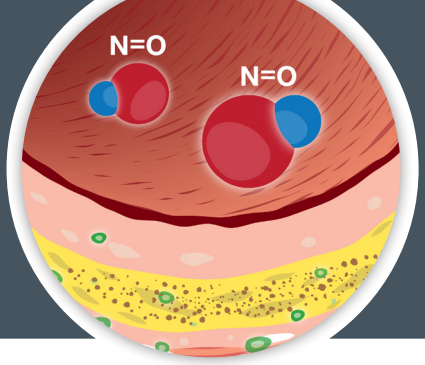
ADMA/SDMA

CPT Code 82542
Order Code C301

Sample Type Serum
Tube Type Tiger Top



inflammation

Elevated levels of ADMA may identify:

- Endothelial dysfunction
- Pre-diabetes/diabetes
- Subclinical cardiovascular disease

Elevated levels of SDMA may identify:

- Reduced renal function and progressive kidney failure

Description

One of the earliest manifestations of endothelial dysfunction is nitric oxide (NO) deficiency, which promotes atherosclerosis. Asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA), its structural isomer, are metabolites of L-arginine, an amino acid that is catalyzed to L-citrulline and NO by nitric oxide synthase (NOS).

Both ADMA and SDMA have distinct pathophysiologies and manifestations. ADMA is a competitive inhibitor of NOS thereby reducing NO production and promoting endothelial dysfunction. SDMA also interferes with NO production, but does so indirectly by reducing the cellular availability of arginine. ADMA is primarily cleared through enzymatic degradation in the bloodstream and identifies subclinical cardiovascular disease (CVD). Conversely, SDMA is primarily excreted in the urine and identifies reduced renal function.

Clinical Use

ADMA/SDMA may be measured in individuals with multiple risk factors for the development of CVD.

Clinical Significance

Cardiovascular Significance:

- Elevated ADMA levels are associated with the presence of hypertension[1], insulin resistance[1], and hyperlipidemia[2].
- Elevated ADMA levels are associated with subclinical atherosclerosis:
  - Elevated ADMA concentrations correlate with internal carotid artery bulb intimal media thickness[3], a hemodynamically unstable region vulnerable to nitric oxide deficiency[4] and plaque formation.
  - Elevated ADMA in young adults has been associated with increased coronary artery calcification[5].
- Individuals with established coronary artery disease and elevated ADMA levels have more than twice the risk for adverse events (myocardial infarction, stroke) than those with normal ADMA levels[6].

Renal Significance:

- Elevated SDMA levels positively correlate with reduced renal function as measured by estimated glomerular filtration rate[7].

Sample Type

The ADMA/SDMA test should be performed on a serum sample. Fasting is recommended, but not required.

Testing Frequency

ADMA/SDMA testing is determined by an individual's medical history, but may be performed semi-annually or annually as necessary. If the initial test result is abnormal, then follow-up testing may be performed within 3-6 months following treatment.

Commercial Insurance or Medicare Coverage

Coverage guidelines have not been established or posted by CMS (Medicare & Medicaid). We have reviewed the larger carriers (Aetna, United Healthcare, Cigna, Blues) and information is limited or has not been posted.

Understanding Medical Necessity

The following ICD-10 codes for ADMA/SDMA listed below, and in the Cleveland HeartLab Practitioner Guide, are provided as a convenience for the ordering physician. Additional diagnostic codes can be referenced on the CMS website or guidelines specified by insurance carriers. 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
Pure Hypercholesterolemia, Unspecified	E78.00
Familial Hypercholesterolemia	E78.01
Mixed Hyperlipidemia	E78.2
Hyperlipidemia, Unspecified	E78.5
Metabolic Syndrome	E88.81
Essential (primary) Hypertension	I10
Atherosclerotic Heart Disease of Native Coronary Artery without Angina Pectoris	I25.10
Abnormal Finding of Blood Chemistry, Unspecified	R79.9

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RELATIVE RISK

ADMA
(ng/mL)

<100 Low	100-123 Moderate	>123 High

REFERENCE RANGE

SDMA
(ng/mL)

73 - 135 Low	>135 High

TEST ADMA	TEST SDMA	Interpretation
Low	Low	• Normal endothelial function
Med / High	Low	• Endothelial dysfunction and possible presence of pre-diabetes/diabetes or CVD
Low	High	• Reduced renal function
Med / High	High	• Endothelial dysfunction and possible presence of pre-diabetes/diabetes or CVD • Reduced renal function

Treatment Considerations

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

✓**Assess LDL-C levels.**

- If not at goal, consider lipid-lowering therapies described in the National Cholesterol Education Program/Adult Treatment Panel III (NCEP ATP III) Guidelines[8].

✓**Assess blood pressure.**

- If not at goal, consider initiating, or titrating, antihypertensive therapy.

  NOTE: Elevated blood pressure contributes to endothelial dysfunction and the development of coronary artery disease and subsequent renal disease.

- Consider L-Arginine or L-Citrulline supplementation to improve vasodilation and vascular tone.

  NOTE: L-Arginine and L-Citrulline enhance the production of nitric oxide which has anti-inflammatory, antithrombotic, antihypertensive, and antioxidant effects.

✓**Assess risk for pre-diabetes/diabetes.**

- If abnormal fasting glucose or oral glucose tolerance test (OGTT), consider proliferator-activated receptor (PPAR) agonists, metformin or dipetidyl peptidase-4 (DPP-IV) inhibitors if not contraindicated.

✓**Assess the presence of coronary artery disease (CAD) with imaging techniques such as carotid intima-media thickness (CIMT) testing or coronary artery calcium (CAC) scoring.**

- Consider aspirin therapy if not contraindicated.
- Consider clopidogrel if history of CAD (i.e. myocardial infarction or revascularization) and/or cerebrovascular disease (i.e. transient ischemic attack or stroke).

References

1. Stühlinger MC et al. Relationship between insulin resistance and an endogenous nitric oxide synthase inhibitor. *JAMA.* 2002; 287: 1420-1426.
2. Böger RH et al. Asymmetric dimethylarginine (ADMA): A novel risk factor for endothelial dysfunction its role in hypercholesterolemia. *Circulation*. 1998; 98: 1842-1847.
3. Maas R et al. Association of the endogenous nitric oxide synthase inhibitor ADMA with carotid artery intimal media thickness in the Framingham Heart Study offspring cohort. *Stroke*. 2009; 40: 2715-2719.
4. Malek AM et al. Hemodynamic shear stress and its role in atherosclerosis. *JAMA*. 1999; 282: 2035-2042.
5. Iribarren C et al. Asymmetric dimethyl-arginine and coronary artery calcification in young adults entering middle age: the CARDIA Study. *Eur J Cardiovasc Prev Rehabil*. 2007; 14: 222-229.
6. Schnabel R et al. Asymmetric dimethylarginine and the risk of cardiovascular events and death in patients with coronary artery disease: Results from the AtheroGene study. *Circ Res*. 2005; 97: e53-e59.
7. Kielstein JT et al. Marked increase of asymmetric dimethylarginine in patients with incipient primary chronic renal disease. *J Am Soc Nephrol*. 2002; 13: 170-176.
8. Third report of the National Cholesterol Education Program (NCEP). Expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *National Institutes of Health*. September 2002. NIH Publication No. 02-5215.

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