



## Review

# Trimethylamine *N*-oxide: A harmful, protective or diagnostic marker in lifestyle diseases?



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## ABSTRACT

Diet has been considered a general health determinant for many years. Recent research shows a connection between gut microbiota composition that is shaped by our diet and lifestyle diseases. Several studies point to a positive correlation between elevated plasma trimethylamine *N*-oxide (TMAO), a gut bacteria metabolite, and an increased risk for cardiovascular diseases, diabetes, and cancer. Therefore, it has been suggested that TMAO is a link between the diet, gut microbiota, and illness. Emerging experimental and clinical evidence shows that TMAO may be involved in the etiology of hypertension, atherosclerosis, coronary artery disease, diabetes, and renal failure. On the contrary, a number of studies have shown protective functions of TMAO, such as stabilization of proteins and protection of cells from osmotic and hydrostatic stresses. Finally, it is possible that TMAO is neither a causative nor a protecting factor, but may be merely a marker of disrupted homeostasis. Blood TMAO level depends on numerous factors including diet, gut microbiota composition and activity, permeability of the gut–blood barrier, activity of liver enzymes, and the rate of methylamines excretion. Therefore, the usefulness of TMAO as a specific biomarker in lifestyle diseases seems questionable. Here, we review research showing both physiological and pathophysiological actions of TMAO, as well as limitations of using TMAO as a biomarker.

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## Introduction

Despite significant progress in diagnosis and treatment, the morbidity and mortality of lifestyle diseases remain very high. This can be partially due to significant gaps in the understanding of their pathophysiology [1,2].

Diet is one of the main factors influencing prevalence of “diseases of affluence.” Recent clinical studies suggest a correlation between elevated plasma trimethylamine *N*-oxide (TMAO) levels and a risk for lifestyle diseases, such as diabetes or atherosclerosis in its different forms, including coronary artery disease (CAD) and peripheral vascular disease [3–6]. Plasma TMAO originates from gut bacteria metabolism of dietary L-carnitine, betaine, and choline. As red meat and eggs are abundant sources of L-carnitine and choline, it has been proposed that TMAO, disturbing hormonal and lipid homeostasis, may be a link between diet and

cardiovascular diseases (CVDs) [7–9]. Seafood, however, is thought to be a health-beneficial component of our diet, despite being a rich source of TMAO [10]. Furthermore, a number of studies highlight TMAO as a protective factor in many organisms. For instance, fish use TMAO to maintain cell volume and protect themselves from the influence of high hydrostatic and osmotic pressures [3,11].

Risk assessment is a strategic tool for improving treatment and outcome in lifestyle diseases. Therefore, there is a continuous search for reliable new diagnostic biomarkers, and TMAO blood level has recently drawn a lot of attention. However, there may be significant limitations with regard to TMAO specificity because its blood level depends on numerous factors such as diet, gut bacteria composition and activity, gut–blood barrier function, liver function, and excretion. In short, TMAO plasma levels in humans increase after choline, betaine, and L-carnitine ingestion; it also rises quite rapidly (within 15 min) after consumption of TMAO- and trimethylamine (TMA)-rich products [12]. Choline, betaine, and L-carnitine are metabolized to TMA by bacteria in large intestine. Most of TMA is absorbed into bloodstream and rapidly oxidized to TMAO by flavin-containing

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monooxygenase-3 (FMO-3), an enzyme present in the liver [13–15]. Other FMO forms (FMO-1, FMO-2, FMO-4, FMO-5) are not present in humans nor do they play any important role in TMA metabolism [16]. Final elimination of TMAO is dependent on urination, sweating, and exhalation [17,18].

Here we review the latest research showing both physiological and pathophysiological actions of TMAO, as well as limitations of using TMAO as a biomarker.

### Gut microbiota and gut–blood barrier in health and disease

It has been well established that diet affects the composition and activity of gut bacteria [19–24]. Recent evidence suggests that gut dysbiosis and microbiota metabolites may be involved in the etiology of hypertension and some other lifestyle diseases [25–31].

It is well documented that human homeostasis depends on a mutualistic relationship with gut microbiota. This subtle balance may be disturbed in pathologic conditions and become harmful for the host. Gut microbiota contribute not only to the synthesis of vitamins, such as vitamins B and K, but also to metabolism of bile acids, sterols, xenobiotics, and other compounds. Importantly, gut bacteria produce numerous biologically active molecules, some of which may contribute to the regulation of the circulatory system and energy balance [5,8,32–34]. Apart from many metabolites, mammalian gut flora produces several methylamines, including TMA, dimethylamine, and monomethylamine [13].

The bloodstream is guarded against the access of bacterial metabolites by the intestinal barrier, also called the gut–blood barrier. It is a functional, immunologic, and anatomic unit, separating intestinal lumen from the circulating blood, preventing bacterial adhesion and regulating transport. The barrier is a complex, multilayer system, consisting of endothelium, epithelial cells, and mucosa [35]. It is well established that integrity and permeability of biological barriers, such as the gut–blood barrier or the blood–brain barrier, is dependent on sufficient blood perfusion. Therefore, lifestyle diseases characterized by compromised perfusion of peripheral tissues, both in central (e.g., heart failure) and peripheral mechanisms (angiopathy in course of atherosclerosis, hypertension, or diabetes), may disturb the intestinal barrier structure and affect its permeability [35, 36]. Blood-borne methylamines and other gut microbiota metabolites may reach nearly all tissues as small molecules, and thus affect both peripheral and neurohormonal regulatory mechanisms. Recent studies provide evidence for a link between gut dysbiosis, gut–blood barrier dysfunction (increased permeability) and pathophysiology of gastrointestinal as well as extraintestinal diseases, such as heart failure, metabolic syndrome, diabetes, and psychiatric disorders [35–38].

### TMAO as a potentially harmful molecule

Until recently, the clinical significance of TMA metabolism was limited to trimethylaminuria, also called the “fish odor syndrome,” which is a rare, hereditary autosomal recessive disease. This descriptive name comes from the characteristic odor of urine, sweat, and exhaled air of patients suffering from trimethylaminuria. The disease is caused by accumulation of TMA in patients due to significant reduction in FMO3 activity; however, some unidentified factors may also play a role in its pathophysiology [39,40].

A number of studies point to a positive correlation between an elevated plasma TMAO level and an increased risk for CVDs

[5,6,30–32,41,42]. Zhu et al. said that high TMAO concentrations directly contribute to platelet hyperreactivity, leading to augmented intracellular  $\text{Ca}^{2+}$  release and enhanced thrombotic potential, independently predicting incident thrombosis risk [43]. TMAO, as a metabolite of dietary compounds that are present in red meat and egg yolks, has been proposed to be both a marker and a link between diet and CVDs [44–46]. Furthermore, several experimental studies show that TMAO affects lipid and hormonal homeostasis, providing indirect evidence for TMAO contribution to the development of CVDs. For example, TMAO has been found to inhibit the substrate-dependent respiration, thus leading to a decrease in  $\beta$ -oxidation of fatty acids by heart muscle cells [47]. Koeth et al. [8] showed that TMAO modulated cholesterol and sterol metabolism, promoting progress of atherosclerosis, whereas we found that TMAO prolonged the hemodynamic effects of chronically infused angiotensin II [9], a crucial hormone in the circulatory system homeostasis. It has been shown that TMAO may not only exacerbate inflammatory reactions of vascular wall, activating NLRP3 inflammasome and inducing reactive oxygen species production, but also impair cholesterol reverse transport, being involved in development of atherosclerosis [44,48]. Furthermore, TMAO has been suggested to play a role in the etiology of diabetes [4,33,49,50]. Finally, high plasma TMAO levels have been shown to be positively associated with colorectal cancer [27], another disease thought to be associated with lifestyle and diet.

### TMAO: A beneficial agent?

There are some observational and experimental data showing that TMAO may have a positive effect in lifestyle diseases. Fish, rich in TMAO, are important components of the Mediterranean diet, which is considered to have a beneficial effect on the circulatory system [51,52]. Additionally, high concentrations of TMAO in urine in the Japanese population compared with that of a North American population were reported [53]. In this context, according to the World Health Organization data for 2012, age-adjusted mortality was significantly higher in the United States than in Japan [54]. Taken together, this data may suggest that an increased concentration of TMAO is not positively correlated with an increased risk for lifestyle diseases.

Moreover, a direct link between TMAO and diet may be considered doubtful. In studies on the European population, plasma TMAO levels exhibited significant intraindividual variation throughout the year, which was independent of diet [55]. Other groups of researchers found a positive association of TMAO only with dairy consumption [56], but this finding has not been confirmed in other clinical trials. That is, Obeid et al. found no significant differences between vegans and lactoovovegetarians [57]. In another study, a diet containing three eggs per week did not influence TMAO plasma levels [58], contrary to the results obtained by Miller et al. [59]. Furthermore, several-fold higher TMAO plasma concentrations were observed after fish intake compared with intake of red meat or eggs [12]. Moreover, Cheung et al. provide evidence supporting the claim that TMAO is the best biomarker of fish intake when compared with a diet of different composition [60]. Therefore, a diet thought to be health beneficial seems to be concomitant with high TMAO blood levels.

Moreover, there are several studies showing a possible protective effect of TMAO. For example, it has been found that TMAO slows aortic lesion formation in the mouse model [61], and that TMAO promotes normal protein folding, thereby neutralizing endoplasmic reticulum stress in diabetic rats [62]. Additionally, we found that an experimental 100-fold increase in plasma

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