The measurement and consequences of daily glucose variability

Chapter 10

Scientific and societal impact

This chapter reflects on the scientific and societal impact of this thesis by identifying—in the context of the research field and current clinical practice—the different short- and long-term contributions of its findings.

Research field and main objectives of this thesis

Diabetes mellitus is a metabolic disease that is characterized by elevated blood glucose values[1]. At present, approximately 463 million individuals are affected by diabetes worldwide; a figure that is expected to rise to 700 million by 2045[2,3]. This is problematic because diabetes lowers life expectancy[4-6] and strongly increases the chances of several diseases, including cardiovascular disease[7], eye, kidney, and nerve disease[8,9], and dementia[10]. More and more studies show that having prediabetes, which is the stage between normal glucose metabolism and diabetes, is also unhealthy[9-12]. This is concerning because the number of individuals with prediabetes is increasing worldwide as well[13,14].

Diabetes and its related diseases have a negative effect on quality of life[15] and represent a large share of the global health spending[16,17]. Prevention of these diseases will, thus, benefit the individual as well as society. However, this requires knowledge of the ways through which diabetes and prediabetes can cause disease. While decades of stellar research have led to great insights, and consequently have improved treatment and prevention[18], much is still unclear. Relatively recently, daily glucose fluctuations, also known as daily glucose variability, were suggested to be harmful[19]. Hence, a main objective of this thesis was to study whether daily glucose variability is indeed related to cardiovascular disease, eye, kidney, and nerve disease, and cognitive decline.

At the start of this century, a new device was introduced to improve diabetes care[20]. This device enables continuous glucose monitoring (CGM) and, thus, is able to record hundreds of glucose values per day. This allows for detailed study of daily glucose patterns. Hence, it is a device that is particularly suited to assess the degree of daily glucose variability[21]. Partly because of this, it is increasingly being used in scientific research and clinical practice. Studies have shown that use of CGM can improve diabetes care[20], and that the specific values calculated with CGM, in particular the intuitive index time in range, are important to individuals with diabetes[22]. However, several important aspects of CGM and the measurement of daily glucose variability have been insufficiently studied. Therefore, a main objective of this thesis was to do so in order to improve both future studies and clinical practice.

Relevance of the key findings

Continuous glucose monitoring and daily glucose variability measurement

In this thesis, we studied how many days are needed to get a reliable CGM recording. This is relevant because CGM is quite expensive and undergoing it can be a burden[23],

especially when daily fingerpricks are required to calibrate the device[20]. Regarding short-term scientific value, knowledge of the minimum number of days needed can prevent both too short or too long recording periods, which would enhance measurement quality and limit participant strain in future studies, respectively. This information may also be used to reduce such burden in the clinical care of individuals with diabetes who intermittently wear a CGM. We believe that these findings can be used to improve the next *International Consensus Report* on *Clinical Targets for CGM Data Interpretation*[21].

CGM is also used in closed-loop insulin delivery systems, which can dose insulin based on the glucose values measured with CGM[24,25]. These systems are a very promising option to improve diabetes care in the near future[26-29]. These devices may be improved by addressing certain inherent shortcomings related to CGM, such as sensor delay and brief periods of sensor malfunction[24, 30, 31]. In this thesis, we developed a model to predict future glucose values in order to improve the CGM part of closed-loop insulin delivery systems. Our model was able to accurately and safely predict glucose values at 15- and 60-minute intervals, which could be useful in case of short periods of CGM malfunction. Our aim is to explore the possibility of further optimizing these prediction models in cooperation with companies that are specialized in diabetes care.

A large number of values can be measured with CGM, such as the average glucose and degree of daily glucose variability[23]. In this thesis, we studied, using data of participants with normal glucose metabolism, what the normal ranges of these values are. Interestingly, the daily glucose variability target that is currently recommended by the *International Consensus Report* lies much higher than the normal values found[21]. Future research should assess whether the target values should be lowered to more reflect the normal values by establishing whether daily glucose variability is harmful, and if so, at what point it becomes too damaging of unsafe.

In this thesis, we also investigated new ways to measure the amount of daily glucose variability. First, we found that the 'glucotype'[32], which garnered substantial scientific attention[33-36], did not live up to the expectation when used in other studies than the original one. Critical assessment of reproducibility is an important but often overlooked aspect of science[37]. Second, we showed that the incremental glucose peak during an oral glucose tolerance test (OGTT) as well as the 1-hour OGTT values can be used as measures of daily glucose variability, albeit predominantly in a research setting. This has short-term scientific value because studies that have such data available can immediately start contributing to the study of daily glucose variability. In addition, it puts the results of previous studies on the 1-hour OGTT value in a new light[38].

In this thesis, we also extensively reflected on the methods and statistics used in all of its chapters with the aim of providing insights that can help improve future research. For example, we showed that researchers should be especially on their guard for the statistical phenomenon called multicollinearity, which occurs due to a strong

relationship between two or more measures[39], when studying the consequences of daily glucose variability.

The consequences of daily glucose variability

In this thesis, we have studied whether daily glucose variability is associated with several measures that precede actual diseases. We show that higher glucose variability is related to higher stiffness of the aorta, which reflects cardiovascular disease and mortality, to lower thickness of the nerves in the eye, which reflects neurodegeneration, and to worse cognitive performance, which reflects cognitive decline. Our findings thereby add to growing evidence that lowering of daily glucose variability (e.g., through lifestyle interventions or specific therapeutic regimens) could be important to prevent disease[40,41]. However, it is too early to reach such definite conclusions based on our findings. Namely, we assessed precursors of disease rather than actual diseases. In addition, we studied the relationships at one point in time, which makes it difficult to establish cause and effect[42]. As such, the short-term merit of our research lies in the fact that we provide directions for future research on the consequences of daily glucose variability. In the long run—especially if studies convincingly show that daily glucose variability causes future disease and that its treatment can prevent such disease—we hope to be able to state that we have made a meaningful contribution to diabetes care with our initial studies on the effects of daily glucose variability.

Other key findings

In this thesis, we additionally found that prediabetes, diabetes, and measures of average glucose are also related to thickness of the nerves in the eye. This can have several implications for clinical practice. Measurement of the nerves in the eye could help select individuals who are at risk for developing eye or nerve disease. This would be feasible clinically because such measurement is non-invasive, inexpensive, and easy[43]. In addition, it further indicates early lowering of blood glucose values, possibly already in prediabetes, is key in the early prevention of eye and nerve disease.

Knowledge dissemination to target groups

The impact of this thesis is primarily scientific. Namely, we report multiple ways to improve the quality of scientific research into CGM and daily glucose variability. As such, the scientific community is the main target group of this thesis. Publication of the results in scientific journals is one of the main ways to inform this community. In addition, the results of this thesis have been presented at several national and international conferences (see *Curriculum vitae*). As a result, it seems that these findings are starting to get noticed. For example, the incremental glucose peak has

recently received attention from one of the experts in the glucose variability field[40]. Further, our findings on CGM recording period reliability have been used by other authors to justify their recording period length[44]. In the end, the aim of scientific research is to improve society. If this thesis' suggestions on research quality continue to be applied in the coming years, this thesis will indirectly, positively impact society in the near future.

To a lesser extent, this thesis also has a direct societal impact, predominantly related to healthcare. Namely, certain key findings can have short- and long-term impact on diabetes care, such as reducing CGM burden and altering future therapy. As such, individuals with diabetes and prediabetes, as well as their relatives, are a target group of this thesis. While most of the findings of the current thesis are insufficient to alter the diabetes care of tomorrow, they do make a contribution to a field that can potentially improve the lives of a very large group of people (approximately 700 million in 2045)[3]. At present, it is debatable whether this target group would profit from being extensively updated on the current results. Regardless, the findings of this thesis have been presented in layman's terms on two separate occasions as part of the popular public symposium that is organized annually for the interested participants of The Maastricht Study.

References

1. American Diabetes A. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43(Suppl 1):S66-S76.
2. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018;14(2):88-98.
3. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res Clin Pract. 2019;157:107843.
4. Preis SR, Hwang SJ, Coady S, Pencina MJ, D'Agostino RB, Sr., Savage PJ, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. Circulation. 2009;119(13):1728-35.
5. Taylor KS, Heneghan CJ, Farmer AJ, Fuller AM, Adler AI, Aronson JK, et al. All-cause and cardiovascular mortality in middle-aged people with type 2 diabetes compared with people without diabetes in a large U.K. primary care database. Diabetes Care. 2013;36(8):2366-71.
6. Bragg F, Holmes MV, Iona A, Guo Y, Du H, Chen Y, et al. Association Between Diabetes and Cause-Specific Mortality in Rural and Urban Areas of China. JAMA. 2017;317(3):280-9.
7. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical Update: Cardiovascular Disease in Diabetes Mellitus: Atherosclerotic Cardiovascular Disease and Heart Failure in Type 2 Diabetes Mellitus - Mechanisms, Management, and Clinical Considerations. Circulation. 2016;133(24): 2459-502.
8. American Diabetes A. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43(Suppl 1):S135-S51.
9. Stehouwer CDA. Microvascular Dysfunction and Hyperglycemia: A Vicious Cycle With Widespread Consequences. Diabetes. 2018;67(9):1729-41.
10. Xue M, Xu W, Ou YN, Cao XP, Tan MS, Tan L, et al. Diabetes mellitus and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 144 prospective studies. Ageing Res Rev. 2019;55:100944.
11. Cai X, Zhang Y, Li M, Wu JH, Mai L, Li J, et al. Association between prediabetes and risk of all cause mortality and cardiovascular disease: updated meta-analysis. BMJ. 2020;370:m2297.
12. Wong MS, Gu K, Heng D, Chew SK, Chew LS, Tai ES. The Singapore impaired glucose tolerance follow-up study: does the ticking clock go backward as well as forward? Diabetes Care. 2003;26(11):3024-30.
13. Bullard KM, Saydah SH, Imperatore G, Cowie CC, Gregg EW, Geiss LS, et al. Secular changes in U.S. Prediabetes prevalence defined by hemoglobin A1c and fasting plasma glucose: National Health and Nutrition Examination Surveys, 1999-2010. Diabetes Care. 2013;36(8):2286-93.
14. Mainous AG, 3rd, Tanner RJ, Baker R, Zayas CE, Harle CA. Prevalence of prediabetes in England from 2003 to 2011: population-based, cross-sectional study. BMJ Open. 2014;4(6):e005002.
15. Jing X, Chen J, Dong Y, Han D, Zhao H, Wang X, et al. Related factors of quality of life of type 2 diabetes patients: a systematic review and meta-analysis. Health Qual Life Outcomes. 2018;16(1):189.
16. Bommer C, Heesemann E, Sagalova V, Manne-Goehler J, Atun R, Barnighausen T, et al. The global economic burden of diabetes in adults aged 20-79 years: a cost-of-illness study. Lancet Diabetes Endocrinol. 2017;5(6):423-30.
17. Bommer C, Sagalova V, Heesemann E, Manne-Goehler J, Atun R, Barnighausen T, et al. Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030. Diabetes Care. 2018;41(5):963-70.
18. Zinman B, Skyler JS, Riddle MC, Ferrannini E. Diabetes Research and Care Through the Ages. Diabetes Care. 2017;40(10):1302-13.
19. Brownlee M, Hirsch IB. Glycemic variability: a hemoglobin A1c-independent risk factor for diabetic complications. JAMA. 2006;295(14):1707-8.

20. Lin R, Brown F, James S, Jones J, Ekinci E. Continuous glucose monitoring: A review of the evidence in type 1 and 2 diabetes mellitus. Diabet Med. 2021:e14528.
21. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019;42(8):1593-603.
22. Advani A. Positioning time in range in diabetes management. Diabetologia. 2020;63(2):242-52.
23. Rodbard D. The challenges of measuring glycemic variability. J Diabetes Sci Technol. 2012;6(3): 712-5.
24. Cobelli C, Renard E, Kovatchev B. Artificial pancreas: past, present, future. Diabetes. 2011;60(11):2672-82.
25. Bruttomesso D. Toward Automated Insulin Delivery. N Engl J Med. 2019;381(18):1774-5.
26. Kovatchev BP, Kollar L, Anderson SM, Barnett C, Breton MD, Carr K, et al. Evening and overnight closed-loop control versus 24/7 continuous closed-loop control for type 1 diabetes: a randomised crossover trial. Lancet Digit Health. 2020;2(2):e64-e73.
27. Blauw H, Onvlee AJ, Klaassen M, van Bon AC, DeVries JH. Fully Closed Loop Glucose Control With a Bihormonal Artificial Pancreas in Adults With Type 1 Diabetes: An Outpatient, Randomized, Crossover Trial. Diabetes Care. 2021.
28. Bergenstal RM, Nimri R, Beck RW, Criego A, Laffel L, Schatz D, et al. A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): a multicentre, randomised, crossover trial. Lancet. 2021;397(10270):208-19.
29. Amadou C, Franc S, Benhamou PY, Lablanche S, Huneker E, Charpentier G, et al. Diabeloop DBLG1 Closed-Loop System Enables Patients With Type 1 Diabetes to Significantly Improve Their Glycemic Control in Real-Life Situations Without Serious Adverse Events: 6-Month Follow-up. Diabetes Care. 2021.
30. Rodbard D. Continuous Glucose Monitoring: A Review of Successes, Challenges, and Opportunities. Diabetes Technol Ther. 2016;18 Suppl 2:S3-S13.
31. Blauw H, Keith-Hynes P, Koops R, DeVries JH. A Review of Safety and Design Requirements of the Artificial Pancreas. Ann Biomed Eng. 2016;44(11):3158-72.
32. Hall H, Perelman D, Breschi A, Limcaoco P, Kellogg R, McLaughlin T, et al. Glucotypes reveal new patterns of glucose dysregulation. PLoS Biol. 2018;16(7):e2005143.
33. Zaccardi F, Khunti K. Glucose dysregulation phenotypes - time to improve outcomes. Nat Rev Endocrinol. 2018;14(11):632-3.
34. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med. 2019;25(1):44-56.
35. Hamideh D, Arellano B, Topol EJ, Steinhubl SR. Your digital nutritionist. Lancet. 2019;393(10166):19.
36. Li J, Li X, Zhang S, Snyder M. Gene-Environment Interaction in the Era of Precision Medicine. Cell. 2019;177(1):38-44.
37. Begley CG, Ioannidis JP. Reproducibility in science: improving the standard for basic and preclinical research. Circ Res. 2015;116(1):116-26.
38. Bergman M, Jagannathan R, Buysschaert M, Pareek M, Olsen MH, Nilsson PM, et al. Lessons learned from the 1-hour post-load glucose level during OGTT: Current screening recommendations for dysglycaemia should be revised. Diabetes Metab Res Rev. 2018;34(5):e2992.
39. Vatcheva KP, Lee M, McCormick JB, Rahbar MH. Multicollinearity in Regression Analyses Conducted in Epidemiologic Studies. Epidemiology (Sunnyvale). 2016;6(2).
40. Ceriello A. Glucose Variability and Diabetic Complications: Is It Time to Treat? Diabetes Care. 2020;43(6):1169-71.
41. Zhou Z, Sun B, Huang S, Zhu C, Bian M. Glycemic variability: adverse clinical outcomes and how to improve it? Cardiovasc Diabetol. 2020;19(1):102.
42. Rothman KJ, Greenland S. Causation and causal inference in epidemiology. Am J Public Health. 2005;95 Suppl 1:S144-50.
43. Srinivasan S, Dehghani C, Pritchard N, Edwards K, Russell AW, Malik RA, et al. Optical coherence tomography predicts 4-year incident diabetic neuropathy. Ophthalmic Physiol Opt. 2017;37(4):451-9.

44. Mo Y, Ma X, Lu J, Shen Y, Wang Y, Zhang L, et al. Defining the target value of the coefficient of variation by continuous glucose monitoring in Chinese people with diabetes. J Diabetes Investig. 2020.