HHS Public Access

Author manuscript

J Am Coll Cardiol. Author manuscript; available in PMC 2021 May 05.

Published in final edited form as:

J Am Coll Cardiol. 2020 May 05; 75(17): 2273–2275. doi:10.1016/j.jacc.2020.02.062.

Circulating Ceramide 16:0 in Heart Failure with Preserved Ejection Fraction

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Keywords

ceramide; HFpEF; sphingolipid

Ceramides are a class of bioactive sphingolipids increasingly recognized in metabolic disease, heart failure (HF), atherosclerosis, and cardiovascular death (1). Despite accumulating evidence linking ceramides to HF risk, little is known about circulating ceramides and clinical outcomes in HF.

We performed targeted sphingolipidomics to test whether circulating ceramides are associated with death or heart failure admission (DHFA) among participants with heart failure with preserved ejection fraction (HFpEF) in the TOPCAT trial. TOPCAT data and samples were obtained from the National Heart, Lung, and Blood Institute Biolincc repository. Serum concentrations of 76 sphingolipids were determined for all participants with available samples (n = 433) using liquid chromatography-tandem mass spectrometry at the Virginia Commonwealth University Lipidomics Core Facility (Richmond, VA). Analyses were conducted in a blinded manner.

Compared to participants without available samples, the prevalence of myocardial infarction (25.1% vs 31.9%), coronary artery bypass surgery (12.1% vs 18.2%), atrial fibrillation (34.3% vs 42%), and a history of smoking (40.2% vs 47.9%) was higher in the subset with available samples (all $P<0.05$). Subjects in this subset also had higher body mass index (30.8 kg/m^2 vs 32 kg/m^2) BNP levels (mean 397 pg/ml vs 508 pg/ml) and were more frequently from the Americas (49.4% vs 44.1%; all $P<0.05$). Amongst the 433 subjects, 103 reached the endpoint of DHFA. In univariate Cox models adjusted for multiple comparisons by a modified Bonferroni correction based on the principal components explaining >95% of the

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variability in measured species, increased concentrations of ceramides 16:0, 18:0 and 18:1 were associated with increased risk of DHFA (Figure 1A). When further adjusted for the MAGGIC risk score (the time of heart failure diagnosis was not available, and excluded from the score), increased concentrations of ceramides 16:0 and 18:0 were associated with the risk of DHFA (Figure 1B). Amongst these, ceramide 16:0 exhibited the most significant association (HR 1.35 95% CI 1.13–1.63, P=0.0011). Both ceramide 16:0 and 18:0 were also associated with all-cause death. When participants were stratified by tertiles of ceramide 16:0, we found no significant differences in clinical variables including age, gender, race, history of myocardial infarction, coronary revascularization, chronic obstructive pulmonary disease, hypertension, diabetes, atrial fibrillation, smoking, body mass index, use of insulin, aspirin, statins, beta blockers, renin-angiotensin-aldosterone system inhibitors, estimated glomerular filtration rate, hematocrit, or natriuretic peptide levels. We did not observe significant interactions between baseline ceramide 16:0 levels and randomization to spironolactone therapy (P = 0.60), statin therapy, or BMI for the outcome of DHFA.

Although increased ceramide 24:0 levels, the most abundant very long-chain ceramide species, were previously associated with reductions in all-cause mortality (3), we found no association between ceramide 24:0 and DHFA. Moreover, increased ceramide 16:0 was associated with DHFA in a model adjusted for ceramide 24:0 (Standardized HR = 1.35; 95%CI = 1.12–1.61; P = 0.0012).

In this study, we identify that increased circulating concentrations ceramide 16:0 and 18:0 are associated with DHFA in HFpEF, consistent with the growing body of literature that long-chain ceramides are associated with cardiovascular outcomes (3,4). In contradistinction to prior reports suggesting very-long chain ceramides are associated with reduced risk(2), we did not observe any associations between increased ceramide species and reduced DHFA risk. Our findings are consistent with the recent report by Lemaitre et al. who found that increased ceramide 16:0 is associated with incident HF (4).

Because palmitate is the most abundant fatty acid in the Western diet and we have measured predominantly palmitate-derived ceramides, our studies are consistent with the possibility that that long-chain ceramides are potential mediator of the link between poor diet and poor health outcomes. Our samples were not necessarily obtained in the fasting state, which could have confounded our results. Regardless of diet, carbon chain lengths of ceramide species are also dependent on particular ceramide synthases. Ceramide synthase 5 (CerS5), for example, is involved in the synthesis of ceramide 16:0 species. In murine models of high fat feeding, genetic ablation of CerS5 leads to decrease in ceramide 16:0 and 18:0 species in multiple tissues, decreased weight gain, and reduced white adipose tissue inflammation (5). In summary, ceramide 16:0 concentrations are associated with risk of incident heart failure, DHFA in HFpEF, and metabolic dysfunction and inflammation in animal models.

Acknowledgments:

We acknowledge the VCU Lipidomics/Metabolomics Core, the NIH-NCI Cancer Center Support Grant P30 CA016059 to the VCU Massey Cancer Center, as well as a shared resource grant (S10RR031535) from the National Institutes of Health.

Funding: This study was supported by NIH grants P30DK056341, R56HL-124073-01A1 (J.A.C), R01 HL 121510-01A1 (J.A.C), 5-R21-AG-043802-02 (J.A.C) and a VISN-4 research

grant from the department of Veterans Affairs (J.A.C). AJ is supported by K08HL138262-01.

Disclosures: Dr. Chirinos is supported by NIH grants R01-HL 121510-01A1, R61-HL-146390, R01-AG058969, 1R01-HL104106, P01-HL094307, R03-HL146874-01 and R56-HL136730. He has received consulting honoraria from Sanifit, Microsoft, Fukuda-Denshi, Bristol-Myers Squibb, OPKO Healthcare, Ironwood Pharmaceuticals, Pfizer, Akros Pharma, Merck, Edwards Lifesciences, Bayer and JNJ. He has received research grants from the NIH, Microsoft, Fukuda-Denshi and Bristol-Myers Squibb. He is named as inventor in an UPenn patent for the use of inorganic nitrates/nitrites for the treatment of HF and Preserved Ejection Fraction and a patent application for the use of novel neoepitope biomarkers of tissue fibrosis in heart failure. Dr. Javaheri is supported by K08HL138262-01 and a named co-inventor on the patent application for the use of fusion protein nanodiscs for the treatment of heart failure.

Other authors have no disclosures.

Abbreviations:

HF	heart failure
HFpEF	heart failure with preserved ejection fraction
BNP	B-type natriuretic peptide
DHFA	death or heart failure admission

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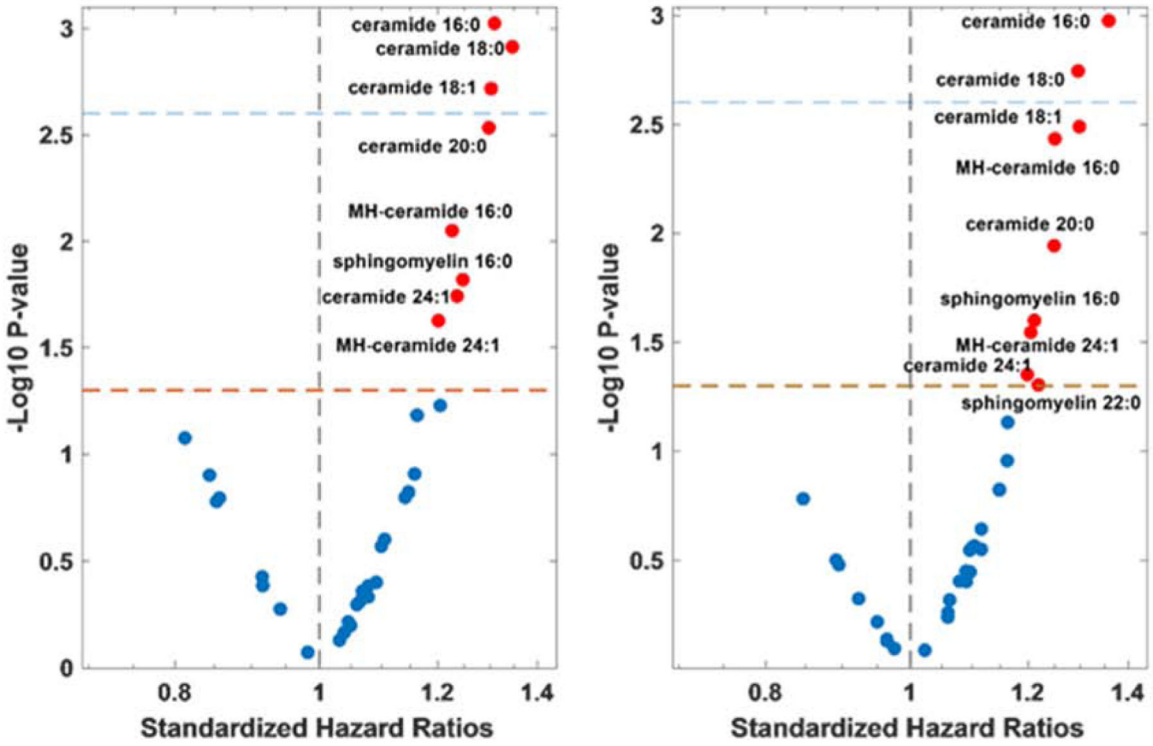

Figure 1. Associations between sphingolipids and outcomes in TOPCAT.

A) Univariate standardized hazard ratios and B) MAGGIC risk score adjusted standardized hazard ratios (x-axis) versus p-values (y-axis). The red-dotted lines indicate p = 0.05, while the blue-dotted lines indicate statistical significance after correction for multiple comparisons (p = 0.0025).

Abbreviations: MH-ceramide- monohexosylceramide