

Plasma Sphingomyelins Are Correlated with Plasma Ceramides, and Relate to Severity of Insulin Resistance in Overconditioned Transition Dairy Cows.

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Sphingomyelins (SM) and ceramides (Cer) are types of sphingolipids that are receiving increasing attention because of their involvement with the progression of insulin resistance in overweight rodents and humans. In these monogastrics, increased availability of saturated fatty acids increases de novo synthesis of Cer, monohexylceramides (MonoHexCer), and dihexylceramides (DiHexCer). Additionally, SM hydrolysis produces Cer, an effect mediated by proinflammatory action. Sphingomyelins and Cer are considered as potential biomarkers for pre-onset insulin resistance in humans. The relationship between sphingolipids and insulin sensitivity in ruminants remains to be delineated; therefore, our objective was to profile plasma SM using a targeted metabolomics LC/MS approach, and to identify metabolic phenotypes associated with changes in insulin sensitivity. Our data set included multiparous Holstein cows grouped according to BCS at d-30 prepartum: lean (BCS <3.0; n=10; LEAN) or overconditioned (BCS >4.0, n=11; OVER), with blood samples collected at d-45, -30, -15 and -7, relative to expected calving, and at d4 postpartum. Data were analyzed using a mixed model with repeated measures that included the random effect of cow and the fixed effects of BCS and time. Non-parametric spearman's correlations were analyzed. Relative to LEAN, OVER had reduced insulin sensitivity and greater NEFA mobilization at d-30, -15 and -7 prepartum ($P < 0.05$). LC/MS analysis detected 11 SM with acyl chains ranging from 16 to 24 carbons. Total SM decreased during transition ($P < 0.001$), and an interaction between BCS and time was observed for total dihydrosphingomyelins (DHSM; $P < 0.05$). The predominant SM were C16:0-SM and C20:0-DHSM, accounting for 65 and 83% of total SM and DHSM, respectively. Of interest, C16:0-SM and C20:0-DHSM concentrations were elevated in OVER relative to LEAN at d-7, and at d-7 and -15, respectively ($P < 0.05$). Multiple SM were positively associated with NEFA, and negatively associated with insulin sensitivity (e.g. C16:0-SM, C24:1-SM, C16:0-DHSM, C20:0-DHSM; $P < 0.05$). In contrast, C18:1-, and C20:1-SM ($P < 0.05$) were negatively associated with NEFA and positively associated with insulin sensitivity. Total DHSM were positively correlated with total SM as well as total Cer ($P < 0.001$). Specifically, C16:0-DHSM and C20:0-DHSM were positively associated with C16:0-SM and C20:0-SM, respectively ($P < 0.001$). Furthermore, multiple DHSM were correlated with MonoHexCer or DiHexCer (e.g. C18:0-DHSM were negatively correlated with C18:0-MonoHexCer; $P < 0.05$). Our data demonstrate remodeling of the dairy cow sphingolipidome during the transition from gestation to lactation; however, the functional role of sphingolipids mediating insulin action remains to be determined.