**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 × 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 × 10^{-3}) and prevalent type 2 diabetes (ORVal_PC ae C32:2 2.64 [95% CI 0.97-7.09], p = 1.0 × 10^{-27}). Furthermore, Val_PC ae C32:2 predicted incident diabetes independent of established risk factors in two epidemiological cohort studies (HRVal_PC ae C32:2 1.57 [95% CI 0.45-5.67]; p = 1.3 × 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 Val_PC ae 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.

**General information**

State: Published

Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, Disease Intelligence and Molecular Evolution, Helmholtz Zentrum München, VU University Medical Centre, Vrije Universiteit Amsterdam, German Institute of Human Nutrition, Leiden University Medical Center, German Center for Diabetes Research, MAX DELBRÜCK CENTER FOR MOLECULAR MEDICINE, University of Oxford, University of Dundee, University of Copenhagen


Pages: 117-129

Publication date: 2018

Peer-reviewed: Yes

**Publication information**

Journal: Diabetologia

Volume: 61

ISSN (Print): 0012-186X

Ratings:

BFI (2019): BFI-level 1

Web of Science (2019): Indexed yes

BFI (2018): BFI-level 1

Web of Science (2018): Indexed yes

BFI (2017): BFI-level 1

Scopus rating (2017): CiteScore 5.09 SJR 3.228 SNIP 1.619

Web of Science (2017): Impact factor 6.023

Web of Science (2017): Indexed yes

BFI (2016): BFI-level 1

Scopus rating (2016): CiteScore 5.23 SJR 3.25 SNIP 1.721

Web of Science (2016): Impact factor 6.08

BFI (2015): BFI-level 1

Scopus rating (2015): CiteScore 5.57 SJR 3.61 SNIP 1.933


Web of Science (2015): Indexed yes