MAYO CLINIC LABORATORIES

MI HEART CERAMIDES

Peer-Reviewed Papers Demonstrate the Benefit and Value of MI-HEART CERAMIDES

Coronary artery disease (CAD) is the most common type of heart disease in the U.S. and the main cause of heart attack. More than 26.6 million adults (11.3%) have been diagnosed with CAD. In 2010, there were 12.4 million physician visits with heart disease (excluding ischemic) as a primary diagnosis.

With so many confirmed/suspected CAD patients being seen at physician offices, it is difficult to know which among them are at the greatest risk and need intervention. Risk conferred by plasma ceramides is independent of LDL cholesterol, HDL cholesterol, C-reactive protein, LDL particles, HDL particles, and Lp-PLA2 (concentration and activity).

These typical markers may not be enough to measure the risk of future cardiac episodes:

- LDL-C: Up to 72% of people who have heart attacks have LDL-C levels below 130 mg/dL.
- LDL-P/ApoB: Good markers, but all measure the same pathway and only predict the likelihood of coronary artery atherosclerosis.
- Lp(a): Provides important information, but is genetically determined, and only 15% of people express pathological concentrations of Lp(a).
- Furthermore, 19.4% cardiovascular events occur in the absence of traditional risk factors.

A BETTER TOOL FOR PREDICTING CV RISK

Ceramides are complex lipids that play a central role in cell membrane integrity, cellular stress response, inflammatory signaling, and apoptosis. Plasma ceramides are predictors of adverse cardiovascular events resulting from unstable atherosclerotic plaque. Risk conferred by ceramides is independent of traditional biomarkers including age, sex, smoking status, and history of CAD.

Plasma ceramides predict adverse cardiovascular events:

- Within 1 year among patients with established coronary artery disease.
- Within 3 to 5 years for patients with suspected CAD and/or chronic heart failure.

The following peer-reviewed publications highlight the clinical value of ceramides.

Ceramide remodeling and risk of cardiovascular events and mortality

Publication/Authors:
J Am Heart Assoc. 2018 May 3.
Peterson LR, Xanthakis, V, Duncan MS, et. al.

Key Point:

- Plasma ceramide concentrations are predictive for incident coronary heart disease, heart failure, and cardiovascular mortality in the Framingham Heart Study. Addition of ceramides to a base model, including standard risk factors, significantly improved the C-statistic.

Plasma ceramides, Mediterranean diet, and incident cardiovascular disease in the PREDIMED trial (prevención con dieta Mediterránea)

Publication/Authors:
Circulation. 2017 May 23.
Wang DD, Toledo E, Hruby A, et. al.

Key Points:

- This study documented a novel positive association between baseline plasma ceramide concentrations and incidental CVD. In addition, a Mediterranean dietary intervention may mitigate potentially deleterious effects of elevated plasma ceramide concentrations on CVD.

Plasma ceramides predict cardiovascular death in patients with stable coronary artery disease and acute coronary syndromes beyond LDL cholesterol

Publication/Authors:
Eur Heart J. 2016 Jul 1.
Laaksonen R, Ekroos K, Sysi-Aho M, et al.

Key Point:

- Distinct plasma ceramide ratios are significant predictors of CV death in patients with stable CAD and ACS over and above currently used lipid markers. This may improve the identification of high-risk patients in need of more aggressive therapeutic interventions.

The following peer-reviewed publications highlight the clinical value of ceramides.

Circulating ceramides predict cardiovascular outcomes in the population-based FINRISK 2002 cohort

Publication/Authors:
Arterioscler Thromb Vasc Biol. 2016 Dec.
Havulinna AS, Sysi-Aho M, Hilvo M, et. al.

Key Points:

- Distinct serum ceramides are associated with the risk of incident MACE in suspected healthy individuals. These results should encourage more detailed analyses of ceramides in cardiovascular pathobiology and suggest new biomarkers of MACE risk.

Molecular lipids identify cardiovascular risk and are efficiently lowered by simvastatin and PCSK9 deficiency

Publication/Authors:
J Clin Endocrinol Metab. 2014 Jan.
Tarasov K, Ekroos K, Suoniemi M, et al.

Key Points:

- These data suggest that distinct ceramides associate significantly with CAD outcome independently of traditional risk factors. The mechanism of lowering lipids is important.

Additional ceramides peer-reviewed publication summary

2019

Hilvo M, Meikle PJ, Pedersen ER, et al. Development and validation of a ceramide- and phospholipid-based cardiovascular risk estimation score for coronary artery disease patients. *Eur Heart J.* 2019;1–10. doi:10.1093/eurheartj/ehz387

2018

Anroedh SS, Hilvo M, Akkerhuis KM, et al. Plasma concentrations of molecular lipid species predict long-term clinical outcome in coronary artery disease patients. *J Lipid Res.* 2018 Jun 1;113: pii: jlr.P081281. [Epub ahead of print]

Hilvo M, Salonurmi T, Havulinna AS, Kauhanen, et al. Ceramide stearic to palmitic acid ratio predicts incident diabetes. *Diabetologia.* 2018 Jun; 61(6):1424–1434.

Hilvo M, Simolin H, Metso J, et al. PCSK9 inhibition alters the lipidome of plasma and lipoprotein fractions. *Atherosclerosis*. 2018 Feb;269:159–165.

Mantovani A, Bonapace S, Lunardi G, et al. Association between plasma ceramides and inducible myocardial ischemia in patients with established or suspected coronary artery diease undergoing myocardial perfusion scintigraphy. *Metabolism.* 2018 May 16; pii: S0026-0495(18)301128-8.]

Peterson LR, Xanthakis V, Duncan MS, et al. Ceramide remodeling and risk of cardiovascular events and mortality. *J Am Heart Assoc.* 2018;7(10):1–11. doi:10.1161/JAHA.117.007931.

Summers SA. Could ceramides become the new cholesterol? *Cell Metab.* 2018;27(2);276–280. doi:10.1016;j.cmet.2017.12.003.

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Cui S, Li K, Ang L, et al. Plasma phospholipids and sphingolipids identify stent restenosis after percutaneous coronary intervention. *JACC Cariovasc Interv.* 2017 July;10(13):1307–1316.

Hammad SM, Baker NL, El Abaid JM, et al. Increased plasma levels of select deoxy-ceramide and ceramide species are associated with increased odds of diabetic neuropathy in type 1 diabetes: a pilot study. *Neuromolecular Med.* 2017 March; 19(1);46–56.

2016

Edsfeldt A, Duner P, Stahlman M, et al. Sphingolipids contribute to human atherosclerotic plaque inflammation. *Arterioscler Thromb Vasc Biol.* 2016 Jun;36(06):1132–40.

Fabbri E, Yang A, Simonsick EM, et al. Cirulating ceramides are inversely assoicated with cardiorespiratory fitness in participants aged 54–96 years from the Baltimore Longitudinal Study of Aging. *Aging Cell.* 2016 Oct;15(5):825–31.

Havulinna AS, Sysi-Aho M, Hilva M, et al. Circulating ceramides predict cardiovascular outcomes in the population-based FINRISK 2002 cohort. *Arterioscler Thromb Vasc Biol.* 2016;36:2424–2430. doi:10.1161/ATVBAHA.116.307497.

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Cheng JM, Suoniemi M, Kardys, et al. Plasma concentrations of molecular lipid species in relation to coronary plaque characteristics and cardiovascular outcome: results of the ATHEROREMO-IVUS study. *Atherosclerosis.* 2015 Dec;243(2):560–6.

Mielke MM, Bandaru VV, Han D, et al. Demographic and clinical variables affecting mid-to-late-life trajectories of plasma ceramide and dihydroceramide species. *Aging Cell.* 2015 Dec;14(6):1014–23.

Ng TW, Ooi EM, Watts GF, et al. Association of plasma ceramides and sphingomyelin wlth VLDL apoB-100 fractional catabolilc rate before and after rosuvastatin treatment. *J Clin Endocrinal Metab.* 2015 Jun;100(6):249–-501.

Warshauer JT, Lopez X, Gordillo R, et al. Effect of pioglitazone on plasma ceramides in adults with metabolic syndrome. *Diabetes Metab Res Rev.* 2015 Oct;31(7):734–44.

Yu J, Pan W, Shi R, et al. Ceramide is upregulated and associated with mortality in patients with chronic heart failure. *Can J Cardiol.* 2015 Mar;31(3):357–63.

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Freed JK, Beyer-AM, LoGiudice JA, Hockenberry JC, et al. Ceramide changes the mediator of flow-induced vasodilation from nitric oxide to hydrogen peroxide in the human microcirculation. *Circ Res.* 2014 Aug 15;115(5):525–32.

Moreno L, Moral-Sanz J, Morales-Cano D, et al. Ceramides mediates acute oxygen sending in vascular tissues. A*ntioxid Redox Signal.* 2014 Jan 1;20(1):1–14.

Ng TW, Ooi EM, Watts GF, et al. Dose-dependent effects of rosuvastatin on the plasma sphingolipidome and phospholipidome in the metabolic syndrome. *J Clin Endocrinol Metab.* 2014 Nov;99(11):E2335–40.

Pan W, Yu J, Shi R, et al. Evaluation of ceramide and activation of secretory acid sphingomyelinase in patients with acute coronary syndromes. *Coron Artery Dis*. 2014 May;25(3):230–5.

Weil BR, Canty JM Jr. Ceramide signaling in the coronary microcirculation: a double edged sword? *Circ Res*. 2014 Aug 15;115(5)(;475–7.

2013
Boon J, AJ Stark R, Brown RD, et al. Ceramides contained in LDL are elevated in type 2 diabetes and promote inflammation and skeletal muscle insulin resistance. *Diabetes*. 2013 Feb;62(2):401–10.

Heneghan HM, Huang H, Kashyap SR, et al. Reduced cardiovascular risk after bariatirc surgery is linked to plasma ceramides apolipoprotein-B100, and ApoB100/A1 ratio. *Surg Obes Relat Dis.* 2013 Jan-Feb;9(1):100–7.

Kirwan JP. Plasma ceramides target skeletal muscle in type 2 diabetes. *Diabetes.* 2013 Feb;62(2):352–4.

Lopez X, Goldfine AB, Holland WL, et al. Plasma ceramides are elevated in female children and adolescents with type 2 diabetes. *J Pediatr Endocrinol Metab.* 2013;26(9–10):995–8.

Symons JD, Abel ED. Lipotoxicity contributes to endothelial dysfunction: a focus on the contribution from ceramide. *Rev Endocr Metab Disord*. 2013 Mar;14(1):59–68.

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