Research ties gut microbial TMAO pathway to chronic kidney disease

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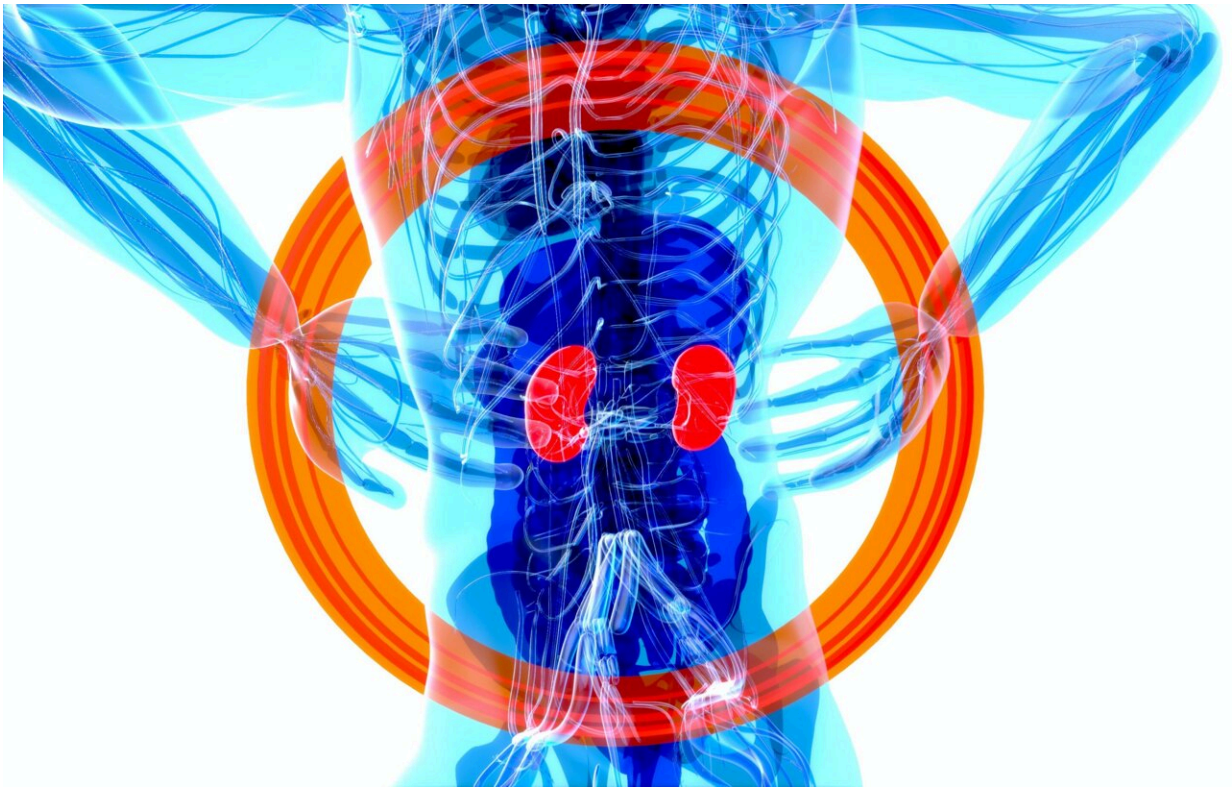

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New findings from Cleveland Clinic and Tufts University researchers show high blood levels of TMAO (trimethylamine N-oxide) predict future risk of developing chronic kidney disease over time.

The findings build on more than a decade of research spearheaded by Stanley Hazen, M.D., Ph.D., and a team related to the gut microbiome's role in cardiovascular health and disease, including the adverse effects of TMAO, a byproduct formed by the gut bacteria from nutrients abundant in red meat, eggs and other animal source foods.

The study, published in the *Journal of the American Society of Nephrology,* was a collaboration between a Cleveland Clinic research team led by Dr. Hazen and investigators from the Food is Medicine Institute at the Friedman School of Nutrition Science and Policy at Tufts University, including first author Meng Wang, Ph.D., and co-senior author Dariush Mozaffarian, M.D., Dr.PH.

The large-scale study measured blood levels of TMAO over time in two large National Institutes of Health populations and followed the kidney function of more than 10,000 U.S. adults with normal kidney function at baseline over an average follow-up period of 10 years. The investigators found that participants with elevated TMAO blood levels were at increased risk for future development of chronic kidney disease.

Higher TMAO levels were also associated with a faster rate of declining kidney function in people with normal or impaired kidney function at baseline. These associations were independent of sociodemographic characteristics, lifestyle habits, diet and other known risk factors for kidney disease. The findings also are consistent with earlier reported preclinical model studies showing TMAO directly fosters both kidney functional decline and tissue fibrosis.

"The findings indicate a remarkably strong clinical link between elevated TMAO and increased risk for developing chronic kidney disease," said Dr. Hazen, chair of the Department of Cardiovascular and Metabolic Sciences and at Cleveland Clinic's Lerner Research Institute and co-section head of Preventive Cardiology in the Heart, Vascular & Thoracic

Institute.

"The results are from individuals of diverse ethnic and sociodemographic backgrounds who had normal kidney function at the start. The diversity of the participants helps ensure the results are generalizable."

Chronic kidney disease is a major and growing public health challenge in both the U.S. and globally, affecting about 10–15% of the population worldwide. It also is a strong risk factor for cardiovascular disease. The study showed that TMAO levels were as strong or even stronger an indicator of chronic kidney disease risk than the well-known risk factors such as diabetes, hypertension, advancing age and race.

The study results reinforce the growing body of evidence indicating that lowering TMAO with prescribed drugs could be an effective treatment in patients at risk for, or with early signs of, kidney disease.

"Our study is a crucial complement to studies in preclinical models supporting TMAO as a novel biological risk factor for chronic kidney disease," said Dr. Wang, research assistant professor at the Friedman School.

"TMAO levels are highly modifiable by both lifestyle-like diet and pharmacologic interventions. Besides using novel drugs to lower TMAO in patients, using dietary interventions to lower TMAO in the general population could be a cost-efficient and low-risk preventive strategy for chronic kidney disease development."

Plans for future studies include examining genetic data to help assess the potential cause-and-effect relationship between TMAO and chronic kidney disease, as well as studying more definitively whether lifestyle changes may prevent chronic kidney disease development and

progression.

Dr. Hazen also directs Cleveland Clinic's Center for Microbiome and Human Health and holds the Jan Bleeksma Chair in Vascular Cell Biology and Atherosclerosis.

More information: The Gut Microbial Metabolite Trimethylamine N-oxide, Incident Chronic Kidney Disease, and Kidney Function Decline in Two Community-Based Cohorts, *Journal of the American Society of Nephrology* (2024). DOI: 10.1681/ASN.0000000000000344

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