

Sphingolipid signatures at the extremes of energy balance: a comparative study of obesity and anorexia nervosa in women.

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Frontiers in Endocrinology 17: 1890712, 2026.

Background: anorexia nervosa (AN) and obesity (OB) represent opposite extremes of energy balance and are both associated with profound metabolic alterations. Increasing evidence suggests that sphingolipids play a central role in cardiometabolic regulation, inflammation, and insulin signaling; however, clinical sphingolipidomic studies have largely investigated AN and OB separately. Direct comparative studies using a harmonized analytical framework are currently lacking.

Objectives: the primary objective of this study was to determine whether women with AN or OB exhibit distinct plasma sphingolipidomic signatures compared with a normal-weight healthy (NWH) group and with each other. Secondary objectives included identifying multivariate sphingolipid patterns associated with nutritional phenotype and evaluating associations between plasma sphingolipids and cardiometabolic parameters.

Methods: in this cross-sectional study, 114 women were enrolled (28 with AN, 37 with OB, and 49 NWH controls). Plasma sphingolipidomics was assessed using targeted liquid chromatography–tandem mass spectrometry (LC–MS/MS). Clinical, anthropometric, biochemical, inflammatory, and hemodynamic variables were collected in all participants. Group comparisons were performed using non-parametric statistics with Benjamini–Hochberg false discovery rate (FDR) correction. Multivariate analyses included principal component analysis (PCA), hierarchical clustering analysis (HCA), partial least squares discriminant analysis (PLS-DA), and variable importance in projection (VIP) analysis. Age-adjusted regression analyses were performed to investigate associations between sphingolipid variables and cardiometabolic predictors.

Results: clinical and metabolic variables differed among the AN, NWH, and OB groups. After FDR correction, 38 of 45 sphingolipid variables differed significantly among groups, involving ceramides, dihydroceramides, sphingomyelins, glycosphingolipids, sphingoid-base-related metabolites, and ceramide ratio indices. AN was characterized by increased levels of several sphingomyelins, lactosylceramides, GM3 species, S1P, and DhS1P. In contrast, OB showed enrichment of selected dihydroceramides and ceramide ratio indices together with lower levels of several very-long-chain glycosphingolipids. The direct OB-versus-AN comparison yielded the largest number of FDR-significant variables among the three pairwise comparisons. PCA, hierarchical clustering, and PLS-DA consistently demonstrated structured multivariate separation among groups. The supervised PLS-DA model achieved an overall accuracy of 0.851 and identified DHCer 24:1, DHCer 18, HexCer 22, Cer 24:1, SM 24:1, and DHCer 18:1 among the variables with the highest VIP scores. Age-adjusted analyses revealed significant associations between sphingolipid variables and BMI, HOMA-IR, blood pressure, CRP, triglycerides, and HDL-cholesterol.

Conclusions: women with AN and OB exhibit distinct but partially overlapping plasma sphingolipidomic signatures, characterized by coordinated remodeling across multiple sphingolipid pathways. AN was predominantly associated with sphingomyelin- and glycosphingolipid-enriched patterns, whereas OB was

characterized by dihydroceramide- and ceramide-ratio-associated remodeling. These findings support the concept that severe undernutrition and obesity represent biologically distinct states of sphingolipid dysregulation and suggest that plasma sphingolipid signatures may serve as candidate biomarkers of metabolic remodeling and cardiometabolic risk across the extremes of energy balance.

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