HYPO RESOLVE

Hypoglycaemia - REdefining SOLutions for better liVEs

Executive Summary

4th Project Period

Period covered: 01/05/2021 to 30/04/2022

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Context and Objectives

Diabetes is a major non-communicable threat to global health that imposes an increasing burden on global health care resources. Lowering glucose levels to those in the non-diabetic range reduces the risk of vascular complications and mortality. However, treatment with insulin and insulin secretagogues, which stimulate insulin secretion independent of the glucose level, is associated with increased risk of hypoglycaemia (low blood sugar). On average, hypoglycaemic events occur at a weekly to monthly basis in people with type 1 and type 2 diabetes treated with insulin, respectively. Hypoglycaemia causes profound physical and mental stress, and is associated with adverse clinical consequences, including death, psychological stress, poor quality of life and elevated costs.

However, although the adverse clinical, psychological and health-economic consequences of severe hypoglycaemia (in which cognitive dysfunction requires assistance from another person for recovery) are reasonably well described, this is much less clear for so-called 'non-severe' hypoglycaemia, in which the person maintains cognitive function sufficient for self-help. It also remains to be established which underlying mechanism(s) explain the association between hypoglycaemia and cardiovascular events and below which glucose level hypoglycaemia is associated with adverse outcomes. Finally, the pathophysiology underlying impaired awareness of hypoglycaemia has not been fully explained and it is unclear how hypoglycaemia detected by continuous glucose monitoring (CGM) should be considered in clinical practice or in trials. Clarifying these uncertainties is fundamental in providing the classification of hypoglycaemia in diabetes with sufficient evidence base.

The overall aim of the current project is to reduce the burden and consequences of hypoglycaemia in people with diabetes by increasing our understanding of hypoglycaemia. This objective will be achieved by answering the abovementioned questions using a comprehensive multi-layered approach, in which academia, industry and people affected by or living with diabetes closely collaborate in a non-competitive way.

Partners

STICHTING RADBOUD UNIVERSITAIR MEDISCH CENTRUM - KING'S COLLEGE LONDON - MEDIZINISCHE UNIVERSITAT GRAZ - THE CHANCELLOR MASTERS AND SCHOLARS OF THE UNIVERSITY OF CAMBRIDGE - CENTRE HOSPITALIER UNIVERSITAIRE MONTPELLIER - SYDDANSK UNIVERSITET - UNIVERSITE DE LAUSANNE - THE UNIVERSITY OF SHEFFIELD - REGION HOVEDSTADEN - UNIVERSITY OF DUNDEE - EURICE EUROPEAN RESEARCH AND PROJECT OFFICE GMBH - SIB INSTITUT SUISSE DE BIOINFORMATIQUE - UNIVERSITA DEGLI STUDI DI PADOVA - THE UNIVERSITY OF EDINBURGH - NOVO NORDISK A/S - Eli Lilly and Company Limited - ABBOTT DIABETES CARE - MEDTRONIC INTERNATIONAL TRADING SARL - JDRF INTERNATIONAL - FEDERATION INTERNATIONALE DU DIABETE - UNITIO INC - THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST – THE UNIVERSITY OF LEICESTER

Scientific Results

A governance structure has been set in place to provide support for individual scientists, monitor progress and coordinate project activities. A website, twitter account and dissemination toolkit have been established to create awareness of the project's mission, vision and progress, whereas a short animated clip explains the project for a general audience and there are podcast videos between WP leads and members from the Patient Advisory Committee. The large, secure and sustainable Hypo-RESOLVE database has been constructed, containing data on hypoglycaemia and other clinical parameters from 98 individual clinical trials involving >60,000 people with diabetes treated with insulin. Initial analyses show that hypoglycaemia, whether severe or non-severe, predicts future hypoglycaemia of any kind, and associations between severe hypoglycaemia and increased risks for CV events in type 1 and type 2 diabetes, whereas a similar link exists for IHSG level 2 hypoglycaemia in type 2 diabetes. The multicentre Hypoglycaemia Measurement ThResholds and ImpaCtS (Hypo-METRICS) study, which examens the clinical, psychological and health-economic impact of sensor-detected hypoglycaemia, is close to achieving its intended number of enrolling 600 people with type 1 or type 2 diabetes. In this study, participants are followed for 10 weeks with blinded glucose sensors on top of their usual glucose monitoring device (i.e. 'conventional' glucose meters or glucose sensors), activity trackers and a specifically developed app (Hypo-METRICS app) with daily entries on quality of life and related questions. Using some in-house datasets, models have been developed for carb counting error, and meal and snack timing. Sensitivity analysis have been initiated to factor in delays to mealtime boluses. The hyperinsulinaemic hypoglycaemic glucose clamp experiments, involving 110 people with type 1 or type 2 diabetes or without diabetes, have all been completed. This study shows that glucose <3.0 mmol/l causes cognitive decline of about similar magnitude in all participants, irrespective of diabetes duration, HbA1c or level of hypoglycaemic awareness, thus supporting the IHSG classification. A meta-analysis of stepped hypoglycaemic clamps showed glycaemic thresholds for counterregulatory hormone responses among people without diabetes to align with IHSG level 1 hypoglycaemia. The clamp study also shows that hypoglycaemia causes long-term pro-inflammatory effects on multiple levels in all groups, with no signs of mitigation by exposure to antecedent hypoglycaemia or reduced hypoglycaemic awareness. Animal studies have further established the role of FGF15 neurons in the hypothalamus controlling glucagon secretion and how glycaemic control and post-hypoglycaemic recovery modifies the impact of hypoglycaemia on the brain. Work is ongoing with regard to transcriptomic and proteomic analysis of the hypothalamus and cortex in response to a defective counterregulatory response and to optimize a mouse model of impaired awareness of hypoglycaemia. Various systematic reviews have been published that summarize the data collected on the impact of hypoglycaemia on quality of life among people with type 1 or type 2 diabetes, as well as family members of people with diabetes, also identifying knowledge gaps. A qualitative multi-country online survey and a quantitative follow-up study both show that hypoglycaemia exerts emotional, social, cognitive and behavioural impacts on relationships, work/studies, leisure, everyday life, sleep, sex life and physical and mental health among adults with diabetes, limiting their spontaneity. Also, for these studies, a new measure to assess the impact of hypoglycaemia was validated. Finally, activity is progressing with respect to the development of the hypoglycaemia-specific patient reported outcome (PRO), including in-depth interviews with people with diabetes and clinicians. After having held a stakeholder meeting with representatives from professional and patient organisations, HTA bodies, regulators and other stakeholders, and an Innovation Task Force (ITF) meeting with representatives from the European Medicines Agency (EMA), official Qualification Advice was obtained from EMA for this purpose.

Expected final results and impact

Data coming out of this project will advance our understanding of predictors for and clinical, psychological and health-economic consequences of hypoglycaemia. The project will also elucidate mechanism(s) underlying the association of hypoglycaemia with long-term (cardiovascular) consequences and the clinical relevance of low interstitial glucose values (as measured by CGM). The project is expected to provide the evidence currently missing for refining the classification of hypoglycaemia in people with diabetes at risk of medication-associated hypoglycaemia. Adoption of the refined classification in relevant guidelines will have significant impact on the diabetes community, including people with diabetes, HCPs, regulators, scientists and industry, and for adoption of hypoglycaemia as an efficacy outcome for future clinical trials. Also, the Hypo-METRICS app that has been developed for ecological momentary assessments in the Hypo-METRICS study and the new hypoglycaemia-specific PRO will be made available for use in clinical trials.

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