RHAPSODY Final Symposium

"Biomarkers for precision therapy and prevention of type 2 diabetes"

EVENT SUMMARY *by* ANDREAS FESTA

Presentation by Andreas Festa

Andreas Festa started the meeting by introducing the topic from a clinician's point of view. He mentioned the tremendous progress that has been made in diabetes in recent years. Many more pharmacological options are available nowadays, and also technologies such as Continuous glucose monitors (CGM) systems and insulin pumps. Therefore, the challenge clinicians are facing in caring for patients with diabetes today is not a lack of options, but making the right choice for an individual patient. How to decide upon the right drug, for the right patient, at the right time in the course of type 2 diabetes? RHAPSODY has the potential to help improve the diagnosis of the disease and hence advance precision medicine.

Presentation by Elizabeth Robertson

Elizabeth Robertson summarized the patients' perspective in her talk. The mission of Diabetes UK was explained, also the tremendous increase in diabetes prevalence worldwide. RHAPSODY has addressed a few of the most urgent questions a typical patient with diabetes may worry about, such as:

- "How to identify high risk individuals?"
- "How to help the disease from developing?"
- "Why does type 2 diabetes progress and how to stop the progression?".

Strengths of RHAPSODY include the multi-disciplinary approach in solving research questions, considering both pre-diabetes and progression of diabetes, and also moving towards precision medicine. Interactions with regulatory authorities - such as the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) - are also significant achievements of RHAPSODY. Dr Robertson concluded by emphasizing the need for a personalised approach in diabetes. Also, more investment is needed to ultimately benefit people living with diabetes and those at risk.

Presentation by Claire Varin

Claire Varin explained the value of the Innovative Medicines Initiative (IMI) for research and ultimately for the care of people with diabetes. IMI is a European public-private partnership funding health research and innovation. Its mission is to facilitate open collaboration in research to advance the development of, and accelerate patient access to, personalised medicines for the health and wellbeing of all, especially in areas of unmet medical need. IMI oversees a budget of more than 3 billion Euros, almost 10% of this budget is dedicated to diabetes research. Several dedicated projects have been designed to tackle key questions in diabetes, including pre-diabetes, and also complications of diabetes. Main deliverables of RHAPSODY include the successful set-up of a federated database across Europe covering approximately 50.000 patients from 10 cohorts, in whom clinical, genetic, and omics data (plasma) are stored. Also, stratification in 5 different clusters was successfully done. Finally, biomarkers of disease progression were identified (proteins, metabolites and lipids).

Presentation by Bernard Thorens

Bernard Thorens, academic coordinator of RHAPSODY, started by explaining the step-wise nature of the development of type 2 diabetes. Also, he gave a definition of biomarkers, which are molecules that can be objectively measured and evaluated as an indicator of normal biological or pathogenic processes, as well as pharmacological response to a therapeutic intervention. Key questions asked in RHAPSODY were:

- Can we identify biomarkers that are prognostic of type 2 diabetes susceptibility and deterioration?
- Can such biomarkers predict dysfunctions in ß-cells or in insulin target tissues?
- Can we identify the tissues and metabolic pathways controlling the production of these biomarkers?

In RHAPSODY, preclinical models were used successfully to identify plasma biomarkers for type 2 diabetes susceptibility. These biomarkers could be demonstrated to correlate with the function of pancreatic ß-cells. Finally, comparative analysis in mice and humans of the correlation between plasma triacylglycerols (TAGs) and islet gene expression allowed to characterise a so far unknown regulator of insulin secretion.

Presentation by Emma Ahlqvist

Emma Ahlqvist summarised recent findings from diabetes sub-classification ("clustering"). The research question is: "Can we divide diabetes patients into smaller more homogeneous groups that are clinically useful for predicting progression and need for medication?". From these analyses, we have learned that patients can reproducibly be divided into five subgroups with different characteristics and different disease progression. The clustering approach, as presented by Dr Ahlqvist, has been replicated in numerous cohorts. The insulin deficient and insulin resistant subtypes have the highest risk of complications. Dr Ahlqvist concluded by saying that "better science today should lead to better treatment in the near future!".

Presentation by Roderik Slieker

Roderik Slieker presented results from RHAPSODY extending the clustering approach. Importantly, the identified clusters (n=5 in RHAPSODY, as opposed to the original four as presented earlier by Dr Ahlqvist) were compared to other data types, namely genetic/inherited risk, metabolites, lipids and proteins, using omics analytical methods. Data showed that BCAAs (branch-chain amino acids) indicate insulin resistance (high levels in the insulin-resistant cluster). In terms of lipids, diacylglycerol is linked to higher insulin resistance, as opposed to phosphatidylcholines. Proteins of insulin signalling were lower in insulin resistant people, while cytokines, including satiety hormones were higher in the high BMI (body mass index) cluster. In summary, RHAPSODY found that molecular signatures were very distinct across clusters, although all individuals were initially diagnosed to have type 2 diabetes. The insulin resistant and high HDL (high-density lipoprotein) groups showed opposite effects; these findings provide a starting point for personalised medicine.

Panel discussion "Why does it matter"

During the panel discussion moderated by Andreas Festa, panelists agreed unanimously that the (ambitious) goals of RHAPSODY have been achieved, even that some deliverables went far beyond expectation. The value of the federated database was emphasised. Steven Kahn (Univ of Seattle, Washington, US), who acted as an external advisor for RHAPSODY throughout the entire duration of the project, encouraged all partners involved in RHAPSODY to not only keep the federated database available for ongoing research but also to consider merging it with other databases, namely in the US, such as the DPP study or the GRADE study. This should be of interest for the EU from a patient-focussed research perspective, but also for the US/NIH, and ultimately globally.

Panelists also engaged directly with participants to answer questions about the impact of life styles, the pros and cons of patient sub-classification etc.

Conclusions

The RHAPSODY Final Symposium was successful, allowing to gather a broad audience with various expertise, backgrounds and expectations. Despite the online format, the panel discussion was fruitful.

This symposium was an excellent opportunity to showcase key achievements of RHAPSODY, which will without doubt pave the way for the next steps, including the translation of research findings into practice. "