TMAO

Linking Diet, Gut Microbiota, and Cardiovascular Risk

Recently, the gut microbiome has gained increasing attention for its role in the development and progression of chronic, neurological, and oncological diseases. It is now clear that the microbiome produces a variety of metabolites depending on a person's diet and their microbial composition—though the full impact of many of these metabolites on human health remains to be elucidated. One such metabolite, trimethylamine (TMA), and its oxidized form, trimethylamine-N-oxide (TMAO), have been associated with inflammation, obesity, atherosclerosis, and cardiovascular disease in general [1, 2]. Emerging research also suggests a potential link to neurodegenerative disorders [3]. Elevated TMAO levels are thus considered a significant risk factor for the development of various diseases.

From Precursors to TMAO

Trimethylamine (TMA) is an intermediate metabolite produced in the gut during the digestion of certain food constituents. Key dietary sources that promote TMA synthesis include **betaine, L-carnitine, ergothioneine, choline, and choline-containing compounds** [4, 5]. The conversion of these precursors into TMA is carried out by specific gut bacteria via various enzymes. Bacterial genera involved in this process include *Desulfovibrio, Gammaproteobacteria* (e.g., *E. coli, Citrobacter, Klebsiella pneumoniae, Providencia*), as well as members of the *Firmicutes* and *Actinobacteria* phyla [6]. Once TMA has been synthesisedby the gut microbiome, TMA is absorbed and transported to the liver, where it is oxidized to trimethylamine N-oxide (TMAO) by flavin-containing monooxygenases (primarily FMO3). The resulting concentration of TMAO in the bloodstream is primarily influenced by three key factors: diet, microbial composition, and hepatic FMO3 activity [2]. Elevated TMAO levels have been linked to the development of atherosclerosis and may, therefore, over time contribute to the onset of cardiovascular disease (see figure below).

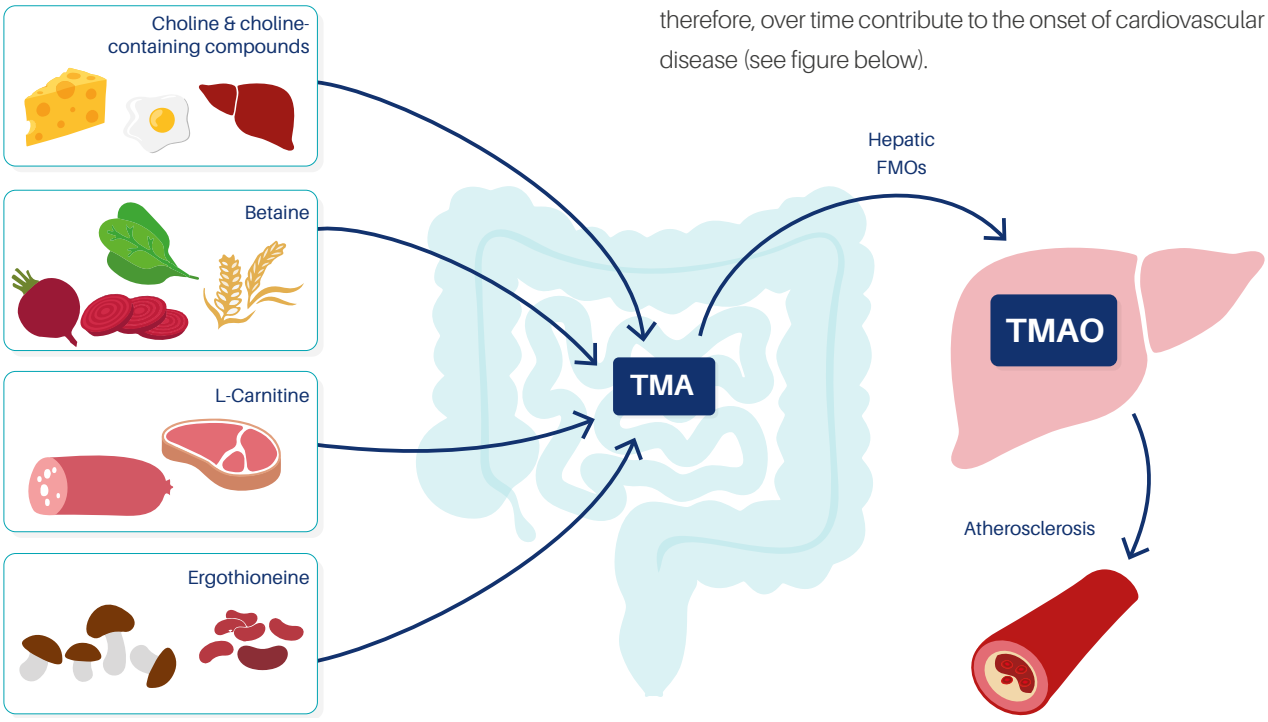

Fig. *Schematic representation of TMAO synthesis. Choline and choline-containing compounds (e.g., lecithin), along with betaine, L-carnitine, and ergothioneine, are ingested through various foods such as cheese, eggs, liver, beetroot, spinach, wheat, sausages, meat products, mushrooms, and beans. These compounds—referred to as TMA precursors—are enzymatically converted into trimethylamine (TMA) in the intestine by specific gut bacteria. Once absorbed, TMA is transported to the liver, where it is oxidized by flavin-containing monooxygenases (primarily FMO3) into trimethylamine N-oxide (TMAO). Elevated TMAO levels have been linked to the development of atherosclerosis and cardiovascular disease (Adapted from M. H. Janeiro et al., 2018).*

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Quantity Matters

Betaine, L-carnitine, choline, and choline-containing compounds such as phosphatidylcholine (lecithin) are regularly consumed through everyday nutrition. These nutrients are considered **semi-essential** and are known for their **protective properties**. For example, betaine helps lower homocysteine levels, L-carnitine is crucial for lipid metabolism, and choline is essential for synthesizing compounds that stabilize cell membranes and maintain acetylcholine levels, a key neurotransmitter [5]. However, since these same compounds are also precursors of TMAO synthesis, they can no longer be regarded as having an exclusively protective effect.

CAUTION!

As the precursors are **essential nutrients**, it is important to measure their concentrations to distinguish between their **beneficial physiological roles** and their **potentially harmful effects**.

Interpreting and Treating Elevated TMAO Levels

For a long time, TMAO was considered a mere waste product of choline metabolism with no significant biological effect. However, recent studies have disproven this notion. Chronic exposure to TMA or TMAO can have harmful effects, mainly due to the continuous conversion of dietary precursors by specific gut bacteria or flavin-containing monooxygenases (FMOs). When interpreting TMAO levels, it is important to consider both interindividual and intraindividual variations. Factors such as the patient's **age** and **FMO3 activity**, which can be influenced by bile acid and hormone metabolism, exert significant effects on a person's TMAO levels.

Managing elevated TMAO concentrations primarily focuses on **dietary adjustments** alongside the use of **prebiotics** and **probiotics**. This involves both reducing the intake of TMA precursors to a suitable level and promoting beneficial gut bacteria while minimizing the growth of TMA-producing strains. Additionally, another approach is to block microbial TMA synthesis through compounds like **DMB** (3,3-dimethyl-1-butanol), which can be found in cold-pressed olive oil, grape seed oil, red wine, and balsamic vinegar [7].

Sample Material: stabilised urine from test set 928
Pre-Analytics: Consumption of **fish and seafood should be avoided** for at least 48 hours prior to testing, as these foods contain high levels of TMAO. Therefore, these foods may lead to false-positive results.

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Got any questions? Feel free to give us a call– we look forward to speaking with you!

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