Metabolite ratios as potential biomarkers for type 2 diabetes: a DIRECT study - DTU Orbit

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**Metabolite ratios as potential biomarkers for type 2 diabetes: a DIRECT study**

**Aims/hypothesis:** Circulating metabolites have been shown to reflect metabolic changes during the development of type 2 diabetes. In this study we examined the association of metabolite levels and pairwise metabolite ratios with insulin responses after glucose, glucagon-like peptide-1 (GLP-1) and arginine stimulation. We then investigated if the identified metabolite ratios were associated with measures of OGTT-derived beta cell function and with prevalent and incident type 2 diabetes.

**Methods:** We measured the levels of 188 metabolites in plasma samples from 130 healthy members of twin families (from the Netherlands Twin Register) at five time points during a modified 3 h hyperglycaemic clamp with glucose, GLP-1 and arginine stimulation. We validated our results in cohorts with OGTT data (n = 340) and epidemiological case-control studies of prevalent (n = 4925) and incident (n = 4277) diabetes. The data were analysed using regression models with adjustment for potential confounders. Results: There were dynamic changes in metabolite levels in response to the different secretagogues. Furthermore, several fasting pairwise metabolite ratios were associated with one or multiple clamp-derived measures of insulin secretion (all $p < 9.2 \times 10^{-7}$). These associations were significantly stronger compared with the individual metabolite components. One of the ratios, valine to phosphatidylcholine acyl-alkyl C32:2 (PC ae C32:2), in addition showed a directionally consistent positive association with OGTT-derived measures of insulin secretion and resistance ($p = 5.4 \times 10^{-3}$ and prevalent type 2 diabetes (ORVal_PC ae C32:2 2.64 [I$^p$ 0.97 $\pm$ 0.09], $p = 0.58$ $\pm$ 0.01). Valine-PC ae C32:2 predicted incident diabetes independent of established risk factors in two epidemiological cohort studies (HRVal_PC ae C32:2 1.57 [I$^p$ 0.45 $\pm$ 0.06], $p = 1.3 \times 10^{-15}$), leading to modest improvements in the receiver operating characteristics when added to a model containing a set of established risk factors in both cohorts (increases from 0.780 to 0.801 and from 0.862 to 0.865 respectively, when added to the model containing traditional risk factors + glucose). Conclusions/interpretation: In this study we have shown that the Valae C32:2 metabolite ratio is associated with an increased risk of type 2 diabetes and measures of insulin secretion and resistance. The observed effects were stronger than that of the individual metabolites and independent of known risk factors.

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