deterioration in patients with high levels of TMAO concentrations is due to its effect on the progression of atherosclerosis lesions.

Discussion

TMAO-targeting interventions for mitigating cardiometabolic diseases

Prebiotics: Prebiotics are nondigestible materials that have the ability to confer health benefits to the host by modulating the microbiome. To date, there are several prebiotics with promising results that have been tried as a therapeutic strategy in mitigating various cardiometabolic diseases associated with elevated TMAO levels

[18]. A randomized cross-over study among patients with chronic kidney disease was performed to investigate the effect of prebiotic Arabinoxylan Oligosaccharides (AXOS) on urinary TMAO levels and it showed that 24 hours of urinary TMAO levels did not fall after treatment with AXOS, however further longitudinal study with strong power and validity was suggested to be done for deep understandings. Another randomized controlled trial was done to investigate the effect of prebiotic fructooligosaccharide on another uremic toxin which is normally elevated together with TMAO in CKD patients. It was found that fructooligosaccharide reduces the urinary excretion of P-Cresyl Sulfate (PCS) a gut-derived microbialmetabolite among CKD patients. Additionally, Ranitidine and finasteride drugs are not prebiotics but have been shown in addition to their pharmacologic effects they can reduce TMAO levels through modulation of gut microbiota similar to prebiotics [19]. Further researches on other prebiotics like inulin, resistant starch and galactooligosaccharide are required to gain more evidence of their effects on other cardiometabolic diseases like diabetes and vasculopathies.

Probiotics: Probiotics are non-pathogenic living microorganisms, which when taken in large quantities, become beneficial to the host by enhancing its microbial balance. A number of researches have been done to investigate the role of probiotics in curbing the deleterious effect of TMAO in cardiometabolic diseases. However, there have been controversies in the findings observed among the studies. A study in mice showed *Lactobacillus plantarum* ZDY04 strain was able to reduce serum TMAO levels and TMA levels in mice by reducing the abundance of Lachnospiraceae, Erysipelotrichaceae and Bacteroidaceae and the genus *Mucispirillum* in mice and it was also associated with inhibition of atherosclerosis lesions progression in ApoE/mice. Comparable findings were observed in choline-fed mice using Enterobacter aerogenes ZDY01. Albeit the studies in mice show promising evidence of conceivable usages of probiotics in curbing cardiometabolic diseases, studies among CKD patients did not coincide with the findings in mice [20]. It was observed that probiotic supplementation among CKD patients and patients undergoing hemodialysis failed to reduce serum TMAO levels emanating from gut microbiome metabolism. Also, a study conducted using a probiotic called *Lactobacillus casei* Shirota (LcS) in patients with cardiometabolic syndrome failed to show a reduction in serum TMAO levels after 12 weeks of intake of LcS. Evidence from systematic reviews show that probiotic supplementation can restore the gut microbiome when there are perturbations or dysbiosis otherwise their effects are blurred in normal gut microbiota population habitation. This would be one of the reasons for annulling the effect of probiotic supplementation in reducing levels of TMAO among RCT.

Antibiotics: A number of researches with promising results have shown a reduction in TMAO levels after oral supplementation with antibiotics which have the ability to deplete the gut microbiome responsible for converting food nutrients into TMA and subsequently TMAO. For instance, a prospective clinical study using phosphatidylcholine and broad-spectrum antibiotic (metronidazole and ciprofloxacin) revealed that oral supplementation for one week with broad-spectrum antibiotics to the phosphatidylcholine challenged patients resulted in a tremendous decline in plasma TMAO levels. Additionally, it was also found that the TMAO levels replete after the withdrawal period of the antibiotics coupled with the subsequent re-establishment of the gut microbiome. Albeit the mitigation of cardiometabolic diseases using antibiotics has shown the ability to reduce TMAO levels tremendously but they pose some challenges including the development of antimicrobial resistance and the depletion of normal flora which are crucial in normal body physiology. Other studies have found abnormal weight gain and obesity on prolonged usage of antibiotics. Because of the potential ability of the microbiome to out power the inhibitory effects of antibiotics on prolonged use, it cannot be recommended as a way forward to mitigate cardiometabolic diseases.

Inhibitors of the TMAO synthesis pathway

A plethora of studies has been done to validate the use of inhibitors of the TMAO synthetic pathway particularly inhibitors of enzymes used in the conversion of L-carnitine, choline, and betaine into TMA in the gut and the conversion of TMA into TMAO in the liver by hepatic flavin containing monooxygenase enzyme (FMO_3). One appealing approach is the use of a choline analog called 3,3 Dimethyl Butanol (DMB) which competitively inhibits microbial TMA lyase enzyme and therefore reduces the formation of TMA, however, it does not eliminate all TMAO in the circulation because of other potential precursors of TMAO like butyrobetaine. DMB can be found abundantly in various foods such as balsamic vinegar and red wines. One can hypothesize that consuming these foods could be a protective advantage against various cardiometabolic diseases. Similar to DMB, iodomethylcholine and fluoromethylcholine have been tested and shown to efficiently reduce TMA and TMAO levels in mice by inhibiting microbial choline TMA lyase enzyme. Another molecule called meldonium, an analog of GBB, a TMA synthesis precursor, is well-known for its use in the treatment of ischemic heart disease. It has been widely studied and found to reduce TMAO levels through intricate mechanisms.

Another approach is the inhibition of hepatic FMO_3, a hepatic enzyme system responsible for TMA's oxidation into TMAO. In mice models, the knockout of the enzyme has been shown to alter the lipid and cholesterol metabolism in a similar way to the harbinger of dyslipidemia. However, its practicability is limited because FMO_3 is vital in catalyzing other biochemical reactions aside from the oxidation of TMA into TMAO and the possible development of trimethylaminuria, a condition characterized by voiding urine with excessive fish odor. Additionally, TMAO synthesis can be inhibited by a molecular mechanistic approach through molecular inhibition of *CutC* and *CutD* gene clusters in gut microbes which are the sources of microbial TMA lyase enzyme. The enzyme is responsible for the formation of TMA from choline and upon its suppression can reduce the plasma and urine levels of TMAO. Also, molecular inhibition of the *CntA* and *CntB* gene clusters responsible for the conversion of L-carnitine to choline has shown promising results in reducing TMAO levels. Similarly, research reveals that aspirin in addition to its known application was found to reduce TMAO levels by inhibiting microbial TMA lyase (Figure 1).

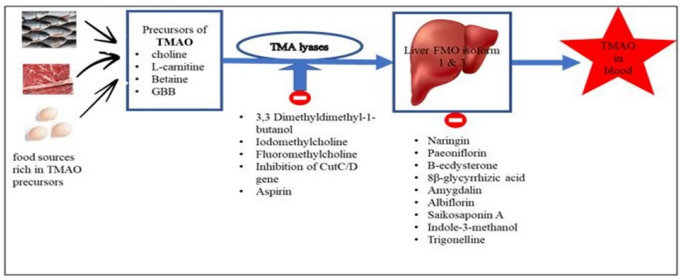

Figure 1. Illustrates molecules with the potential to inhibit the enzymes involved in the TMAO synthesis pathway.

Using natural remedies

The use of natural products in reducing TMAO levels has attracted considerable interest among different authors. A natural phytoalexin product called resveratrol was found to reduce TMAO levels, atherosclerotic lesions and bile acids de-conjugation and excretion in C57BL/6J and ApoE/mice. Recently comparable results have been observed in C57BL/6J and ApoE KO mice fed with a choline-supplemented chow diet and treated with berberine. Another plant called *Gynostemma pentaphyllum* is widely used as a Chinese herbal medicinal plant in the treatment of type 2 diabetes, dyslipidemia and obesity has been revealed to have an inhibitory effect on the phosphatidylcholine to TMAO conversion pathway and eventually reduce the plasma TMAO levels. Black raspberries with enormous amounts of polyphenols antioxidants have also been found to reduce TMAO levels *via* modulation of the gut microbiome and have the ability

to mitigate hypercholesterolemia and inflammation. Other products that have shown promising results in reducing TMAO levels *via* modulation of the gut microbiome are *Alisma orientalis* beverage *Ganoderma lucidum*, allicin, black beans and fructus ligustri lucidi. Another interesting flavonoid molecule called nobiletin which is extracted from citrus fruits has shown appealing benefits in reducing TMAO levels and counteracting HUVEC cell proliferation, decreasing TMAO-induced HUVEC cells apoptosis and significantly reduces TMAO induced vascular inflammation *via* inhibition of the NF-κB/MAPK pathways in Sprague–Dawley rats. Moreover, another product called trigonelline from *Trigonella foenum-graecum*, a plant that has been widely used in the treatment of cardiovascular diseases has also been shown to scale down TMAO levels by inhibiting FMO3 and hence impeding conversion of TMA into TMAO.

Conclusion

Despite its harmful effects, TMAO is not necessarily harmful to all animals and body tissues. It can confer protection to marine animals like elasmobranchs by offsetting the effect of osmotic pressure and hydrostatic pressure and abrogating protein misfolding in some neurodegenerative diseases. Nonetheless in human's elevated levels of TMAO levels emanating from excessive consumption of choline, betaine and L-carnitine-rich diets can lead to the development of various cardiometabolic diseases. Therefore, it is of paramount importance for further studies to develop new non-lethal antagonists of TMAO which can be used to mitigate cardiometabolic diseases including extensive research into dietary patterns interventions that can be suitable for maintaining TMAO levels to the benign levels at the same time the consumer is not deprived of essential nutrients. Recently studies have shown dietary intervention can deplete TMAO levels and vegetarians have low levels of TMAO in comparison to people who consume animal protein. Based on the current stance of available literature on the effect of TMAO, the development of a validated non-lethal antagonist would confer protection and extend the life of patients with cardio-metabolic and other chronic diseases.

Ethics Approval and Consent to Participate

Not applicable (NA).

Consent for Publication

Not applicable (NA).

Availability of Data and Materials

Not applicable (NA).

Competing Interests

The authors declare that they have no competing interests.

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Authors Contributions

OM conceptualized and wrote the manuscript, SK, TM, AMM, JJR, and HAS reviewed the manuscript; FM reviewed and supervised manuscript writing process.

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