Sphingolipidomic profiling of peripheral blood mononuclear cells reveals a distinct immunometabolic signature across patients with essential obesity and metabolic syndrome compared to normal-weight healthy subjects.

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Background: While sphingolipid alterations in obesity and metabolic syndrome (MS) have been extensively studied in plasma, their intracellular regulation within immune cells remains poorly characterized. Here, we introduce a PBMC-based sphingolipidomic approach that provides a novel immunometabolic perspective beyond traditional analyses of circulating lipids.

Methods: Targeted sphingolipidomics was performed in peripheral blood mononuclear cells (PBMCs) from normal-weight healthy (NWH) subjects, and patients with essential obesity (EO) or MS. Multivariate integration (principal component analysis [PCA], hierarchical clustering, and partial least squares discriminant analysis [PLS-DA]) was combined with selected univariate models to explore lipid patterns and associations with cardiometabolic variables.

Results: PBMC profiling identified a selective intracellular sphingolipid signature, with 10 species significantly altered across groups (FDR < 0.05), including ceramides, dihydroceramides, glycosphingolipids, and ceramide ratio indices. PCA showed that the first two components explained ~72% of total variance, with PC2 driving group separation. EO and MS displayed partial overlap, consistent with a shared metabolic phenotype, while both differed from NWH. Multivariate models highlighted ceramide ratios (e.g., CER16/24, and CER18/24) as key discriminators. Associations with cardiometabolic variables were limited and modest (adjusted R2 ≈ 0.06-0.09), indicating that lipid alterations reflect integrated metabolic dysregulation rather than single clinical drivers.

Conclusions: PBMC-based sphingolipidomics reveals a distinct intracellular immunometabolic remodeling in EO and MS, capturing aspects not detectable in plasma. These findings support the relevance of immune cell lipid profiling as a potential source of integrative biomarkers and provide insight into immune-metabolic crosstalk underlying metabolic disease.