Title: Are Todays Continuous Glucose Monitoring Precise and Can They be Used to Reveal and Reduce Glycaemic Variability?

NCT: NCT03842683

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Mandatory elements to be included in access requests

Data Sharing Agreement

Please refer to the Data Sharing Agreement

Potential conflicts of interest outside the funding of the proposed research

Please refer to the Data Sharing Agreement

Funding of the proposed research

None

Research team information

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Abbreviated CV's for all team members are attached.

Research proposal information

Title of the proposed research

Are todays Continuous Glucose Monitoring precise and can they be used to reveal and reduce glycaemic variability?

Scientific rationale and relevance of the proposed research describing the objectives and the hypotheses corresponding to the objectives of the research.

Continuous Glucose Monitoring (CGM) provides an interstitial glucose reading every 5 minutes and is thus a powerful and important tool to identify glycaemic variability in people with diabetes. [1] CGM is valuable for people with diabetes to understand their glucose metabolism and it has the potential to be used for detection and prediction of glycaemic excursions, such as, the potentially fatal and inevitable events of hypoglycaemia, [2] [3] or even as a component in the holy grail of diabetes technology; the artificial pancreas. [4]

However, CGM has been criticised for being inaccurate and unreliable, amongst others, due to the physiological and a device-related delay between plasma glucose (PG) and interstitial glucose (IG). [5] [6] Nevertheless, CGM keeps on being popular and in February 2017 an international consensus was established at the Advanced Technologies & Treatments for Diabetes (ATTD) congress that even considers CGM data as a valuable and meaningful end point to be used in clinical trials of new drugs and devices for diabetes treatment where accuracy is of high importance. [7]

The above mentioned use cases entail that the CGM data are accurate. Therefore, the first part of this research proposal is to investigate whether the newest state-of-the-art CGM devices used in Novo Nordisk trials are in fact accurate. Based on these results, it is investigated to which degree glycaemic variability can be revealed.

Short lay summary of the proposed research intended for public disclosure

Use of devices for continuous monitoring of the blood sugar is valuable for people with diabetes to understand their disease and to help prevent low blood sugar. Furthermore, continuous monitoring should be used in drug development to evaluate efficacy and safety. However, the devices have been criticised for being too inaccurate. This investigation sought to reveal the inaccuracies of current devices and to assess the subsequent usability related to the mentioned use cases.

Research methodology and data (brief description of the intended method for the use of the requested data and a detailed description of the different data sources of the data that is intended to be included)

To investigate the accuracy of CGM, mean absolute relative difference (MARD) will be calculated and presented and the impact of the delay assessed by time shifting CGM measurements. Furthermore, correlation analyses, between for example, PG and first derivative of IG, will be performed to try to understand when CGM devices tend to measure inaccurate. Lastly, machine learning and/or deep learning approaches will be utilised to reveal glycaemic patterns and to detect/predict outcomes, such as, hypoglycaemia.

Different glycaemic variability investigations will be undertaken:

- Test of PG vs IG and effect on clinical research. [analysis of differences]
- Correlation between PG values at bedtime and nocturnal hypoglycaemic events [correlation analyses]
- Effect of main evening meal and meal-time dose on nocturnal hypoglycaemic events [correlation analyses]
- Prediction of PG-confirmed hypoglycaemic events with CGM, dose and meal data as input [machine learning]
- The optimal dose and meal distribution and least CGM variability / eHbA1c [machine learning]
- Algorithm to suggest optimal dosing in relation to glycaemic variability [machine learning]

Requested data are demographic, CGM, meal, dose and hypoglycaemia data from the following trial. The analyses are independent of treatment and therefore the treatment arm can be blinded.

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Statistical analysis plan (include a description of the endpoints and their time points and the planned statistical analyses including the analysis set, the analysis models (with factors and covariates), any transformation of data, plans for handling of missing data, plans for addressing multiplicity issues and plans for sensitivity analyses)

Please refer to the Data Sharing Agreement

Publication plan (list the planned number of abstracts and manuscripts (i.e. 'working title of these') and the scientific congresses under consideration for presentation of the research findings. Include the anticipated timelines)

Please refer to the Data Sharing Agreement

References

[1] D. Rodbard, »Continuous Glucose Monitoring: A Review of Recent Studies Demonstrating Improved Glycemic Outcomes,« *Diabetes Technology & Therapeutics,* årg. 19, nr. S3, 2017.

[2] M. H. Jensen, T. F. Christensen, L. Tarnow, E. Seto, M. Dencker Johansen og O. K. Hejlesen, »Real-Time Hypoglycemia Detection from Continuous Glucose Monitoring Data of Subjects with Type 1 Diabetes,« *Diabetes Technology & Therapeutics,* 2013.

[3] M. Jensen, T. Christensen, L. Tarnow, Z. Mahmoudi, M. Johansen og O. Hejlesen, »Professional continuous glucose monitoring in subjects with type 1 diabetes: Retrospective hypoglycemia detection,« *Journal of Diabetes Science and Technology,* årg. 7, nr. 1, 2013.

[4] F. H. El-Khatib, C. Balliro, M. A. Hillard, K. L. Magyar, L. Ekhlaspour, M. Sinha, D. Mondesir, A. Esmaeili, C. Hartigan, M. J. Thompson, S. Malkani, J. P. Lock, D. M. Harlan, P. Clinton, E. Frank, D. M. Wilson, D. DeSalvo, L. Norlander, T. Ly, B. A. Buckingham, J. Diner, M. Dezube, L. A. Young, A. Goley, M. S. Kirkman, J. B. Buse, H. Zheng, R. R. Selagamsetty, E. R. Damiano og S. J. Russell, »Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial,« *The Lancet,* 2017.

[5] K. Rebrin, N. F. Sheppard og G. M. Steil, »Use of Subcutaneous Interstitial Fluid Glucose to Estimate Blood Glucose: Revisiting Delay and Sensor Offset,« 2010.

[6] B. P. Kovatchev, S. D. Patek, E. A. Ortiz og M. D. Breton, »Assessing Sensor Accuracy for Non-Adjunct Use of Continuous Glucose Monitoring,« *Diabetes Technology & Therapeutics,* 2015.

[7] T. Danne, R. Nimri, T. Battelino, R. M. Bergenstal, K. L. Close, J. H. DeVries, S. Garg, L. Heinemann, I. Hirsch, S. A. Amiel, R. Beck, E. Bosi, B. Buckingham, C. Cobelli, E. Dassau, F. J. Doyle, S. Heller, R. Hovorka, W. Jia, T. Jones, O. Kordonouri, B. Kovatchev, A. Kowalski, L. Laffel, D. Maahs, H. R. Murphy, K. Nørgaard, C. G. Parkin, E. Renard, B. Saboo, M. Scharf, W. V. Tamborlane, S. A. Weinzimer og M. Phillip, »International consensus on use of continuous glucose monitoring,« *Diabetes Care,* 2017.