Metabolic mechanisms behind the type 2 diabetes susceptible phenotype in low birth weight individuals - DTU Orbit (01/01/2019)

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Background and aims: Low birth weight (LBW) individuals have an increased risk of developing insulin resistance and type 2 diabetes compared with normal birth weight (NBW) individuals. Accordingly, young, healthy, LBW men of the study population examined in the present plasma metabolome studies show impaired hepatic insulin sensitivity and, in contrast to NBW men, develop impaired peripheral insulin sensitivity in response to a 5-day high-fat overfeeding. However, the metabolic mechanisms behind the type 2 diabetes susceptible phenotype in LBW individuals are not clear. Our primary aim of the present studies was to get novel insights into such mechanisms. LBW men of the present study population have lower pre-adipocyte mRNA expression levels of several differentiation markers, which may potentially lead to an impaired fatty acid storage capacity of these cells and a resulting increased fatty acid load to non-adipose tissue. Also, the LBW men display an increased fatty acid oxidation and a decreased glucose oxidation during both the isocaloric control diet and 5-day high-fat, high-calorie (HFHC) diet. Our specific aims of the present studies were to test the hypotheses that LBW men could have 1) an increased, incomplete fatty acid beta-oxidation in mitochondria, 2) an altered amino acid metabolism to ensure an adequate supply of tricarboxylic acid (TCA) cycle intermediates and thereby enable an efficient acetyl-CoA oxidation, and 3) an increased fatty acid flux into lipogenesis, including de novo ceramide synthesis, in non-adipose tissue.

Methods: Fasting plasma levels of 45 acylcarnitines, 15 amino acids, and 27 ceramides were measured in the young, healthy, LBW (≤ 10th percentile) and NBW (50-90th percentile) men of the above mentioned study population after the isocaloric control diet and 5-day HFHC (60 E % from fat, 50 % extra calories) diet intervention.

Results and interpretations: LBW men had higher plasma C2 and C4-OH acylcarnitine levels after the control diet, compared with NBW men, indicating an increased, incomplete fatty acid beta-oxidation in mitochondria with the limiting step at the acetyl-CoA oxidation via the TCA cycle and an increased ketogenesis, respectively. Furthermore, LBW men had higher plasma C6-DC, C10-OH/C8-DC, and total hydroxyl-/dicarboxyl-acylcarnitine levels after the control diet, compared with NBW men, suggesting an increased fatty acid omega-oxidation in the endoplasmic reticulum of mainly the liver. Interestingly, the total hydroxy-/dicarboxyl-acylcarnitine level was negatively associated with the fasting serum insulin level and hepatic insulin resistance after this diet. An increased omega-oxidation rate may therefore limit the amount of fatty acid substrates available for lipogenesis, including the synthesis of lipotoxic lipids such as ceramides and diacylglycerols that impair insulin signalling. In the second study, we demonstrated that LBW men had higher plasma alanine, proline, methionine, citrulline, and total amino acid levels after the HFHC diet compared with NBW men. The alanine level was negatively associated with the plasma C2 acylcarnitine level after this diet. A higher alanine level in the LBW men after the HFHC diet could therefore be accompanied by an increased anaplerotic formation of oxaloacetate to enable an efficient acetyl-CoA oxidation via the TCA cycle. Furthermore, the alanine and total amino acid levels tended to be negatively associated with the insulin-stimulated glucose uptake rate after the HFHC diet. Higher alanine and total amino acid levels in the LBW men after this diet could therefore be a consequence of their reduction in skeletal muscle insulin sensitivity due to high-fat overfeeding with a following increased skeletal muscle proteolysis and/or may potentially contribute to the impaired insulin sensitivity. Moreover, the alanine level was positively associated with the hepatic glucose production after the HFHC diet. A higher alanine level in the LBW men could therefore also be accompanied by an increased gluconeogenesis in the liver. In the third study, we found that LBW men did not show altered plasma ceramide levels after the control or HFHC diet compared with NBW men. An increased fatty acid oxidation rate in the LBW men during both diets may limit the amount of fatty acids available for de novo ceramide synthesis and thereby compensate for a likely increased fatty acid load to non-adipose tissue in these individuals.

Conclusions: LBW men showed alterations in fasting plasma acylcarnitine and amino acid levels after the isocaloric control diet and 5-day HFHC diet, respectively, that have been described to be associated with insulin resistance and type 2 diabetes. Additional plasma and tissue metabolome studies in LBW and NBW individuals, as well as supplementary functional studies, are needed to further explain the metabolic events leading to the altered plasma metabolite profiles in LBW men, and moreover to determine the extent to which these events may be part of the type 2 diabetes susceptible phenotype in LBW individuals.