REVIEW ARTICLE

Trimethylamine N-Oxide From Gut Microbiota in Chronic Kidney Disease Patients: Focus on Diet

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Low-protein diet is the recommended nutritional intervention for nondialysis chronic kidney disease (CKD) patients because excess protein intake can damage kidney function and produce uremic toxins. Some of these toxins are generated from amino acids breakdown by gut microbiota as p-cresyl sulfate and indoxyl sulfate that have been clearly associated with cardiovascular mortality in CKD patients. Another uremic toxin, trimethylamine N-oxide (TMAO), a degradation product of choline and L-carnitine (which come mainly from animal protein such as red meat and eggs) is now considered as a proatherogenic metabolite. In the present review, we will highlight the relationship between TMAO, diet and cardiovascular aspects, and the potential concerns about TMAO in nondialysis CKD patients.
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Introduction

CARDIOVASCULAR DISEASE (CVD) is a major problem in chronic kidney disease (CKD) patients.[1,2] In addition to traditional cardiovascular risk factors, the nontraditional ones are gaining attention in scientific community like the possible imbalance of gut microbiota. In fact, recent studies have identified the gut microbiota imbalance as a new factor that may contribute to inflammation and oxidative stress leading to CVD.[3,4]

To date, little information is available about the imbalance of gut microbiota in CKD patients. Vaziri et al.[5] showed by microarray data that hemodialysis (HD) patients presented similar mean relative richness (the number of bacterial taxa in a sample) when compared with healthy individuals; however, there was a significant difference in the relative abundances of bacterial groups within the subfamilies.

In another study from our group, nondialysis patients also presented similar average number of bands evaluated by denaturing gradient gel electrophoresis technique, but data suggest possible differences in the gut microbiota between nondialysis CKD patients and healthy individuals.[3]

Although there are few studies on the composition of gut microbiota in CKD patients,[3,5–7] it is well known that the uremic toxins such as p-cresyl sulfate (PCS) and indoxyl sulfate (IS) both derived from breakdown of amino acids by gut microbiota are accumulated in these patients. These uremic toxins have been associated with cardiovascular mortality[8,9] and metabolic disturbances.[10] More recently, trimethylamine N-oxide (TMAO), also produced by gut microbiota, has been recognized as a proatherogenic metabolite.[11]

The high consumption of some animal protein sources, especially red meat and eggs may contribute to high TMAO levels because these foods contain high amount of its precursors, choline, and L-carnitine.[11–13] TMAO is excreted in the urine via kidney and can be removed in a HD session.[13,14] However, the hypothesis is that, in nondialysis CKD patients, TMAO levels would be increased. This review provides an overview of the studies focusing on diet and TMAO and future perspectives for nutritional therapy in nondialysis CKD patients.

TMAO and the Diet

The dietary carnitine and choline (derived from lecithin-phosphatidylcholine) when reaching the gut are metabolized by microbiota and produce an intermediate compound known as trimethylamine that is oxidized in the liver by enzyme flavin-containing monooxygenase 3 (FMO_3) in TMAO.[11,13]

Some varieties of normal gut bacteria, such as species of *Acinetobacter* convert dietary carnitine and lecithin into TMAO.[15] Analysis of bacterial 16S RNA sequences in fecal specimens revealed that subjects with enriched bacteria of

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the genus *Prevotella*, which is increased by high-fat diets, presented higher TMAO levels than subjects with an enrichment of the genus *Bacteroides*.[11] In the same study, the authors grouped volunteers by dietary status as either vegan or vegetarian ($n = 23$) or omnivore ($n = 30$) and performed a challenge that consisted of ingestion of a steak. The authors observed that the amount of both urinary and plasma TMAO increased in omnivore individuals, but not in vegans or vegetarians.[11]

In a very elegant study, Hartiala et al.[16] demonstrated in mice and humans by comparative genome-wide association studies that the levels of TMAO were only slightly predisposed by genes suggesting that the diet is an important axis for controlling TMAO levels in humans.

The greatest dietary sources of choline (lecithin) are eggs, liver, beef and pork, and red meat contains a great amount of L-carnitine that is endogenously converted into TMAO.[11,15,17]

The Nutrition Board of the Institute of Medicine[18] estimated an adequate intake of choline to be 550 mg per day for men and 425 mg per day for women. According to United States Department of Agriculture database for the choline content of common foods, the richest food in choline is egg (yolk; ~250 mg of total choline/100 g), followed by meat and fish (~75 mg of total choline/100 g), whole grains (<75 mg of total choline/100 g), breakfast cereals (~50 mg of total choline/100 g), vegetables and fruits (~30 mg of total choline/100 g), milk (~10 mg of total choline/100 g), and fat and oils (~5 mg of total choline/100 g).[19]

L-carnitine, the second precursor of TMAO, is a nutrient considered as a conditionally essential nutrient that transports long-chain fatty acids through the interior of mitochondrial membranes to produce energy.[20] According to the Annals of the New York Academy of Sciences,[21] the supplementation of L-carnitine is not necessary for adults and healthy children because carnitine is not considered an essential nutrient. Dietary reference intakes and recommended dietary allowance for carnitine was not established.[22] In individuals with normal renal function, excess of carnitine is excreted via kidneys.[13]

According to Tang et al.,[13] an excessive intake of food containing phosphatidylcholine and choline must be avoided because these metabolites lead to increased production of TMAO. In addition, a vegetarian diet or a diet with high intake of fibers could reduce total choline intake. However, it is important to recall that choline is a semi essential nutrient; and therefore, food containing choline should not be totally excluded from the diet.[19]

Lenz et al.[23] compared metabolomics urinary profile of British and Swedish population and showed higher urinary excretion of TMAO in Swedish population due to fish-based food, which was not seen in British population who were asked to avoid fish intake 24 hours before urine collection. One of the International Study of Macro/Micronutrients and Blood Pressure study publications[24] compared metabolomics profiles of different populations (Japan, China, and North America) and the Japanese population, regularly following a diet rich in fish, presented higher urinary excretion of TMAO. Lloyd et al.[25] compared dietary intake of different groups of food in a randomized trial and observed association between salmon intake and urinary TMAO excretion. Taken together, these data would suggest that fish intake would contribute to increased production of TMAO. However, a study showed that TMAO was associated with urinary nitrogen excretion for both meat and fish intake.[26] Taken together these data suggest that the composition of the diet is of upmost importance, as it was showed in an experimental study that a high-fat and high-caloric diet increased serum TMAO levels.[27]

Bennet et al.[28] examined dietary, genetic, and hormonal factors regulating TMAO levels in mice and human. The experimental study showed that FMO_3 (FMO family member with highest specificity activity) was reduced in males due to downregulation by androgens as compared with females. In humans, they also demonstrated the higher expression of FOM_3 in women as compared with men. The authors demonstrated that the supplementation of the control diet with choline (1%) did not affect the expression of hepatic FMO_3 in either male or female mice. Thus, compared to a chow diet, choline supplementation in both male and female mice increased plasma TMAO levels, which were markedly increased in females. In addition, TMAO-fed and choline-fed mice experienced increased kidney injury marker.[29]

Koeth et al.[11] performed an interesting experimental and clinical study on TMAO and showed that the reduced ingestion of L-carnitine and total choline by vegans and vegetarians (humans) was associated with decreased TMAO levels. On the other hand, gut microbiota of omnivores produced higher levels of TMAO because of the increased ingestion of L-carnitine mainly from red meat. Similar data have been previously shown by Xu et al.[30] as lactovegetarians presented decreased urinary concentration of TMAO. Stella et al.[31] reported high urinary TMAO excretion in response to meat intake. Intake of food rich in choline such as egg may be also implicated with higher TMAO production. In fact, Miller et al.[12] showed that egg intake (≥2 eggs/day) was associated with high levels of plasma and urine TMAO levels.

It is important to highlight that the urinary clearance of TMAO is supported by the high correlation between urine and plasma levels. Therefore, an efficient excretion mechanism is needed to counteract accumulation of TMAO.[13] In addition, studies have shown that the consumption of food containing high levels of TMAO precursors (L-carnitine and choline) such as red meat and eggs is implicated with atherosclerosis.[11,15] Recently, TMAO has been associated to CVD in general population.[8,13]

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