HYPO RESOLVE

Hypoglycaemia - REdefining SOLutions for better liVEs

Executive Summary
2nd Project Period

Period covered: 01/05/2019 to 30/04/2020

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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 (secretagogues) is associated with increased risk of hypoglycaemia (low blood sugar), which on average occurs at a weekly to monthly basis in people with type 1 and type 2 diabetes, respectively. Hypoglycaemia causes profound physical and mental stress, and is associated with adverse clinical and psychological consequences 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 harm. Finally, the pathophysiology underlying impaired awareness of hypoglycaemia has not been fully explained and it is unclear how hypoglycaemia detected by CGM (continuous glucose monitoring) should be considered. 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

Radboud university medical center/STICHTING KATHOLIEKE UNIVERSITEIT - 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 - SANOFI-AVENTIS DEUTSCHLAND GMBH - ABBOTT DIABETES CARE - MEDTRONIC INTERNATIONAL TRADING SARL - JDRF INTERNATIONAL - FEDERATION INTERNATIONALE DU DIABETE - UNITIO INC - THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST

Scientific Results

The work has been distributed over a total of 8 different work packages. With respect to project management, 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. A key part of the project is the construction of a large, secure and sustainable database with data on hypoglycaemia and other clinical parameters from 100 clinical trials involving people with diabetes treated with insulin. The Hypo-RESOLVE database has been set in place and now contains data from >50,000 individuals participating in 86 clinical trials, including 16 with data on continuous glucose monitoring (CGM). Apart from data on hypoglycaemic events, information is available on demographics, vital signs, laboratory measurements, and other types of data, such as adverse events, medical history, questionnaires and concomitant medication. A statistical analysis plan, based on a Bayesian inferential framework, has been established and iteratively refined to analyse these data, one pertaining on prediction of hypoglycaemia, and another on the consequences of hypoglycaemia. Stakeholders meetings have been held to discuss the classification of hypoglycaemia. Human and animal experimental studies are being conducted to uncover mechanisms underlying cardiovascular and other clinical consequences of hypoglycaemia. As such, 45 people with type 1 or type 2 diabetes or without diabetes already have been examined during and after undergoing experimental hypoglycaemia. Also, animal models have been developed to study new hypoglycaemia sensing pathways and how to quantify symptoms of hypoglycaemia in animals. A systematic literature review to map hypoglycaemia detection techniques and identify gaps that have not been addressed is underway. Using some in-house datasets, models have been developed for carb counting error, and meal and snack timing. Sensitivity analysis has been initiated to factor in delays to mealtime boluses. The study protocol for the multi-centre clinical study, Hypo-METRICS, which will examine the clinical relevance and consequences of asymptomatic, CGM-detected low glucose values among 600 patients with type 1 or insulin-treated type 2 diabetes, has been finalised and submitted for ethics approval. An app for smart phones has been developed to capture and monitor patient-reported outcomes (PROs) related to hypoglycaemia throughout the 10 weeks of follow-up in this study. A systematic review on 7 'hypoglycaemia-specific' PROs currently used in studies involving hypoglycaemia, revealed the content and structural validity to be inconsistent or otherwise unsatisfactory, justifying the need for a new PRO. Data that come out Hypo-METRICS will therefore be used to develop a hypoglycaemia-specific PRO for future studies. Searches have been completed for a series of systematic reviews to determine the impact of hypoglycaemia on quality of life in people with diabetes and family members and preparations for reviews on its effect on cognitive function and academic performance have begun. The protocol of an online qualitative study to explore the impact of hypoglycaemia on quality of life and the needs of people with diabetes and their family members is in its final stage and close to submitting for ethics approval. Finally, a review on the definition and classification of hypoglycaemia in guidelines and consensus reports showed a very large variety in how hypoglycaemia is defined, in part due to newer glucose measurement technology. A stakeholder meeting has been organised to establish and maintain a dialogue with key regulators, HTA body representatives and other key stakeholders. Also, the dialogue with key regulators was further advanced via an Innovation Task Force (ITF) meeting with the European Medicines Agency (EMA) and by starting preparations for an EMA Qualification Advice on the development of the new PRO.

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). These data are 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, health care professionals, regulators, scientists and industry, and for adoption of hypoglycaemia as an efficacy outcome for future clinical trials. Also, the new hypoglycaemia-specific PRO will be made available for use in clinical trials.

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