Identification of a specific plasma sphingolipid profile in a group of normal-weight and obese subjects: a novel approach for a "biochemical" diagnosis of metabolic syndrome?

A. E. Rigamonti, M. Dei Cas, D. Caroli, A. De Col, S. G. Cella, R. Paroni, A. Sartorio

International Journal of Molecular Sciences 24: 7451, 2023.

Metabolic syndrome is nosographically defined by using clinical diagnostic criteria such as those of the International Diabetes Federation (IDF) ones, including visceral adiposity, blood hypertension, insulin resistance and dyslipidemia. Due to the pathophysiological implications of the cardiometabolic risk of the obese subject, sphingolipids, measured in the plasma, might be used to biochemically support the diagnosis of metabolic syndrome. A total of 84 participants, including normal-weight (NW) and obese subjects without (OB-SIMET-) and with (OB-SIMET+) metabolic syndrome, were included in the study, and sphingolipidomics, including ceramides (Cer), dihydroceramides (DHCer), hexosyl-ceramides (HexCer), lactosyl-ceramides (LacCer), sphingomyelins (SM) and GM3 ganglosides families, and sphingosine-1-phosphate (S1P) and its congeners, was performed in plasma. Only total DHCers and S1P were significantly higher in OB-SIMET+ than NW subjects ($p < 0.05$), while total Cers decreased in both obese groups, though statistical significance was reached only in OB-SIMET- (vs. NW) subjects ($p < 0.05$). When considering the comparisons of the single sphingolipid species in the obese groups (OB-SIMET- or OB-SIMET+) vs. NW subjects, Cer 24:0 was significantly decreased ($p < 0.05$), while Cer 24:1, DHCer 16:0, 18:0, 18:1 and 24:1, and SM 18:0, 18:1 and 24:1 were significantly increased ($p < 0.05$). Furthermore, taking into account the same groups for comparison, HexCer 22:0 and 24:0, and GM3 22:0 and 24:0 were significantly decreased ($p < 0.05$), while HexCer 24:1 and S1P were significantly increased ($p < 0.05$). After having analyzed all data via a PLS-DA-based approach, the subsequent determination of the VIP scores evidenced the existence of a specific cluster of 15 sphingolipids endowed with a high discriminating performance (i.e., VIP score > 1.0) among the three groups, including DHCer 18:0, DHCer 24:1, Cer 18:0, HexCer 22:0, GM3 24:0, Cer C24:1, SM 18:1, SM 18:0, DHCer 18:1, HexCer 24:0, SM 24:1, S1P, SM 16:0, HexCer 24:1 and LacCer 22:0. After having run a series of multiple linear regressions, modeled by inserting each sphingolipid having a VIP score > 1.0 as a dependent variable, and waist circumference (WC), systolic/diastolic blood pressures (SBP/DBP), homeostasis model assessment-estimated insulin resistance (HOMA-IR), high-density lipoprotein (HDL), triglycerides (TG) (surrogates of IDF criteria) and C-reactive protein (CRP) (a marker of inflammation) as independent variables, WC was significantly associated with DHCer 18:0, DHCer 24:1, Cer 18:0, HexCer 22:0, Cer 24:1, SM 18:1, and LacCer 22:0 ($p < 0.05$); SBP with Cer 18:0, Cer 24:1, and SM 18:0 ($p < 0.05$); HOMA-IR with DHCer 18:0, DHCer 24:1, Cer 18:0, Cer 24:1, SM 18:1, and SM 18:0 ($p < 0.05$); HDL with HexCer 22:0, and HexCer 24:0 ($p < 0.05$); TG with DHCer 18:1, DHCer 24:1, SM 18:1, and SM 16:0 ($p < 0.05$); CRP with DHCer 18:1, and SP1 ($p < 0.05$). In conclusion, a cluster of 15 sphingolipid species is able to discriminate, with high performance, NW, OB-SIMET- and OB-SIMET+ groups. Although (surrogates of) the IDF diagnostic criteria seem to predict only partially, but congruently, the observed sphingolipid signature, sphingolipidomics might represent a promising "biochemical" support for the clinical diagnosis of metabolic syndrome.