TMAO

CPT Code 82542
Sample Type Serum

Order Code C524
Tube Type Tiger Top

metabolic

Elevated levels of TMAO may identify:

- Gut dysfunction
- Risk of adverse cardiac events
- Individuals who may benefit from intensive dietary intervention

Description

Gut microbes live symbiotically within the human digestive tract and play important roles in host defense, immunity, and nutrient processing and absorption. This diverse community is unique to each person and influenced by both acute and chronic dietary exposures to various food sources.

Nutrients such as phosphatidylcholine (also known as lecithin), choline, and L-carnitine are abundant in animal-derived products such as red meat, egg yolk and full-fat dairy products. When consumed, these nutrients are processed by gut bacteria resulting in the release of various metabolites including TMA (trimethylamine) into the blood. TMA is then transported to the liver where it is converted into TMAO (trimethylamine N-oxide). TMAO has been shown to regulate various physiological processes which are involved in the development of atherosclerosis[1,2] as well as reverse cholesterol synthesis[3] and platelet function[4].

Clinical Use

TMAO may be measured in individuals with one or more risk factors for the development of cardiovascular disease and/or individuals whom may benefit from intensive dietary intervention.

Clinical Significance

- There is a dose-response relationship between TMAO and atherosclerotic burden[1] and major adverse cardiovascular events incidence (MACE: MI, stroke or death)[5,6].
- In stable individuals undergoing elective cardiac evaluation, elevated TMAO levels are associated with increased risk of cardiovascular disease[1] and MACE[5].
  - Increased plasma L-Carnitine (a dietary precursor to TMAO) is associated with cardiovascular risk only when TMAO is simultaneously elevated via the metabolism by specific gut microbes[2].
  - In subsets of this population considered 'low risk' (<65 years old, <100mg/dL LDL-C, normal blood pressure, non-smokers, low levels of MPO), elevated TMAO remained a significant predictor of MACE risk[5].
- Elevated TMAO increases 7-year mortality risk in patients admitted to the ER who presented with acute coronary syndrome[6] as well as 5-year mortality risk in patients with CAD receiving optimal therapy[7] and PAD patients[8].

Testing Frequency

The frequency of testing is determined by an individual's medical history, but may be monitored more frequently in those at moderate to high risk for cardiovascular disease.

Sample Type

The TMAO test should be performed on a serum sample. Patients should fast overnight and refrain from consuming fish or other seafood the day before the blood draw to avoid false elevations in TMAO. If the patient is on antibiotics, they should finish their medication and wait one month before testing for TMAO.

Commercial Insurance or Medicare Coverage

Coverage guidelines, also known as NCD (National Coverage Determination) or LCD (Local Coverage Determination) have been established or posted by CMS (Medicare & Medicaid). Guidelines should be reviewed for coverage and limitation. Limited information has been provided by the majority of the larger carriers (Aetna, United Healthcare, Cigna, Blues).

Understanding Medical Necessity

The following ICD-10 codes for TMAO are listed as a convenience for the ordering practitioner. The ordering physician should report the diagnosis code that best describes the reason for performing the test.

Diagnosis	Diagnosis Code
Type 2 Diabetes Mellitus with Hyperglycemia	E11.65
Type 2 Diabetes Mellitus without Complications	E11.9
Other Specified Diabetes Mellitus without Complications	E13.9
Pure Hypercholesterolemia, Unspecified	E78.00
Familial Hypercholesterolemia	E78.01
Mixed Hyperlipidemia	E78.2
Other Hyperlipidemia	E78.4
Hyperlipidemia, Unspecified	E78.5
Metabolic Syndrome	E88.81
Essential (primary) Hypertension	I10
Atherosclerotic Heart Disease of Native Coronary Artery without Angina Pectoris	I25.10
Atherosclerotic Heart Disease of Native Coronary Artery with Unstable Angina Pectoris	I25.110
Impaired Fasting Glucose	R73.01
Impaired Glucose Tolerance Test (oral)	R73.02
Abnormal Finding of Blood Chemistry, Unspecified	R79.9

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RELATIVE RISK

TMAO
(μM)

<6.2 Low	6.2-9.9 Moderate	≥10.0 High

Treatment Considerations

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

✓ **Assess dietary habits**

- Consider implementing a Mediterranean or plant-based diet.
  - A more diverse diet rich in vegetables can improve the health of the gut microbiota.
  - Consider limiting the intake of foods rich in TMA precursors such as red meat, egg yolk, and full-fat dairy products.

NOTE: Certain types of seafood contain high levels of TMAO particularly saltwater fish, sharks, rays, mollusks, and crustaceans. Arctic deep sea fishes are known to be rich in TMAO while surface fishes (trout) contain much less TMAO. These food sources may falsely elevate TMAO levels.

✓ **Assess supplementation**

- Consider probiotic/prebiotic supplementation to promote gut bacterial biodiversity.
- Consider discontinuing the use of lecithin or L-carnitine containing supplements in individuals with elevated TMAO levels.

Implement global risk reduction strategies

✓ **Assess LDL-C levels.**

- If elevated, consider LDL-lowering therapies.

✓ **Assess BMI.**

- If overweight/obese, consider weight management strategies.

References

1. Wang Z et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature*. 2011; 472: 57–63.
2. Koeth RA et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*. 2013; 19: 576-585.
3. Warrier M et al. The TMAO-Generating Enzyme Flavin Monooxygenase 3 Is a Central Regulator of Cholesterol Balance. *Cell Reports*. 2015; 10:326-338.
4. Zhu et al. Gut Microbial Metabolite TMAO Enhances Platelet Hyperreactivity and Thrombosis Risk. *Cell*. 2016; 165:111-24.
5. Tang WH et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med*. 2013; 368:1575-1584.
6. Li SX et al. Gut microbiota-dependent trimethylamine N-oxide in acute coronary syndromes: a prognostic marker for incident cardiovascular events beyond traditional risk factors. *Eur Heart J*. 2017; 0:1-11.
7. Senthong V et al. Intestinal Microbiota-Generated Metabolite Trimethylamine-N-Oxide and 5-Year Mortality Risk in Stable Coronary Artery Disease: The Contributory Role of Intestinal Microbiota in a COURAAGE-Like Patient Cohort. *J Am Heart Assoc*. 2016;5:e002816.
8. Senthong V et al. Trimethylamine N-Oxide and Mortality Risk in Patients With Peripheral Artery Disease. *J Am Heart Assoc*. 2016;5;e004237.

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