SUMMARY FOR PUBLICATION

1. SUMMARY OF THE CONTEXT AND OVERALL OBJECTIVES OF THE ACTION

Diabetes is subdivided into two main forms, Type 1 Diabetes (T1D) and Type 2 Diabetes mellitus (T2D). Of them, T1D is more uniform and accounts for about 10% of all patients, whereas T2D, which accounts for about 80-90% of all patients, is much more heterogeneous, but the extent of this diversity is not known. RHAPSODY will explore whether diverse sub-forms of T2D are characterized by different rates of progression from pre-diabetes to T2D and by differences in disease progression, e.g. development of complications. Establishing a better patient stratification already at diagnosis of diabetes will support the design of novel strategies for precision therapy and prevention of diabetes and of more efficient clinical trials.

2. WORK PERFORMED DURING YEAR 2 AND MAIN RESULTS ACHIEVED SO FAR

Biomarker candidate selection

We have established a list of candidate biomarkers to track evolution from pre-diabetes to T2D and deterioration of T2D and time to insulin requirement. To assess the validity of these candidate biomarkers they are being measured in selected patient populations using our peptidomic, lipidomic and polar metabolites analytic platforms.

Data federation and systems biology

We have progressed in the establishment and functional validation of a secure central database, which all partners can access from their own locations for a global analysis of the data collected from the pre-diabetes and diabetes cohorts. We have completed the full harmonisation of data annotation from 10 cohorts from 5 different European countries, representing more than 30'000 individuals. Each cohort database, located in their original location, can be accessed in a secure manner by authorized partners for analysis of diabetes progression at a global European level, a task impossible to be performed until now.

Predictive biomarkers of glycaemic deterioration

Three separate analyses are being performed to identify biomarkers of i) progression from prediabetes to type 2 diabetes, ii) the rate of type 2 diabetes deterioration, and iii) diabetes relapse after gastric bypass surgery. The most significant progress has been on modelling of T2D progression, where a much acclaimed new stratification of T2D patients into five clusters to which RHAPSODY has contributed, has been achieved using one initial cohort. Following measurement of a missing biomarker (C-peptide) in two additional patient populations (in ~10'000 plasma samples), presence of the five initially identified clusters could be replicated, using the RHAPSODY federated database and analysis platform.

Multi-omics biomarker discovery and assay development

- We strive to coordinate the collection of plasma samples for biomarker identification by omics technologies and to develop imaging techniques to assess the impact of said biomarkers on beta-cells and insulin target tissues. The major achievements of Year 2 are as follows:
- Comprehensive lipidomic analysis of blood plasma samples on a total of 2775 samples from three different cohorts of diabetic patients.
- Polar metabolomics analysis on 2800 plasma samples from two diabetes cohorts ongoing. Plasma samples from 225 patients whose islets obtained for RNASeq analysis.
- Screening of miRNAs has been performed on RNA extracted from 500 blood samples from a diabetes cohort.
- Peptidomic analysis of1200 samples from two diabetes cohorts.
- A robust imaging and analytic platform established to explore the effects of circulating metabolites on islet Ca2+ dynamics, in vitro, and in situ in the mouse eye. Characterization of islets from Elovl2 KO mice (WP6) done using Ca2+ imaging.

Predictive biomarkers of beta cell dysfunction

Data from human islets and related blood samples have been collected and integrated to identify candidate biomarkers of beta cell dysfunction and death in relationship to diabetes pathogenesis. The major achievements have been to increase the collection of pancreatic specimens and islets isolated from metabolically phenotyped pancreatectomized patients and organ donors at various stages of pre- and T2D. In addition, human islet gene expression data previously obtained by three independent centres in Tübingen, Lund and Pisa have been merged to identify genes that are similarly regulated by diabetes in all datasets. The role of some of these genes is being tested in the only available human beta-cell lines (EndoC-ßH1) generated by the IMI1 consortium IMIDIA.

Predictive biomarkers of insulin target tissue dysfunction

We strive to identify circulating biomarkers, which are correlated with progression from pre-diabetes to T2D or rapid deterioration of T2D. We aim at identifying the tissues (liver, fat, muscle) and metabolic pathways, which produce these biomarkers as these pathways may become new therapeutic targets. In Year 2 we have replicated the analysis of plasma dihydroceramides, a previously identified biomarker candidate, in the cohort of gastric bypass surgery before and after diabetes relapse. Twenty-three genes involved in the biosynthesis and degradation of this biomarker were identified. Several of these genes were found associated with T2D; one was found associated with a defect in insulin secretion. The precise role of the latter gene is investigated in genetically modified mice and the EndoC-ßH1 cells. Additional search for biomarkers of pre-diabetes progression have been performed in preclinical studies. We have identified specific groups of lipids in the plasma that correlate strongly with a liver metabolic pathway, which itself correlates with fasting plasma glycemia. We are exploring whether modifying this metabolic pathway can control fasting glycemia.

RHAPSODY – Assessing risk and progression of pre-diabetes and type 2 diabetes to enable disease modification.

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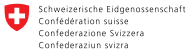

Regulatory consensus for diabetes disease modification

RHAPSODY engages in a dialogue with the European Medicines Agency (EMA) to develop various operational definitions related to the use of biomarkers and to review existing regulatory guidelines for the use of such biomarkers. During Year 2, these different aspects have been discussed and a framework for biomarker qualification is underway. Empirical testing of causal relationships between prediabetes and cardiovascular risks has been initiated.

Modelling economic and public health impact of disease modification

We aim to develop and validate economic models to quantify health outcomes and costs of pre-diabetes and T2D populations that are adaptable across EU jurisdictions and to evaluate the economic usefulness of biomarkers identified by RHAPSODY. During Year 2, to inform on the need to develop an economic model of pre-diabetes populations a systematic review of existing pre-diabetes models was performed. In addition, the PIs of pre-diabetes cohorts have been approached to gain access to the patient level data required to build the pre-diabetes model.

3. PROGRESS BEYOND THE STATE OF THE ART, EXPECTED RESULTS UNTIL THE END OF THE PROJECT AND POTENTIAL IMPACTS (INCLUDING THE SOCIO-ECONOMIC IMPACT AND THE WIDER SOCIETAL IMPLICATIONS OF THE PROJECT SO FAR)

RHAPSODY's ambition to fully characterize novel biomarkers for pre-diabetes and T2D development and deterioration and to validate them for clinical use and pharmacological developments is based on going beyond the current state-of-the-art in scientific knowledge, omics technologies, and data sharing and processing. Biomarker identification, characterization and development for use in clinical and pharmacological applications will be guided by the requirement for their validation by the European Medical Agency and for coherence with cost-benefits assessment. This will ensure that the discovery process of RHAPSODY will minimize the time between biomarker identification and their clinical and commercial use.