Faecal metabolomics reveals relevant metabolic perturbations in type 2 diabetes,

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1. Introduction

Type 2 diabetes is associated with several long-term complications including kidney disease, macrovascular disorders, retinopathy, and neuropathy. Unfortunately, current treatments hold some essential shortcomings, which concurs with the fact that this disease is still not curable nor a steady-state can be achieved. More specifically, pharmaceuticals are assigned limited effectivity and adverse side-effects, personalized guidelines for lifestyle interventions are not available, and adequate knowledge on the role of gut microbiota to justify faecal transplants is lacking. In addition, current diagnostic tests have limited sensitivity and specificity, and no opportunities for large-scale screening. Consequently, about a third of all people with diabetes are not aware of their illness. A better understanding of the underlying mechanisms of type 2 diabetes is thus highly desired to make progress in disease diagnosis and management.

2. Approach

In this study, a strategy of faecal metabolomics was implemented to assess the pathology of type 2 diabetes. To this end, faecal samples were collected from individuals with normal glycaemia (n = 24) and type 2 diabetes (n = 24) (UZ Ghent EC 2016/0673, classification using a HbA_1c threshold of 6%). Faeces was specifically targeted as this specimen can be obtained non-invasively and is able to capture the interactions between the host, gut microbiota, diet, and other exposomal factors. To measure the polar and lipid fraction of the metabolome, two analytical methodologies[1,2] using UHPLC-Q-Exactive™ MS, were implemented.

3. Results

Based on the faecal fingerprints, enclosing 6620 polar and 19831 lipophilic components, PCA-X models and associated score plots were generated, thereby revealing clustering according to health state (Fig. 1). Following this, OPLS-DA modelling was able to differentiate between the study populations in a supervised fashion. Validity of the models was confirmed by p-values ≤ $1.86\ e^{-9}$ and $Q^2Y \geq 0.654$. Discriminating metabolites were selected based on the Jackknifed confidence interval (not across zero), VIP-score (> 1), and S-plot correlation and covariance (|p(corr)| > 0.5 and |p| > 0.02). This rendered 103 lipophilic and 70 polar components, which were presumed to be metabolically involved in type 2 diabetes and further assessed in terms of identity and biological relevance. Tentative identification revealed some interesting chemical classes, for which a role in type 2 diabetes has previously been described based on plasma metabolomics. On the other hand, it was also noted that the use of medication (i.e. metformin) by the patients had a significant impact on the biomarker signature. Indeed, metformin itself as well as metformin fragments, metformin derivatives, and metformin conjugates appeared as marker molecules.

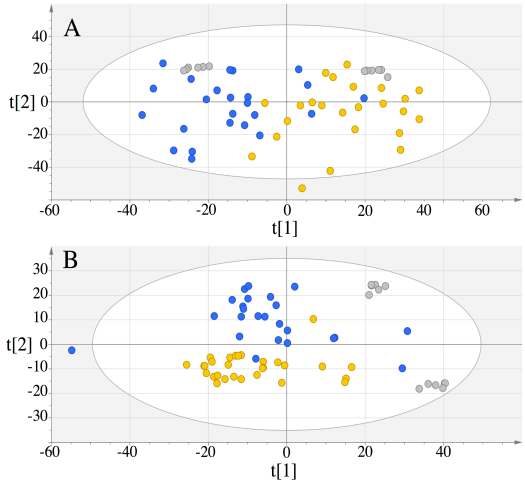

Fig. 1. PCA-X score plots to evaluate clustering of samples for type 2 diabetes (blue), healthy (yellow), and quality control (grey, representing healthy or type 2 diabetes), based on the non-polar (A) and polar (B) metabolic fingerprints.

4. Discussion

Faecal metabolomics was able to reveal a number of interesting metabolic shifts regarding type 2 diabetes, which may lead to better and personalized disease management in terms of prediction, diagnosis, treatment, and follow-up. However, this study also highlighted the substantial impact of medical interventions on the faecal fingerprints, as markers may directly relate to the medical treatment or may indirectly be affected by the medication used. As such, validating the results by including prediabetes patients is designated.

References

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