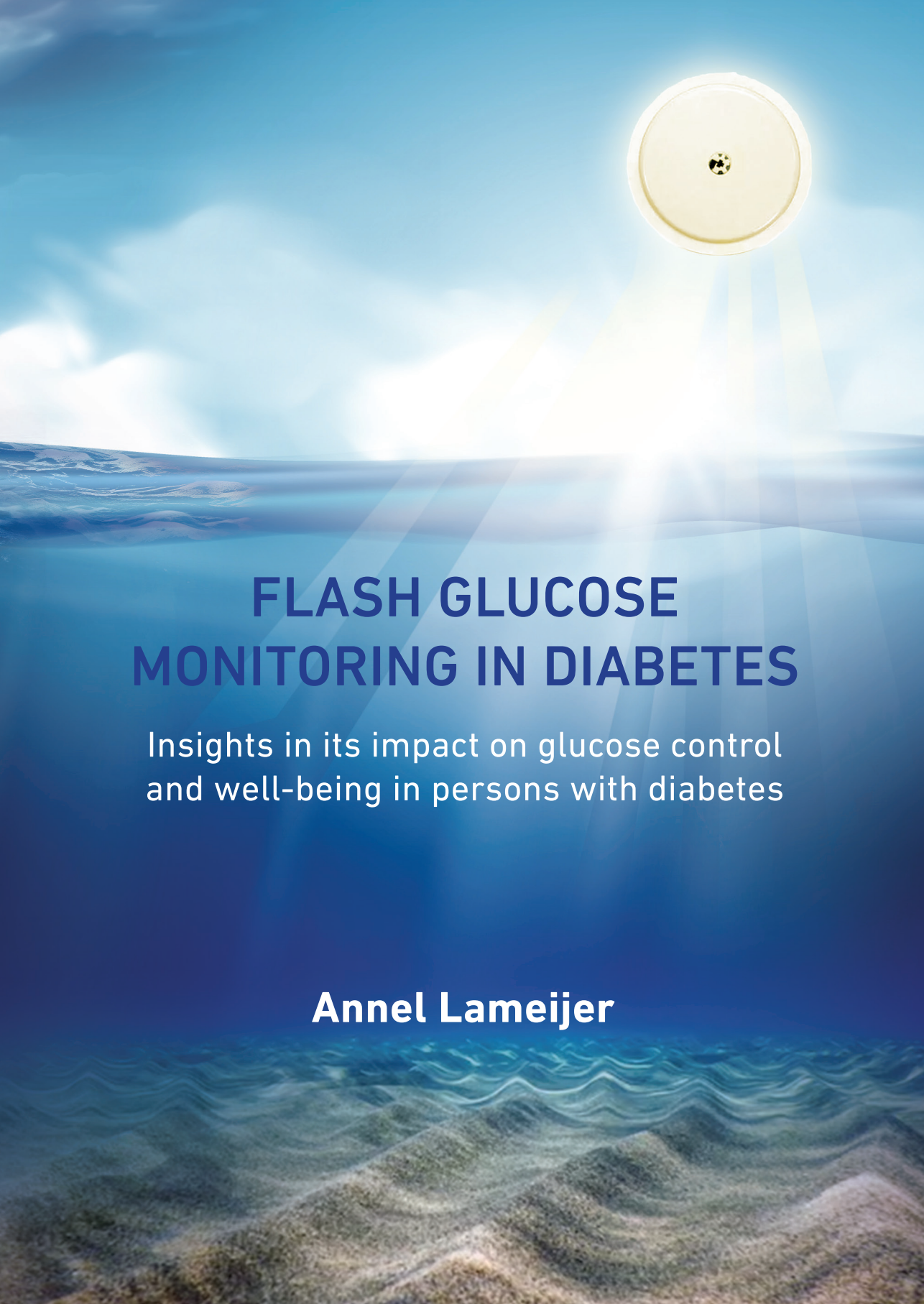
Flash glucose monitoring in diabetes

Lameijer, Annel

DOI:
10.33612/diss.1021051970



FLASH GLUCOSE MONITORING IN DIABETES

Insights in its impact on glucose control and well-being in persons with diabetes

Annel Lameijer

Flash glucose monitoring in diabetes

Insights in its impact on glucose control and well-being in persons with diabetes

Annel Lameijer

Cover design: Joey Roberts | www.ridderprint.nl
Lay-out and printing: Ridderprint | www.ridderprint.nl

rijksuniversiteit groningen

Flash glucose monitoring in diabetes

Insights in its impact on glucose control and well-being in persons with diabetes

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. ir. J.M.A. Scherpen
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

maandag 30 september 2024 om 14.30 uur

door

Annel Lameijer

geboren op 19 juli 1988
te Zwolle

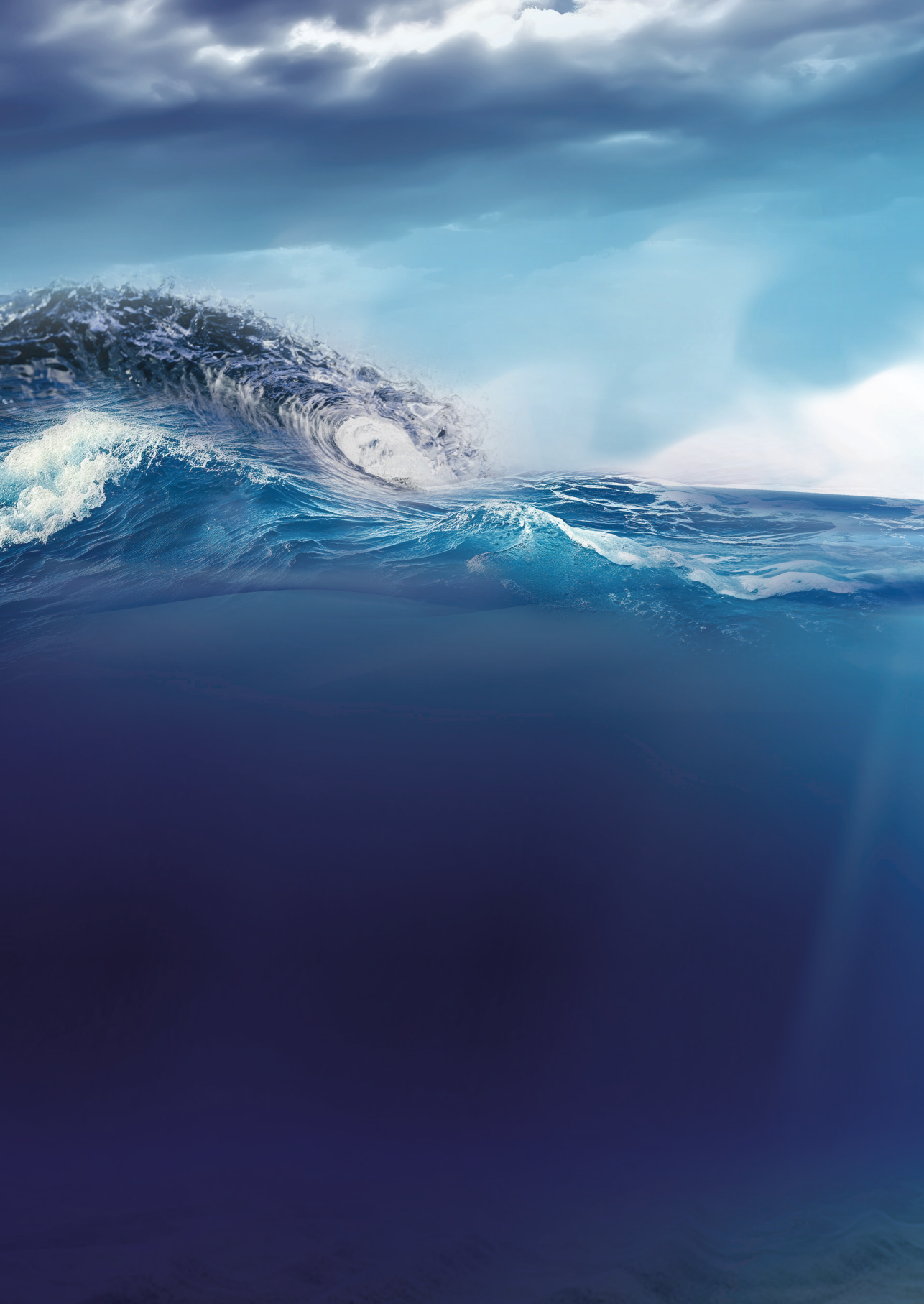
Promotores
Prof. dr. R.O.B. Gans
Prof. dr. H.J.G. Bilo

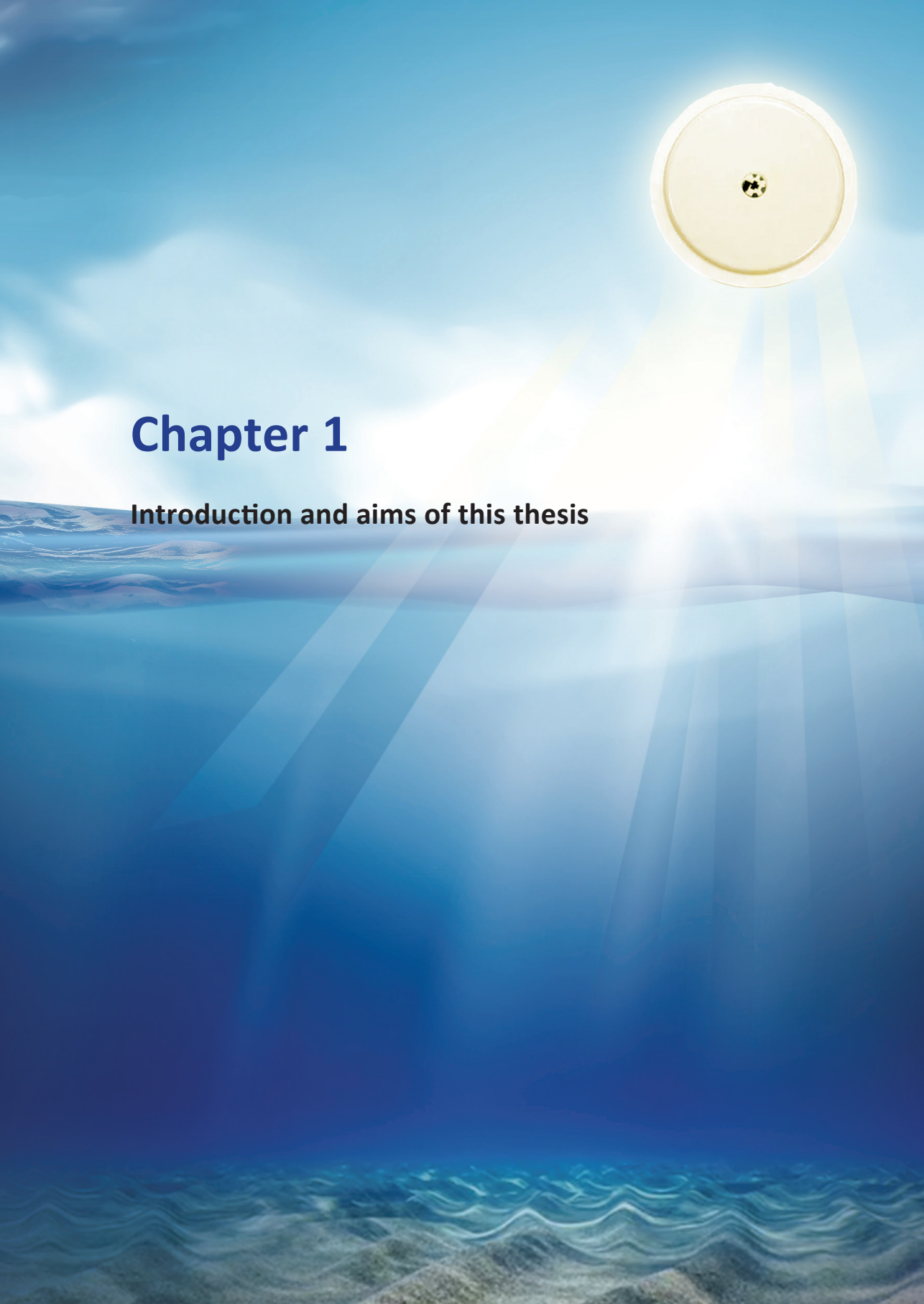
Copromotor
Dr. P.R. van Dijk

Beoordelingscommissie
Prof. dr. B.H.R. Wolffenbuttel
Prof. dr. T.L. Feenstra
Prof. dr. G.D. Laverman

Paranimfen
Sigrid Wapstra
Jolien Menninga

TABLE OF CONTENTS





Chapter 1

Introduction and aims of this thesis

Diabetes

Diabetes mellitus (DM) is a collective term for a group of metabolic disorders characterized by chronic hyperglycemia, due to a deficiency in the production or function of insulin or both. General symptoms include polyuria, polydipsia, weight loss, fatigue and blurred vision. DM is taken from the Greek word *diabainein*, meaning siphon (referring to the excessive urination), and from the Latin word *mellitus* meaning sweet (1).

The diagnosis of DM is based on one of the following criteria: a fasting glucose of ≥ 7 mmol/L, a random glucose of ≥ 11 mmol/L in a person with symptoms of hyperglycemia, a HbA1c ≥ 48 mmol/mol (6.5%) or a glucose of ≥ 11 mmol/L 2 hours after an 75 gram oral glucose loading test (OGTT) (2).

DM can be roughly classified into two categories (2) that include > 90% of cases:

- Type 1 diabetes (T1DM), including latent autoimmune diabetes of adulthood (LADA), caused by auto-immune destruction of pancreatic beta cells, leading to an absolute insulin deficiency. This results in hyperglycemia and ketosis, and therefore insulin replacement is of vital importance (3).
- Type 2 diabetes (T2DM), due to progressive loss of adequate beta cell insulin secretion in combination with insulin resistance, usually on the background of metabolic syndrome.

Other more rare causes of DM are for example maturity onset diabetes of the young (MODY), neonatal diabetes, diseases of the exocrine pancreas (e.g. due to pancreatitis or cystic fibrosis), drug- or chemical-induced diabetes (e.g. after organ transplantation, with glucocorticoid use, or use of anti-retroviral therapy for the treatment of HIV) and gestational diabetes (diagnosed in the second or third trimester of pregnancy in women without diabetes prior to gestation (2)).

In 2021, the prevalence of diabetes worldwide was approximately 537 million adults (20–79 years) (4). This represents 10.5% of the world's population in this age group. A rise to 783 million (12.2%) in 2045 is expected, predominantly in low and middle-income countries. T2DM is the most prevalent type of DM (> 90%) and the incidence of T2DM is globally rising across all regions (4). This rise is thought to be driven by ageing, economic development and increasing urbanization, leading to a more sedentary lifestyle and greater consumption of unhealthy foods linked with obesity (5).

T1DM accounts for about 5-10% of all persons with DM. The incidence peaks in puberty and early adulthood, but onset can occur at any age. The presentation of T1DM is typical

with a more sudden onset of polyuria, polydipsia, and weight loss and commonly with ketosis, in contrast to T2DM which is also far more common at older age. Furthermore, T1DM is associated with the co-occurrence of other autoimmune conditions such as Hashimoto thyroiditis, adrenal insufficiency, celiac disease and pernicious anemia (3).

Treatment of diabetes

T1DM is treated with exogeneous insulin administration. This can be administrated by multiple daily injections (MDI), often as a basal-bolus regimen (i.e. a long-acting insulin to cover the basal insulin needs and (ultra-)short acting insulin to cover the post-prandial glucose peaks), or by continuous subcutaneous insulin infusion (CSII) via an insulin pump (6). The total insulin dose is based on several factors, including weight, carbohydrate intake and anticipated physical activity.

T2DM is treated with lifestyle modification including weight management, blood glucose lowering medication (including metformin, sulfonylureas, DPP4 inhibitors, GLP1 agonists and SGLT2 inhibitors), and additionally – depending on the degree of glycemic dysregulation – with basal insulin or a more intensive scheme with basal-bolus insulin or CSII (6). In adults with T2DM and a high risk of atherosclerotic cardiovascular disease, heart failure or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk (7).

Rationale for glucose measurements and challenges of glycemic control

Adequate and timely glucose level assessment is of utmost importance for persons with DM when aiming for optimal glycemic control with near-normal HbA1c values (8). Ultimately, with optimized glycemic control micro- and macrovascular complications can be delayed or prevented (9–11). Although some improvement over time has been observed, glycemic control remains suboptimal for most people with T1DM (12). To achieve tight glycemic control, intensive self-management is required. Next to self-monitoring of glucose values, diabetes self-management includes several other tasks such as insulin dose adjustments, hypoglycemia management and carbohydrate counting. These tasks can be challenging (13), especially in persons with T1DM with at least 42 factors of influence on glucose values (14), and compliance is often limited (15). Living with T1DM and the associated challenges is accompanied by a substantial psychosocial burden and can interfere with occupational activities (especially when irregular), exercise activities, relationships and parenting (16). In addition, although tight glycemic control with an HbA1c < 53 mmol/mol (< 7%) reduces the risk of long-term complications, it is associated with an increased risk of hypoglycemia (9,17), which contributes to an increased disease burden (18).

The general goal for glycemic control in non-pregnant persons with diabetes is an HbA1c < 53 mmol/mol (< 7%), without significant hypoglycemia. A less stringent HbA1c goal of < 64 mmol/mol (< 8%) may be appropriate for persons with limited life expectancy (8). Although HbA1c remains an important outcome parameter in clinical trials, continuous glucose monitoring (CGM) metrics provide complementary information on glycemic control. Whereas HbA1c reflects glucose levels over the preceding 8–12 weeks, time in range (TIR) captures fluctuations in glucose levels continuously and reflects glucose levels and control over a shorter period. Furthermore, TIR identifies time within a safe range.

In 2019, glycemic targets for continuous glucose monitoring were formulated by an international panel (19). These targets are in general: TIR (glucose 3.9 – 10 mmol/L) > 70%, TBR (glucose < 3.9 mmol/L) < 4%, time in severe hypoglycemia (glucose < 3.0 mmol/L) < 1%, TAR (glucose > 10 mmol/L) < 25%, and time in severe hyperglycemia (> 13.9 mmol/L) < 5%. For persons with frailty or a high risk of hypoglycemia, a target of >50% TIR with < 1% TBR is recommended. For pregnant women and women with gestational diabetes more stringent goals are used. An overview of the specific glycemic targets for each group is shown in Figure 1.

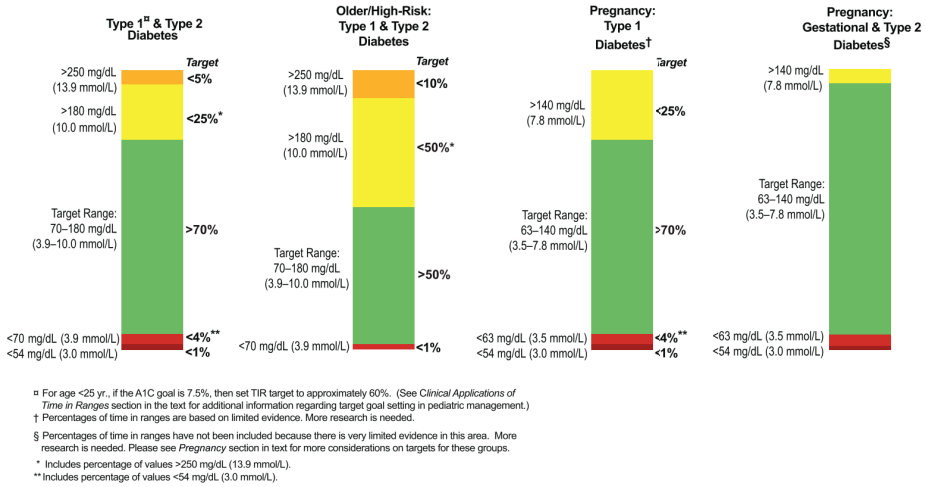
The cut-off of 70% TIR was based on the association between an HbA1c of 7% and a TIR of 70% (20,21). Furthermore, there is increasing evidence linking TIR to diabetes-related complications (22–24). A study validating TIR as an outcome measure, using seven-point capillary glucose measurements of the DCCT study, demonstrated that for every 10% decrease in TIR, the adjusted hazard rate of retinopathy and microalbuminuria increased by 64% and 40% respectively in persons with T1DM (22).

Options for glucose measurements

Fingerprick

Traditionally, patients monitor their glucose level in capillary blood by performing a fingerprick. This has been a a major breakthrough since the late 1970s (25), because previously only dipstick urine analysis was available. However, fingerprick measurements are painful and time consuming and many patients feel reluctant to perform finger pricks many times daily, since it can be disruptive to daily activities. It requires a person with diabetes to be awake, take initiative, and being in the right circumstances. Furthermore, since they are point measurements, no information on glucose trends is provided.

Figure 1. CGM based targets for different diabetes populations.



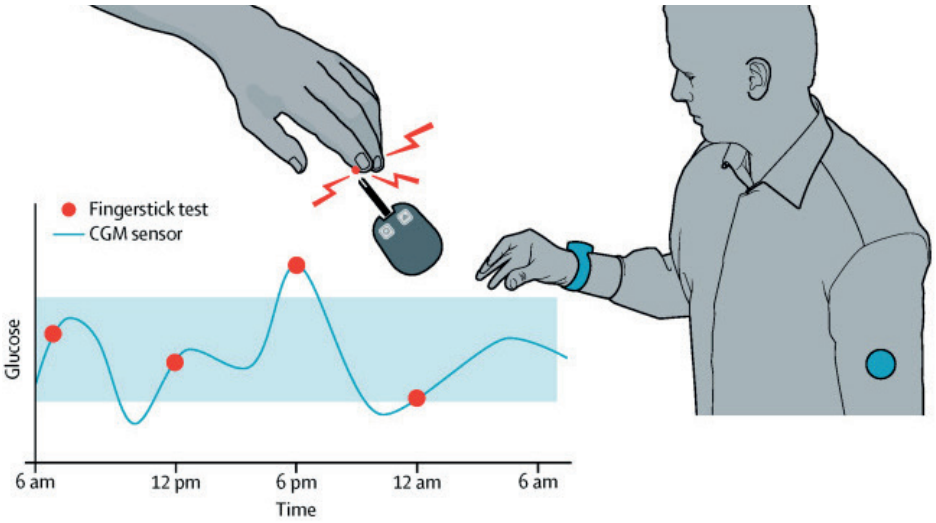
¤ For age <25 yr., if the A1C goal is 7.5%, then set TIR target to approximately 60%. (See *Clinical Applications of Time in Ranges* section in the text for additional information regarding target goal setting in pediatric management.)
† Percentages of time in ranges are based on limited evidence. More research is needed.
§ Percentages of time in ranges have not been included because there is very limited evidence in this area. More research is needed. Please see *Pregnancy* section in text for more considerations on targets for these groups.
* Includes percentage of values >250 mg/dL (13.9 mmol/L).
** Includes percentage of values <54 mg/dL (3.0 mmol/L).

Reprinted with permission from "Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range" by T. Battelino, T. Danne, R.M. Bergenstal, S.A. Amiel, R. Beck, T. Biester, et al., 2019, Diabetes Care, Aug 1;42(8):1593–603 (19).

Continuous Glucose Monitoring (CGM), either by real time CGM (rt-CGM) or by Flash Glucose Monitoring (FGM, also known as intermittently scanned CGM (is-CGM)), allows frequent assessment of glucose concentrations in the interstitial fluid and provides information on glucose trends during day and night. The improved insight into 24-hour glucose values provided by CGM leads to a more comprehensive understanding of a person's unique glucose response to diet and lifestyle. This insight is of great value when aiming for evaluation and adjustment of a treatment regimen. CGM measurements are more easily integrated in daily life than time consuming fingerpricks and glucose values can be obtained quickly in situations where more frequent assessment of glucose values is wanted, such as during exercise or before driving.

The additional information provided via CGM and the limitation of fingerprick point measurements is illustrated in Figure 2. The CGM glucose curve displays glycemic excursions during the day, including the glucose increase and decline after meals and insulin boluses. In this example, hypoglycemia is detected twice by CGM, but missed via fingerprick measurement. Of course, the amount of carbohydrate intake, timing and amount of insulin boluses and activities is necessary for a thorough understanding of the glucose excursions and to make appropriate insulin dose adjustments. Next to the display of glucose values, CGM also allows assessment of other metrics of glucose regulation such as TIR, TAR, TBR and glycemic variability. This innovation has revolutionized diabetes management.

Figure 2. Illustration of differences between fingerprick (point) glucose measurements (red dots) and continuous glucose data (blue line) provided by CGM.



Reprinted with permission from " The beginning of the end of fingersticks?" by M.Y. Song, S.R. Steinhubl and E.J. Topol, 2018, The Lancet, Jul 21;392(10143):203 (25).

Flash glucose monitoring

The FreeStyle Libre flash glucose monitor (Abbott Diabetes Care, Witney, UK) is currently the only available FGM device in The Netherlands. This system was introduced in 2014. The FreeStyle Libre FGM consists of a hair thin canula which pierces the dermis to access the interstitial fluid compartment and is placed as a patch on the back of the upper arm. This FGM needs to be actively scanned ('flashed') by the user to obtain information about the interstitial glucose concentration, either via the smartphone app or a dedicated reading device. The FSL-FGM is factory calibrated and does not need to be calibrated with a fingerprick blood glucose test by the user during the 14-day sensor wear. From December 2020 onwards the FreeStyle Libre version 2 is available. In contrast to the FreeStyle Libre version 1, the second version offers the ability to set alarms for high and low glucose values (26).

From December 2019, FGM is reimbursed in the Netherlands for people with diabetes on multiple daily injection (MDI) insulin therapy and for persons with type 2 diabetes who are pregnant or are planning to become pregnant. One of the studies that supported the reimbursement of FGM was the FLARE-NL4 study (27), based on one-year data from the nationwide FlAsh monitor REgister in The NetherLands (FLARE-NL). This was a prospective observational study that was set up in 2016 in cooperation with the Dutch diabetes patient

organization (Diabetes Vereniging Nederland, DVN) and a large health insurance company in the Netherlands (Zilveren Kruis) to acquire evidence on the effects, efficacy, and safety of use of FGM in the Netherlands. The FLARE-NL 4 study demonstrated improvement of HbA1c and well-being, less diabetes-related hospital admissions and a lower work absenteeism rate after 1 year of FGM use (27).

Apart from the FLARE-NL4 study, other studies also demonstrated the beneficial effects of FGM the last few years: it has been associated with improvement of glycemic control (28–30), improved quality of life (30), less diabetes-distress (31,32), less diabetes-related work absenteeism , fewer hospital admissions (32,33), and reduced hypoglycemic unawareness (32). These studies however are all hampered by a relatively short study period (3-12 months) and further research was needed to assess longer-term effectiveness and clinical outcomes. Besides, most studies mainly focused on HbA1c as outcome parameter instead of including more patient-relevant outcome measures. As data suggested improvement of mental well-being and diabetes distress, more robust data are needed, including the effect on depressive disorders that are more prevalent in diabetes. However, insight into the effects of long-term use of FGM on depressive disorders rates was lacking. The largest improvement of HbA1c was observed in users with the highest baseline HbA1c levels (34). A broader evaluation of factors associated with improvement of HbA1c among persons with DM using FGM was lacking as well, and the suitable target population most likely to benefit from FGM was not yet known. Lastly, a study of changes in glycemic parameters in persons with different levels of glycemic dysregulation was lacking.

Real-time continuous glucose monitoring

Both rt-CGM and FGM provide information about current and previous glucose levels, as well as information on glucose trends, via trend arrows that indicate the direction and rate of glucose change. Rt-CGM provides continuous data about current glucose concentrations, without de need to actively scan the sensor. Additionally, these sensors have features to set up alarms for high and low glucose values and for predicted high and low glucose values, whereas in FGM with the FreeStyle Libre version 2 only alarms for high and low glucose values can be set. Most rt-CGM systems require calibration once or twice daily and have a shorter duration of sensor life (7-10 days versus 14 days with FGM) (26).

Up to 2023, in The Netherlands rt-CGM has been only reimbursed for children, adults with T1DM with an HbA1c >64 mmol/mol (>8%) or hypoglycemia unawareness, pregnant women with T1DM or T2DM, and women with T1DM or T2DM with a pregnancy wish. This limited reimbursement is related to the higher costs of these devices.

Apart from CGM use as a stand-alone approach, a CGM can be used in conjunction with an insulin pump. In 2006 sensor-augmented pump therapy (SAP) was introduced, the first step in controlling insulin delivery through pumps by adjusting the basal rate (35). SAP includes a low glucose suspend feature that automatically halts insulin delivery when sensor glucose levels hit a preset low threshold. This was followed by the development of a predictive low-glucose suspension algorithm that already halts insulin delivery if hypoglycemia is expected within 30 minutes. In 2017, the first hybrid closed-loop (HCL) system became available. In auto(matic) mode, this system automatically controls basal insulin delivery every 5 min based on the CGM values to hold glucose levels tightly to a specific glucose target. Since meal announcements are still necessary (hence 'hybrid'), this is not a fully closed-loop system. The integrated bolus calculator calculates an accurate insulin dose by incorporating expected carbohydrate intake, measured blood glucose values, and previous insulin doses (35). Advanced hybrid closed-loop systems are also able to administer correction boluses. Efficacy and safety of HCL as compared to CGM therapy without a connection to an insulin pump has been demonstrated (36).

Aims and outline of this thesis

CGM is increasingly used as an alternative to self-monitoring of glucose using fingerpricks, as CGM is more convenient and provides more insight in glucose fluctuations during the day. The use of FGM is popular in current (Dutch) diabetes care, since this system is currently reimbursed by health insurance companies for all persons with diabetes and an intensive insulin treatment. Currently there are over 82.000 FGM users in the Netherlands (37). Of notice, in 2019 there were only 15.500 users (37).

In this thesis we aimed to assess longer-term effectiveness of FGM in persons with DM who started FGM. Next to glycemic control, we also included longer term outcomes regarding quality of life, disease burden and more patient relevant outcomes. Furthermore, we aimed to evaluate changes in glycemic parameters in FGM users in more detail, including outcomes in persons with different levels of glycemic control prior to FGM commencement, and in persons with either T1DM or T2DM with different treatment modalities.

This is necessary because previous studies on FGM had a limited follow-up period, were mainly focused on change in HbA1c as outcome parameter and more detailed insight into changes in glycemic parameters in persons with different levels of glycemic (dys)regulation and in persons with different treatment modalities was lacking. Ultimately, with improved insight in the impact of FGM on glycemic outcomes and well-being in persons with DM we want to contribute to the improvement of treatment and quality of life of persons with DM.

In **chapter 2**, we investigated which clinical factors predict HbA1c reduction in patients with diabetes mellitus using FGM for 12 months, to provide more evidence to identify patients who are likely to benefit from the use of FGM with regard to their HbA1c levels. For this analysis we used data from the FLARE-NL registry (described on page 8).

In **chapter 3**, we assessed the effect of FGM use on glycemic control, health-related quality of life and disease burden over a two-year study period, to provide more insight in the effects of long-term use of FGM. Previously the one-year FLARE-NL 4 study had shown improvement in all three domains and several other patient reported outcome measure (PROMS). After this one-year study ended, patients had to pay for the FGM themselves and this resulted in termination of FGM use in a substantial part of participants. In chapter 3 we elaborate on the main reasons for discontinuation of FGM and we investigated differences in outcomes between persons who continued FGM for two years versus persons who stopped FGM before the two-year follow-up period was completed.

Besides the evaluation of changes in quality of life after FGM initiation, we were also interested in the effect of FGM on depression rate, as depressive disorders are more common among persons with diabetes, have a severe impact on well-being and there was very limited data on the effects of FGM use in this particular group of persons. Therefore, in **chapter 4**, we explored the effects of FGM initiation on mental health and on the rate of depressive disorders among persons with diabetes.

As FGM has emerged as a widely used system for glucose monitoring over the past years, insight into the use of FGM under real-life circumstances by larger groups is valuable to evaluate its effects. In **chapter 5**, we evaluated FGM use during real-life circumstances in the Netherlands, with a focus on the association between FGM (scan) frequency and glycemic parameters (estimated HbA1c (eHbA1c), time in normo-, hyper-, and hypoglycemia, and standard deviation of glucose). In addition, monitoring frequency during normo-, hypo- and hyperglycemia was assessed for persons with lower and higher eHbA1c values to identify differences in scanning frequency between persons with good and suboptimal glycemic control. Finally, the monitoring pattern across the day was assessed and comparisons between Dutch data and worldwide data were made.

Next, we aimed to further explore the longer-term effects of FGM use on glycemic parameters in a larger real-life population, including subgroups with different treatment modalities and subgroups with different levels of glycemic control. In **chapter 6**, we evaluated the real-life 24-week changes in glycemic parameters among European users of FGM with either type 1 or type 2 diabetes, with different treatment modalities (basal-bolus insulin, basal insulin or a non-insulin treatment) and different levels of glycemic dysregulation.

Use of glucose sensor technology is unevenly distributed in the population, and this is influenced by factors such as socio-economic status (SES) and ethnicity. However, a comprehensive overview of available evidence regarding use of glucose monitoring systems and the influence of SES was lacking. **Chapter 7** provides an overview of the influence of SES, social determinants and ethnicity on the use of glucose sensor technology. In addition, recommendations to increase CGM use among persons with lower SES and ethnic minorities are given.

A summary is given in **chapter 8**. Finally, in **chapter 9** the main findings of this thesis are discussed and future perspectives are addressed.

References

1. Sapra A, Bhandari P. Diabetes. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jun 29]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK551501/
2. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 2. Classification and Diagnosis of Diabetes: *Standards of Care in Diabetes—2023*. Diabetes Care. 2023 Jan 1;46(Supplement_1):S19–40.
3. Syed FZ. Type 1 Diabetes Mellitus. Ann Intern Med. 2022 Mar 15;175(3):ITC33–48.
4. Magliano DJ, Boyko EJ, IDF Diabetes Atlas 10th edition scientific committee. IDF DIABETES ATLAS [Internet]. 10th ed. Brussels: International Diabetes Federation; 2021 [cited 2023 Jun 29]. (IDF Diabetes Atlas). Available from: http://www.ncbi.nlm.nih.gov/books/NBK581934/
5. Basu S, Yoffe P, Hills N, Lustig RH. The Relationship of Sugar to Population-Level Diabetes Prevalence: An Econometric Analysis of Repeated Cross-Sectional Data. PLoS ONE. 2013 Feb 27;8(2):e57873.
6. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023. Diabetes Care. 2022 Dec 12;46(Supplement_1):S140–57.
7. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 10. Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2023*. Diabetes Care. 2023 Jan 1;46(Supplement_1):S158–90.
8. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 6. Glycemic Targets: Standards of Care in Diabetes-2023. Diabetes Care. 2023 Jan 1;46(Suppl 1):S97–110.
9. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. N Engl J Med. 1993 Sep 30;329(14):977–86.
10. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). The Lancet. 1998 Sep 12;352(9131):854–65.
11. Bebu I, Schade D, Braffett B, Kosiborod M, Lopes-Virella M, Soliman EZ, et al. Risk Factors for First and Subsequent CVD Events in Type 1 Diabetes: The DCCT/EDIC Study. Diabetes Care. 2020 Jan 30;43(4):867–74.
12. Prigge R, McKnight JA, Wild SH, Haynes A, Jones TW, Davis EA, et al. International comparison of glycaemic control in people with type 1 diabetes: an update and extension. Diabet Med. 2022;39(5):e14766.
13. Brazeau AS, Mircescu H, Desjardins K, Leroux C, Strychar I, Ekoé JM, et al. Carbohydrate counting accuracy and blood glucose variability in adults with type 1 diabetes. Diabetes Res Clin Pract. 2013 Jan;99(1):19–23.
14. diaTribe [Internet]. 2018 [cited 2023 Jul 8]. 42 Factors That Affect Blood Glucose?! A Surprising Update. Available from: https://diatribe.org/42-factors-affect-blood-glucose-surprising-update
15. Cramer JA. A Systematic Review of Adherence With Medications for Diabetes. Diabetes Care. 2004 May 1;27(5):1218–24.
16. van Duinkerken E, Snoek FJ, de Wit M. The cognitive and psychological effects of living with type 1 diabetes: a narrative review. Diabet Med. 2020;37(4):555–63.
17. Adverse Events and Their Association With Treatment Regimens in the Diabetes Control and Complications Trial. Diabetes Care. 1995 Nov 1;18(11):1415–27.
18. Kalra S, Mukherjee JJ, Venkataraman S, Bantwal G, Shaikh S, Saboo B, et al. Hypoglycemia: The neglected complication. Indian J Endocrinol Metab. 2013;17(5):819–34.

19. 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 Aug 1;42(8):1593–603.

20. Beck RW, Bergenstal RM, Cheng P, Kollman C, Carlson AL, Johnson ML, et al. The Relationships Between Time in Range, Hyperglycemia Metrics, and HbA1c. J Diabetes Sci Technol. 2019 Jan 13;13(4):614–26.

21. Vigersky RA, McMahon C. The Relationship of Hemoglobin A1C to Time-in-Range in Patients with Diabetes. Diabetes Technol Ther. 2019 Feb;21(2):81–5.

22. Beck RW, Bergenstal RM, Riddlesworth TD, Kollman C, Li Z, Brown AS, et al. Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials. Diabetes Care. 2019 Mar;42(3):400–5.

23. Lu J, Ma X, Zhou J, Zhang L, Mo Y, Ying L, et al. Association of Time in Range, as Assessed by Continuous Glucose Monitoring, With Diabetic Retinopathy in Type 2 Diabetes. Diabetes Care. 2018 Nov 1;41(11):2370–6.

24. Raj R, Mishra R, Jha N, Joshi V, Correa R, Kern PA. Time in range, as measured by continuous glucose monitor, as a predictor of microvascular complications in type 2 diabetes: a systematic review. BMJ Open Diabetes Res Care. 2022 Jan;10(1):e002573.

25. Song MY, Steinhubl SR, Topol EJ. The beginning of the end of fingersticks? The Lancet. 2018 Jul 21;392(10143):203.

26. Cappon G, Vettoretti M, Sparacino G, Facchinetti A. Continuous Glucose Monitoring Sensors for Diabetes Management: A Review of Technologies and Applications. Diabetes Metab J. 2019;43(4):383.

27. Fokkert M, van Dijk P, Edens M, Barents E, Mollema J, Slingerland R, et al. Improved well-being and decreased disease burden after 1-year use of flash glucose monitoring (FLARE-NL4). BMJ Open Diabetes Res Care. 2019 Dec 9;7(1):e000809.

28. Evans M, Welsh Z, Ells S, Seibold A. The Impact of Flash Glucose Monitoring on Glycaemic Control as Measured by HbA1c: A Meta-analysis of Clinical Trials and Real-World Observational Studies. Diabetes Ther Res Treat Educ Diabetes Relat Disord. 2020 Jan;11(1):83–95.

29. Castellana M, Parisi C, Di Molfetta S, Di Gioia L, Natalicchio A, Perrini S, et al. Efficacy and safety of flash glucose monitoring in patients with type 1 and type 2 diabetes: a systematic review and meta-analysis. BMJ Open Diabetes Res Care. 2020 Jun 1;8(1):e001092.

30. Ang E, Lee ZX, Moore S, Nana M. Flash glucose monitoring (FGM): A clinical review on glycaemic outcomes and impact on quality of life. J Diabetes Complications. 2020 Jun 1;34(6):107559.

31. Al Hayek AA, Robert AA, Al Dawish MA. Effectiveness of the Freestyle Libre Flash Glucose Monitoring System on Diabetes Distress Among Individuals with Type 1 Diabetes: A Prospective Study. Diabetes Ther Res Treat Educ Diabetes Relat Disord. 2020 Apr;11(4):927–37.

32. Deshmukh H, Wilmot EG, Gregory R, Barnes D, Narendran P, Saunders S, et al. Effect of Flash Glucose Monitoring on Glycemic Control, Hypoglycemia, Diabetes-Related Distress, and Resource Utilization in the Association of British Clinical Diabetologists (ABCD) Nationwide Audit. Diabetes Care. 2020 Sep;43(9):2153–60.

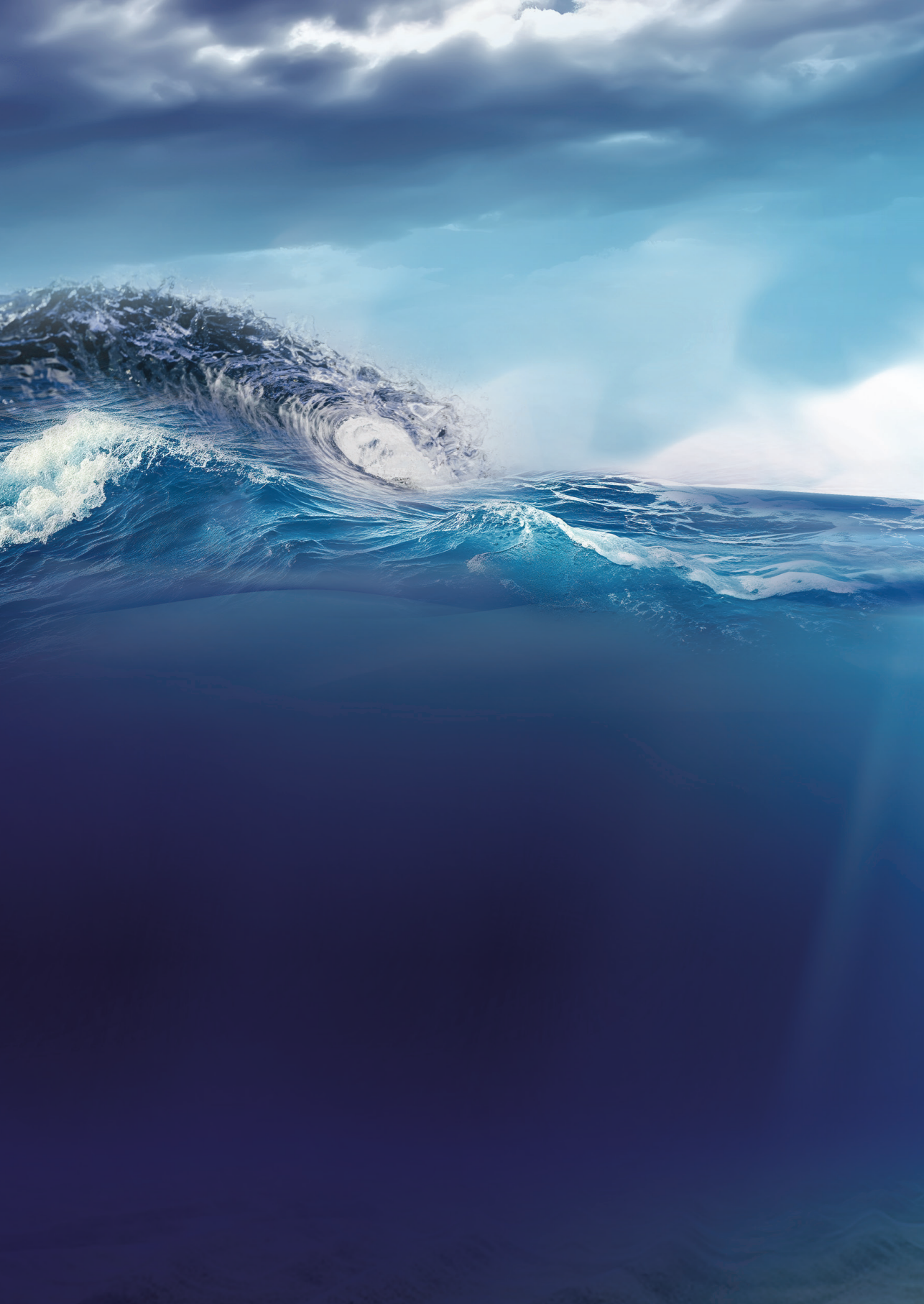
33. Charleer S, De Block C, Van Huffel L, Broos B, Fieuws S, Nobels F, et al. Quality of Life and Glucose Control After 1 Year of Nationwide Reimbursement of Intermittently Scanned Continuous Glucose Monitoring in Adults Living With Type 1 Diabetes (FUTURE): A Prospective Observational Real-World Cohort Study. Diabetes Care. 2020 Feb 1;43(2):389–97.

34. Tyndall V, Stimson RH, Zammitt NN, Ritchie SA, McKnight JA, Dover AR, et al. Marked improvement in HbA1c following commencement of flash glucose monitoring in people with type 1 diabetes. Diabetologia. 2019;62(8):1349–56.

35. Kesavadev J, Saboo B, Krishna MB, Krishnan G. Evolution of Insulin Delivery Devices: From Syringes, Pens, and Pumps to DIY Artificial Pancreas. Diabetes Ther. 2020 Jun;11(6):1251–69.

36. Jiao X, Shen Y, Chen Y. Better TIR, HbA1c, and less hypoglycemia in closed-loop insulin system in patients with type 1 diabetes: a meta-analysis. BMJ Open Diabetes Res Care. 2022 Apr;10(2):e002633.

37. Nederland Z. GIPdatabank.nl [Internet]. Zorginstituut Nederland; [cited 2023 Aug 3]. Available from: https://www.gipdatabank.nl/databank?infotype=h&label=00-totaal&tabel=B_01-basis&geg=gebr&item=F35



Chapter 2

Determinants of HbA1c reduction with FreeStyle Libre flash glucose monitoring (FLARE-NL 5)

A. Lameijer [1], M.J. Fokkert [2], M.A. Edens [3], R.J. Slingerland [2], H.J.G. Bilo [4,5], P.R. van Dijk[1,5]

1. University of Groningen, University Medical Center Groningen, Department of Endocrinology, Groningen, The Netherlands;
2. Isala, Department of Clinical Chemistry, Zwolle, The Netherlands;
3. Isala, Department of Innovation and Science, Zwolle, The Netherlands;
4. University of Groningen, University Medical Center Groningen, Department of Internal Medicine, Groningen, The Netherlands;
5. Isala, Diabetes Research Center, Zwolle, The Netherlands.

Abstract

Aim

To identify factors predicting HbA1c reduction in patients with diabetes mellitus (DM) using FreeStyle Libre Flash Glucose Monitoring (FSL-FGM).

Methods

Data from a 12-month prospective nation-wide FSL registry were used and analysed with multivariable regression. For the present study we included patients with hypoglycaemia unawareness or unexpected hypoglycaemias (n= 566) and persons who did not reach acceptable glycaemic control (HbA1c > 70 mmol/mol (8.5%)) (n= 294). People with other indications for use, such as sensation loss of the fingers or individuals already using FSL-FGM or rtCGM, were excluded (37%).

Results

Eight hundred and sixty persons (55% male with a mean age of 46.7 (±16.4) years) were included. Baseline HbA1c was 65.1 (±14.5) mmol/mol (8.1±1.3%), 75% of the patients had type 1 DM and 37% had microvascular complications. Data concerning HbA1c was present for 482 (56.0%) at 6 months and 423 (49.2%) persons at 12 months. A significant reduction in HbA1c (≥ 5 mmol/mol (0.5%)) was present in 187 (22%) persons. For these persons, median HbA1c reduction was -9.0 [-13.0, -4.0] mmol/mol (-0.82 [-1.19, -0.37]%) at 6 months and -9.0 [-15.0, -7.0] mmol/mol (-0.82 [-1.37, -0.64]%) at 12 months. In multivariable regression analysis with age, gender and SF-12 physical and mental component scores as covariates, only baseline HbA1c was significant: -0.319 (SE 0.025; $p < 0.001$; $R^2 = 0.240$ for the model). In exploratory analysis among subgroups with different indications for FSL-FGM use (hypoglycaemia unawareness or persistently high HbA1c) and persons with a significant HbA1c decrease over the study period, baseline HbA1c remained the only significant predictor.

Conclusions

Among the variables we analysed in the present study, only high HbA1c at baseline predicts significant HbA1c reduction during FSL-CGM use.

Introduction

Accurate glucose monitoring is of utmost importance for persons with diabetes mellitus (DM) in order to achieve optimal metabolic control and thus avoid or delay the development of micro- and macrovascular complications, and maintain quality of life [1,2]. HbA1c is considered to render a reasonably accurate representation of the degree of metabolic control: the lower the HbA1c, the better the average glucose control. However, low HbA1c levels are often accompanied with an increased occurrence of hypoglycaemic episodes. Finding a good balance between adjusting insulin doses, energy intake, and other lifestyle factors influencing blood glucose levels is therefore important.

Classically, self-measurement of blood glucose (SMBG) is based on fingerprick testing. However SMBG only provides information about a single timepoint, and often is painful and cumbersome. Therefore, during the last decades, realtime continuous glucose monitoring (rt-CGM) has been introduced. This system allows a semi-continuous insight, not only in glucose concentrations, but also in trends in time. Furthermore, when combined with continuous subcutaneous insulin infusion (CSII), it allows automated alarms and even adjustments of insulin doses according to the registered interstitial glucose concentrations. During the last years, Flash Glucose Monitoring (FGM) using the Free Style Libre (FSL, Abbott) system was introduced as an alternative for SMBG. The FSL-FGM consists of a sensor, via a needle inserted in the interstitial fluid, and as a patch placed on the back of the upper-arm. Upon scanning the sensor with a reader device it provides semi-continuous information about interstitial glucose concentrations. A recent study showed reasonable accuracy of FSL-FGM arm sensor readings demonstrated against capillary values [3].

Several studies demonstrated that the use of FSL-CGM results in better glycaemic control among persons with type 1 and type 2 DM. Tyndall *et al.* reported among 900 persons with type 1 DM a mean HbA1c reduction of 4 mmol/mol (0.37%) during a period of 245 days with FSL-FGM [4]. Nana *et al.* showed that initiation of FSL-FGM in their hospital (n=90) resulted in a mean HbA1c decrease of 7 mmol/mol (0.64%) over a mean follow-up time of 4.6 months [5]. Recently, our research group reported the one-year results of the nation-wide prospective registry of FSL-FGM use in the Netherlands (FLAsh monitor Registry in The Netherlands, FLARE-NL). Besides a mean HbA1c reduction of 4 mmol/mol (0.37%) (even with less reported hypoglycaemic periods), there was also a reduction in work absenteeism rate, diabetes related hospital admissions, and a marked improvement in quality of life (QoL) [6]

It should be noted however, that the suitable target population most likely to benefit from the FSL-FGM with regards to HbA1c improvement is not yet known. Of course, it stands to reason to expect the largest improvement in users with the highest baseline HbA1c

levels. Indeed, in the study by Tyndall *et al.* higher baseline HbA1c (≥58 mmol/mol (7.5%)) was a predictor of an HbA1c fall of ≥5 mmol/mol (0.5%), whilst older age at diagnosis was independently associated with non-response [4].

As such, the aim of the present study is therefore to provide more evidence to identify patients who are likely to benefit from the use of FSL-FGM with regard to their HbA1c levels. For this purpose we used data from the Flash monitor registry in the Netherlands (FLARE-NL), a nation-wide prospective registry of persons with DM using FSL-FGM.

Patients and methods

The FLARE-NL registry has a prospective, observational design and aimed to assess the effects of use of the FSL-FGM on clinically relevant endpoints, with emphasis on HbA1c (primary outcome), but also changes in frequency and severity of hypoglycaemia, Health Related Quality of Life (HRQoL), and experienced disease burden over a period of 1 year [7]. The study protocol was registered at the Dutch trial register (www.trialregister.nl (NTR6212)). Outcomes for all participants are published previously. The aim of the present analysis was to investigate, in a post-hoc analysis, variables that predict HbA1c decline among persons with type 1 DM during use of FSL-FGM.

Adults (≥18 years) with DM using insulin were eligible for participation in the FLARE-NL registry. All subjects were treated by a hospital-based diabetes team, had a health insurance with the Dutch insurance company Zilveren Kruis (ZK) and belonged to one or more pre-specified targets groups. The definitions of these target groups (indications for FSL-FGM use) were formulated in cooperation with a patient panel and the Dutch diabetes patient organisation, the Diabetes Vereniging Nederland (DVN). These original indications were described in detail previously. For the present analyses we only included persons with hypoglycaemia unawareness (156, original indication number 1), unexpected hypoglycaemias despite an average of 6 or more measurements per day (410, original indication number 2) and persons who did not reach acceptable glycaemic control, as evidenced by a mean HbA1c > 70 mmol / mol (8.5%) over the year preceding the inclusion (294, original indication number 3). As such, from the available population of 1365 subjects, 19 (original indication number 4 i.e. individuals with sensation loss of the fingers), 57 (original indication number 5 i.e. individuals with occupational hazards), 45 (original indication number 6 i.e. persons already using rt-CGM), 100 (original indication number 7 i.e. individuals already using FSL) and 284 (individuals with multiple indications for FSL) subjects (in total 505) were excluded. Therefore, 860 subjects (63%) of the initial total study population were included in the present analyses.

Detailed information concerning the FLARE-NL registry has been published previously [7]. In brief, the departments of Internal Medicine and/or Diabetes Centers of all 95 hospitals in the Netherlands were invited to include individuals based on the inclusion criteria as described above. At baseline, informed consent of the intended FSL-FGM user was obtained. Next, the participant received a link to fill out the various questionnaires in the online registry. The healthcare provider filled out the data necessary for the registry. These data included demographics (age, gender), type of DM, indication for participation, level of HbA1c (preceding 4 values), presence of microvascular (neuropathy, nephropathy, retinopathy) or macrovascular complications, frequency of SMBG, number of DM-related hospitalizations, number of hypoglycaemic events, absenteeism rate and working day losses or reduced functioning due to DM. Furthermore, participants were asked to complete questionnaires related to HRQoL including the 12-Item Short Form Health Survey ^{v2} (SF-12; physical and component scores (PCS and MCS) were calculated) and the 3-level version of EuroQol 5D (EQ-5D-3L; with scores on a tariff scale and a visual analogue scale (VAS)) [8–10].

After 6 and 12 months participants and healthcare providers were asked to report HbA1c results from the preceding 6 months, In addition, participants were asked to report changes in presence of complications, the number of diabetes-related hospitalizations in the previous period, hypoglycaemias (<3 mmol/L) in three months before filling out questionnaires, work absenteeism rate in prior 6 months or reduced functioning (including sports performance) due to dysregulation of DM, and the HRQoL questionnaires.

Results are expressed as mean (with standard deviation (SD)) or median (with interquartile range [IQR]) for normally distributed and non-normally distributed data, respectively. Normality was examined with Q-Q plots. Variables with a skewed distribution were $\log_{10}$ transformed before analysis. We defined a clinically significant HbA1c decrease as a HbA1c difference of ≥ 5 mmol/mol (0.5%) between baseline and the last available HbA1c concentration, according to the NICE guideline, the analysis by Tyndall *et al.* and taking into account the documented variability in HbA1c measurements [11,12].

Univariate analyses for correlation were performed to investigate the association between the difference in HbA1c over the study period and other variables. Variables with a *p* value <0.1, not corrected for multiple testing, were checked for confounding by performing partial correlation analyses. Next, multivariable linear regression analysis (simultaneous entry method) was performed to investigate associations between the difference in HbA1c over the study period as dependent variable and multiple independent covariates. Age, gender, baseline HbA1c and baseline SF-12 MCS and PCS scores were included as covariates in the multivariate model with the difference in HbA1c as dependent variable, based

on previous literature [13]. Furthermore, covariates were included in the multivariable model in case the *p* value was ≤ 0.1 in the univariate analysis. The models were checked for collinearity.

As exploratory analysis, uni- and multivariable analyses were repeated in subgroups: (I) persons who started FSL use because of frequent unexpected hypoglycaemia, or hypoglycaemia unawareness, (II) persons who started FSL use because of inability to reach acceptable glycaemic control and (III) among persons who, during the 1-year duration of the FSL registry study, reached a clinically relevant HbA1c reduction.

A two-sided *p* value < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS software (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.).

Results

Baseline characteristics of the 860 subjects included in the present analysis are presented in Table 1. In brief, 470 (54.7%) was male, mean age was 46.7 (±16.4) years, 643 (74.8%) persons had type 1 DM, 161 (18,7%) type 2 DM and 56 (6,5%) other forms of DM. Baseline HbA1c was 65.1 (±14.5) mmol/mol (8.1±1.3%). Three hundred and sixteen (36.7%) patients had a history of microvascular complication(s) at baseline and 125 (14.5%) a history of macrovascular complication(s).

In the total population, data concerning HbA1c was present for 482 (56.0%) at 6 months and 423 (49.2%) at 12 months. For these patients, the median change in HbA1c was -3.0 [-9.0, 1.0] (-0.27 [-0.82, 0.09]%) and -3.0 [-8.0, 2.0] mmol/mol (-0.27 [-0.73, 0.18]%) at 6 and 12 months respectively. A significant reduction of HbA1c (of ≥ 5 mmol/mol (0.5%)) was present in 187 (22%) persons. For these persons the median HbA1c reduction was -9.0 [-13.0, -4.0] mmol/mol (-0.82 [-1.19, -0.37]%) at 6 months and -9.0 [-15.0, -7.0] mmol/mol (-0.82 [-1.37, -0.64]%) at 12 months.

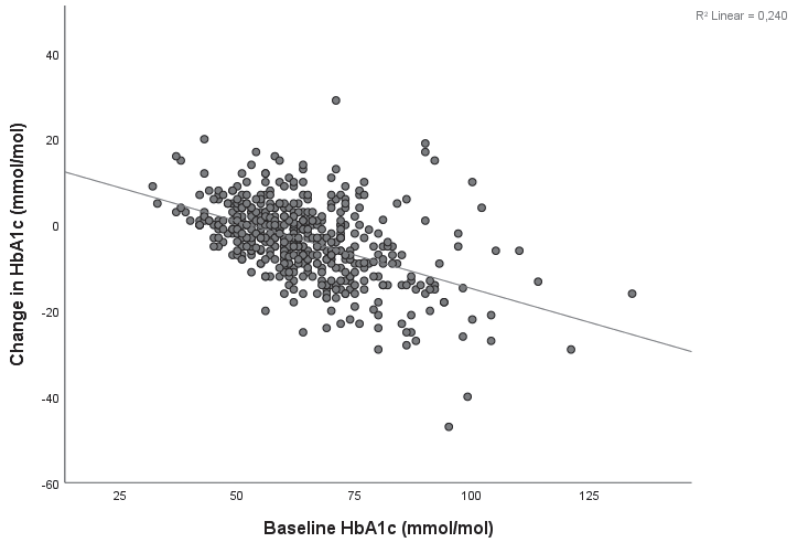
Besides baseline HbA1c (r = -0.490, p<0.001) (Figure 1) none of the variables in table 1 was significantly associated with delta HbA1c over the study period in univariate analysis (data not shown). In multivariable analysis (see Table 2) with age, gender, SF-12 PCS and MCS scores as other covariates, only baseline HbA1c proved to be the significant predictor: -0.319 (SE 0.025, p<0.001; R^2= 0.240 for the model).

Table 1. Baseline characteristics of all persons (n=860) included in the present analysis

	All persons
Male gender, n (%)	470 (54.7)
Age	46.7 (16.4)
HbA1c (mmol/mol)	65.1 (14.5)
HbA1c (%)	8.1 (1.3)
Strips use per day, n	6.1 (3.1)
Presence of any hypoglycaemic events in past 6 months, yes, n (%)	799 (92.9)
Absenteeism rate in past 6 months, yes, n (%)	147 (17.1)
Hospital admissions in past 12 months, yes, n (%)	120 (14.0)
Type of diabetes	
Type 1 diabetes	643 (74.8)
Type 2 diabetes	161 (18.7)
LADA	39 (4.5)
MODY	4 (0.5)
Other forms of diabetes	13 (1.5)
Therapy	
Insulin monotherapy	702 (81.6)
Insulin and OBGLD	158 (18.4)
Complications	
Presence of microvascular complications, n (%)	316 (36.7)
Neuropathy, n (%)	163 (19.0)
Albuminuria, n (%)	168 (19.5)
Retinopathy, n (%)	173 (20.1)
Presence of macrovascular complications, n (%)	125 (14.5)
Angina pectoris, n (%)	23 (2.7)
PCI, n (%)	33 (3.8)
Myocardial infarction, n (%)	21 (2.4)
CABG, n (%)	24 (2.8)
TIA, n (%)	16 (1.9)
CVA, n (%)	12 (1.4)
Peripheral arterial disease, n (%)	35 (4.1)
QoL	
SF-12 PCS	50.5 [44.6, 54.1]
SF-12 MCS	48.9 [40.3, 56.4]
EQ5D Dutch tariff	0.84 [0.77, 1.00]
EQ5D VAS	71.0 [61.0, 81.0]

Data in the second column are presented as number (%), mean (SD) or median [25, 75th percentile]. Abbreviations: CABG, coronary artery bypass grafting; CVA, cerebral vascular event; MCS, mental component scale; OBGLD, oral blood glucose lowering drugs; PCI, percutaneous coronary intervention; PCS, physicial component scale; TIA, transient ischemic attack.

Figure 1. Relationship between baseline HbA1c and delta HbA1c



The relationship between baseline HbA1c concentrations and the 12-month change in HbA1c following start of FSL-FGM (n=423). Pearson r -0,490, p<0.001.

In exploratory multivariable analysis among the subgroups of persons who started FSL-FGM because of hypoglycaemia unawareness (group I), persistently high HbA1c (group II) and persons who had reached a significant HbA1c reduction over the study period (group III), baseline HbA1c remained the only predictor of the difference in HbA1c over the study period (See Supplement).

Table 2. Multivariable analysis for delta HbA1c

	Unstandardized B (SE)	p-value
Age (years)	- 0.023 (0.024)	0.331
Gender (1=male)	0.121 (0.708)	0.917
Baseline HbA1c mmol/mol	**-0.319 (0.025)**	<0.001
SF-12 PCS	-0,028 (0.049)	0.245
SF-12 MCS	0.030 (0.034)	0.384

Multivariable linear regression model. Explained variance R^2= 0.240. Significant outcome presented in bold.

Discussion

In this study we aimed to identify factors that are associated with improvement of HbA1c among persons with DM using FSL-FGM. In both the total population and in different subgroups (i.e. patients with hypoglycaemia unawareness, persistently high HbA1c or significant HbA1c reduction over study period) baseline HbA1c was the single factor predictive of HbA1c decline.

In our previous study, that reported changes in HbA1c when using FSL-FGM and included a larger (though more unselected) subset of patients included in the Dutch FSL-FGM registry, the greatest HbA1c decline was measured in the group with inadequate glycaemic control (HbA1c > 70 mmol/mol (8.5%)) (6). The current study emphasizes this and does not identify other predictors of HbA1c decline. Tyndall *et al.* presented a comparable strong negative correlation between baseline HbA1c and subsequent change in HbA1c (r −0.479) with FSL-FGM use among 900 patients with type 1 DM [13]. Similar to Tyndall *et al.* we found no association between age or sex and change in HbA1c. Furthermore, we found no relation between change in HbA1c and type of DM, number of strips used per day (SMBG) prior to start of FSL-FGM, presence or absence of micro- or macrovascular complications, and quality of life.

Interestingly, we did not observe an association between the frequency of self-monitoring of blood glucose prior to FSL-FGM use and the decrease in HbA1c. Nevertheless, the amount of SMBG with fingerpricks is often used as a criterion for reimbursement of FSL-FGM (also in the Netherlands [14]). In the study by Tyndall *et al.* persons who performed SMBG prior to FSL-FGM use fewer than four times per day more often had a significant fall in HbA1c as compared to persons who did not: 67.7% vs. 45.3% ($p<0.01$). Dunn *et al*. showed a clear association between frequency of FSL-FGM glucose scans and improvement in glycaemic parameters (consistent across different countries) [15]. Although hypothetical, this may implicate that (I) for a proportion of patients the use of FSL-FGM stimulates self-control (and thereby improvement of glycaemic control can be achieved) and (II) therefore the amount of SMBG with finger pricks prior to FSL-FGM use is not a valid criterion for FSL-FGM reimbursement.

Obviously, differences in study populations and health-care settings should be taken into consideration when comparing our results with other studies. In the study population of Tyndall *et al*. FSL-FGM was funded by the NHS (since 2017) for all persons who were using intensive insulin therapy and agreed to scan glucose levels at least six times a day. In the present study, however, patients had to finance half of the cost of the FSL-FGM themselves, because at that time the FSL-FGM was not reimbursed by the Dutch healthcare authorities

and insurance companies. This resulted in a high drop-out rate; financial constraints were the most reported reason (55%). Although speculative, differences in reimbursement criteria may have resulted in a more determined population and thus more pronounced HbA1c reductions. Recently, the Dutch Institute of Care (ZorgInstituut Nederland, ZIN) published their decision on FSL-FGM, allowing use by the vast majority of people with type 1 DM and a selected group of people with type 2 DM [14]. It will be important to assess the eventual effects of this sweeping decision of use on eventual outcomes, amongst others HbA1c levels.

Other limitations of this study should be mentioned. First and foremost, this study lacks a control group. Many data were missing in this real life database. Since participation in the registry was voluntary, efforts to gain (more) information only partly succeeded. In addition, the present population is not extensively characterized. For instance, our dataset lacks data concerning age at diagnosis. As older age at diagnosis was associated with HbA1c non-response in the study by Tyndall *et al*. non-measured variables cq. confounding should be taken into consideration when interpreting this study. Furthermore, the use of strips per day prior to start of FSL-FGM was used as a proxy of frequency of SMBG in the current study. Although this difference may be a little bit semantic here, it could have resulted in an overestimation of the frequency of SMBG. As data were patient-reported, recall bias may be present. Importantly, the current population was a selection of the original FLARE-NL database, which may implicate selection bias. Finally, as participants had to finance half of the costs of the FSL-FGM themselves; this inevitably will contribute to selection bias, since the actual participants probably will be more affluent than the average DM population, at least in the Netherlands.

Conclusions

In summary, a high baseline HbA1c is associated with a more pronounced HbA1c decrease with FSL-FGM use. No other predictive factors of clinically important reduction in HbA1c levels could be identified in this study; both in the total study population and in different subgroups.

Abbreviations

(CABG) Coronary Artery Bypass Grafting, (CGM) Continuous Glucose Monitoring, (CVA) Cerebral Vascular Event, (DM) Diabetes Mellitus, (DVN) Diabetes Vereniging Nederland, (EQ-5D-3L) The 3-level version of EuroQol 5, (FLARE-NL) FLAsh monitor Registry in The Netherlands, (FSL-FGM) Free Style Libre Flash Glucose Monitor, (HRQoL) Health Related

Quality of Life, (IQR) Interquartile Range, (LADA) Latent Autoimmune Diabetes in Adults, (MODY) Maturity-Onset Diabetes of the Young, (OBGLD) Oral Blood Glucose Lowering Drugs, (PCI) Percutaneous Coronary Intervention, (Rt-CGM) Real time Continuous Glucose Monitoring, (SD) Standard Deviation, (SF-12^{v2}) 12-Item Short Form Health Survey^{v2}, (SMBG) Self-Monitoring of Blood Glucose, (TIA) Transient Ischemic Attack, (ZK) Zilveren Kruis (Insurance company).

Funding Statement

This study was supported by an unconditional grant from the Stichting Achmea Gezondheidszorg (SAG). The SAG is an innovation fund of health insurance company Zilverenkruis . The manufacturer of the Free Style Libre (Abbott) did not provide any finances for the proposed study and did not have any influence on study design, nor on definition of the target groups or the study objectives.

References

1. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:854–65.
2. Nathan DM, Cleary PA, Backlund J-YC, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–53. https://doi.org/10.1056/NEJMoa052187.
3. Fokkert MJ, van Dijk PR, Edens MA, Abbes S, de Jong D, Slingerland RJ, et al. Performance of the FreeStyle Libre Flash glucose monitoring system in patients with type 1 and 2 diabetes mellitus. BMJ Open Diabetes Res Care 2017;5:e000320. https://doi.org/10.1136/bmjdrc-2016-000320.
4. Tyndall V, Stimson RH, Zammitt NN, Ritchie SA, McKnight JA, Dover AR, et al. Marked improvement in HbA1c following commencement of flash glucose monitoring in people with type 1 diabetes. Diabetologia 2019;62:1349–56. https://doi.org/10.1007/s00125-019-4894-1.
5. Nana M, Moore SL, Ang E, Lee ZX, Bondugulapati LNR. Flash glucose monitoring: Impact on markers of glycaemic control and patient-reported outcomes in individuals with type 1 diabetes mellitus in the real-world setting. Diabetes Res Clin Pract 2019;157:107893. https://doi.org/10.1016/j.diabres.2019.107893.
6. Fokkert M, van Dijk P, Edens M, Barents E, Mollema J, Slingerland R, et al. Improved well-being and decreased disease burden after 1-year use of flash glucose monitoring (FLARE-NL4). BMJ Open Diabetes Res Care 2019;7. https://doi.org/10.1136/bmjdrc-2019-000809.
7. Fokkert MJ, Damman A, van Dijk PR, Edens MA, Abbes S, Braakman J, et al. Use of FreeStyle Libre Flash Monitor Register in the Netherlands (FLARE-NL1): Patient Experiences, Satisfaction, and Cost Analysis. Int J Endocrinol 2019;2019:4649303. https://doi.org/10.1155/2019/4649303.
8. Ware J, Kosinski M, Keller S. A 12-Item Short-Form Health Survey: Construction of Scales and Preliminary Tests of Reliability and Validity. Med Care 1996;34:220–33.
9. M. Van Reenen and B. Janssen, EQ-5D-3L User Guide: Basic Information on How to Use the EQ-5D-3L Instrument, EuroQol Research Foundation, Rotterdam, Netherlands, 2015. n.d.
10. L. M. Lammers, P. F. M Stalmeijer, J. McDonnell et al., “Kwaliteit van leven meten in economische evaluaties: het Nederlands EQ-5D-tarief,” Nederlands Tijdschrift Voor Geneeskunde, vol. 149, no. 28, pp. 1574–1578, 2005. n.d.
11. Lenters-Westra E, Weykamp C, Schindhelm RK, Siebelder C, Bilo HJ, Slingerland RJ. One in Five Laboratories Using Various Hemoglobin A1c Methods Do Not Meet the Criteria for Optimal Diabetes Care Management. Diabetes Technol Ther 2011;13:429–33. https://doi.org/10.1089/dia.2010.0148.
12. Internal Clinical Guidelines Team. Type 2 Diabetes in Adults: Management. London: National Institute for Health and Care Excellence (UK); 2015 Dec. (NICE Guideline, No. 28.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK338142/. n.d.
13. Tyndall V, Stimson RH, Zammitt NN, Ritchie SA, McKnight JA, Dover AR, et al. Marked improvement in HbA1c following commencement of flash glucose monitoring in people with type 1 diabetes. Diabetologia 2019. https://doi.org/10.1007/s00125-019-4894-1.
14. https://www.zorginstituutnederland.nl/publicaties/standpunten/2019/12/10/fgm n.d.
15. Dunn TC, Xu Y, Hayter G, Ajjan RA. Real-world flash glucose monitoring patterns and associations between self-monitoring frequency and glycaemic measures: A European analysis of over 60 million glucose tests. Diabetes Res Clin Pract 2018;137:37–46. https://doi.org/10.1016/j.diabres.2017.12.015.

Supplemental material

A. Univariate analyses among different subgroups

	Subgroup I (n=566)	**Subgroup II (n=294)**	**Subgroup III (n=187)**
Gender (male = 1)	-0.024	0.040	0.093
Age (years)	-0.035	0.016	0.096
HbA1c (mmol/mol)	**-0.474****	**-0.313****	**-0.552****
Strips use per day (n)	**0.103**	-0.090	0.030
Presence of any hypoglycaemic events in past 6 months (yes)	-0.056	-0.011	**0.247****
Work absenteeism in past 6 months (yes)	-0.055	0.032	**-0.185***
Hospital admissions in past 12 months (yes)	-0.056	-0.002	- 0.108
Type of diabetes			
Type 1 diabetes	0.038	-0.011	**0.137**
Type 2 diabetes	-0.038	-0.005	**-0.205****
LADA	-0.007	0.023	0.120
MODY	-0.087	**0.162***	-0.025
Other forms of diabetes	0.033	-0.112	-0.113
Therapy			
Insulin monotherapy (yes)	-0.058	-0.142	0.031
Complications			
Presence of microvascular complications (yes)	**-0.097**	**0.028**	**-0.149***
Presence of macrovascular complications (yes)	-0.011	-0.065	0.004
QoL			
SF-12 PCS	0.027	0.021	0.079
SF-12 MCS	0.032	0.036	0.051
EQ5D Dutch tariff	0.010	-0.095	0.061
EQ5D VAS	0.064	-0.074	0.107

* p<0.05 ** p<0.01. Bold: p<0.1. NA: not applicable. Subgroups: (I) persons who started FSL use because of frequent unexpected hypoglycaemia or hypoglycaemia unawareness, (II) persons who started FSL use because of inability to reach acceptable glycaemic control and (III) persons who reached a significant HbA1c reduction during the 1-year duration of the FSL registry study.

B. Multivariable regression analysis for HbA1c among subgroups
Subgroup 1: Persons who started FSL use because of frequent unexpected hypoglycaemia or hypoglycaemia unawareness.

	Unstandardized B (SE)	p-value
Age (years)	-0.001 (0.025)	0.971
Male gender (1=male)	-0.177 (0.743)	0.812
HbA1c mmol/mol	-0.379 (0.039)	<0.001
Strips use per day	0.097 (0.146)	0.504
Presence of microvascular complications (yes)	-0.329 (0.845)	0.697
SF-12 MCS	0.024 (0.036)	0.503
SF-12 PCS	-0.004 (0.054)	0.943

Explained variance R^2= 0.236

Subgroup 2: Persons who started FSL use because of inability to reach acceptable glycaemic control.

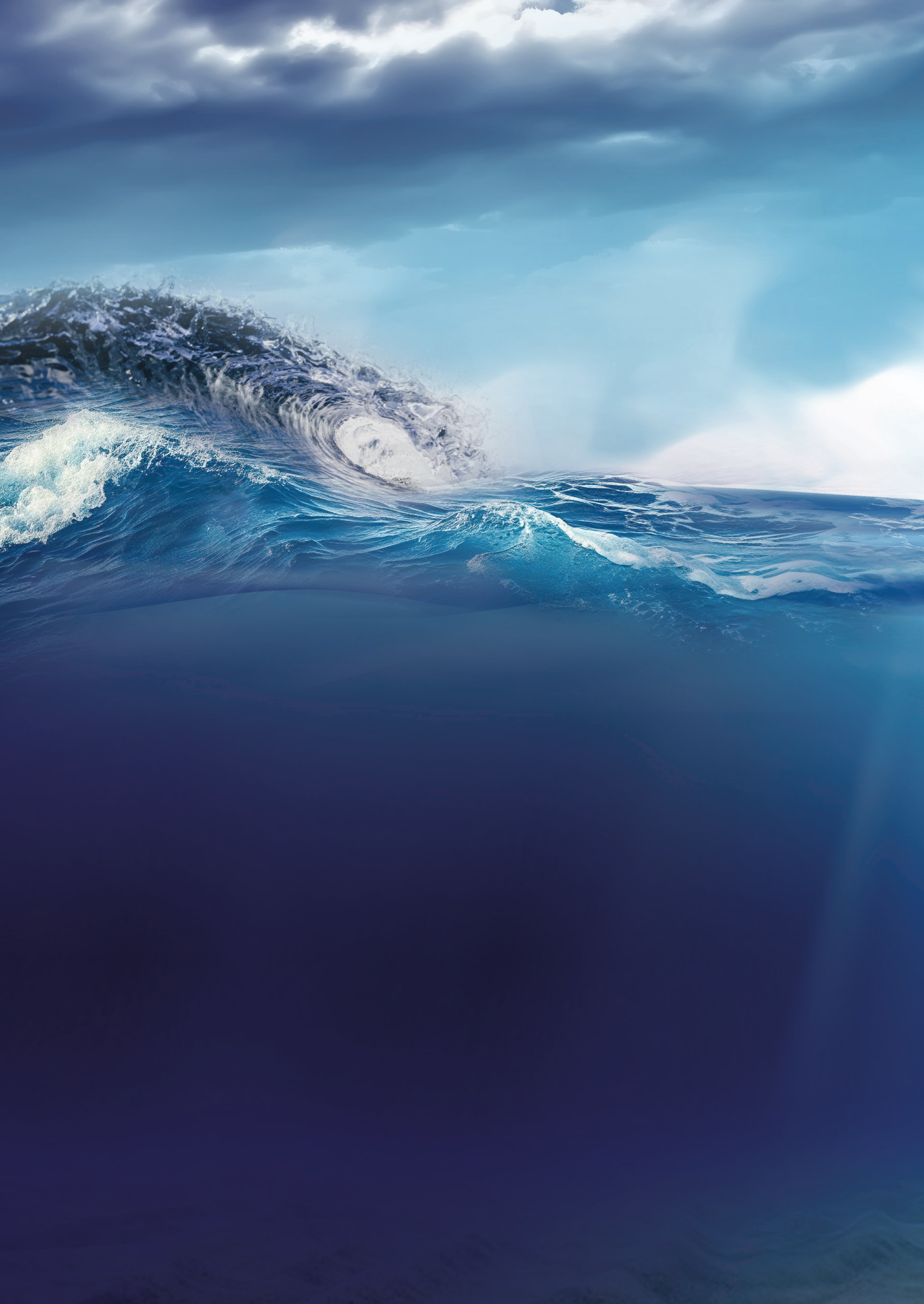
	Unstandardized B (SE)	p-value
Age (years)	-0.030 (-0.059)	0.616
Male gender (1=male)	0.289 (1.642)	0.861
HbA1c mmol/mol	-0.274 (0.070)	<0.001
MODY	17.6 (10.1)	0.084
Presence of microvascular complications (yes)	0.663 (1.735)	0.703
SF-12 MCS	0.017 (0.082)	0.837
SF-12 PCS	-0.033 (0.115)	0.777

Explained variance R^2= 0.123

Subgroup 3: Persons with HbA1c reduction over study period.

	Unstandardized B (SE)	p-value
Age (years)	0.030 (0.025)	0.220
Male gender (1=male)	0.868 (0.663)	0.192
HbA1c mmol/mol	-0.256 (0.025)	<0.001
Presence of any hypoglycaemic events in past 6 months (yes)	3.329 (1.781)	0.064
Work absenteeism	-1.808 (0.912)	0.048
Presence of microvascular complications (yes)	-0.839 (0.742)	0.260
Type 1 diabetes	1.817 (1.449)	0.211
Type 2 diabetes	-0.635 (1.645)	0.700
SF-12 MCS	0.019 (0.034)	0.575
SF-12 PCS	-0.048 (0.046)	0.301

Explained variance R^2= 0.377



Chapter 3

Two-year use of flash glucose monitoring is associated with sustained improvement of glycemic control and quality of life (FLARE-NL 6)

Annel Lameijer, MD,[1] Marion Fokkert, BSc,[2] Mireille Edens, PhD,[3] Reinold O.B. Gans, MD PhD,[4] Henk J.G. Bilo, MD PhD FRCP,[4,5] Peter R. van Dijk, MD PhD[1]

1. University of Groningen, University Medical Center Groningen, Department of Endocrinology, Groningen, The Netherlands;
2. Isala, Department of Clinical Chemistry, Zwolle, The Netherlands;
3. Isala, Department of Innovation and Science, Zwolle, The Netherlands;
4. University of Groningen, University Medical Center Groningen, Department of Internal Medicine, Groningen, The Netherlands;
5. Isala, Diabetes Research Center, Zwolle, The Netherlands.

Abstract

Introduction

The FreeStyle Libre (FSL) is a flash glucose monitoring (FGM) system. Previously the Flash Monitor Register in the Netherlands (FLARE-NL-4) study demonstrated positive effects of FSL-FGM use during one year on glycemic control, quality of life and disease burden among persons with diabetes mellitus (DM). The present follow-up study assesses the effects of FSL-FGM after two years.

Research Design and Methods

Patients included in the FLARE-NL4 study who continued FSL-FGM during the one-year study period were invited to participate (n=687). Data were collected using questionnaires (the SF-12^{v2} and EQ-5D-3L for quality of life), including self-reported HbA1c.

Results

A total of 342 patients agreed to participate: mean age 48.0 (±15.6) years, 52% men and 79.5% type 1 DM. HbA1c decreased from 60.7 (95%CI 59.1, 62.3) mmol/mol before the use of FSL-FGM to 57.3 (95%CI 55.8, 58.8) mmol/mol after one year and 57.8 (95%CI 56.0, 59.5) after two years. At the end of the two-year follow-up period, 260 (76%) persons still used the FSL-FGM and 82 (24%) had stopped. Main reason for stopping FSL-FGM was financial constraints (55%). Concerning the whole two-year period, there was a significant HbA1c decrease among persons who continued FSL-FGM (-3.5 mmol/mol (95%CI -6.4, -0.7)), while HbA1c was unaltered compared to baseline among persons who stopped FSL-FGM (-2.4 mmol/mol (95%CI -7.5, 2.7)): difference between groups 2.2 (95%CI -1.3, 5.8) mmol/mol. After two years, continued FSL-FGM users had a higher SF-12 mental component score (MCS), a higher EQ-5D Dutch tariff score and felt less often anxious or depressed, compared to persons who discontinued FSL-FGM.

Conclusions

Although the considerable number of non-responders limit generalizability, this study suggests that persons who continue to use FSL-FGM for two years may experience sustained improvement of glycemic control and quality of life.

Significance of the study

What is already known about this subject?

- Use of a FreeStyle Libre flash glucose monitoring (FSL-FGM) system is often associated with (short-term) improved glycemic control and quality of life.

What are the new findings?

- This study demonstrates that use of FSL-FGM for two years is associated with sustained improvement of (self-reported) HbA1c.
- Persons who continued FSL-FGM for at least two years, experience improvements in quality of life as compared to persons who stopped FSL-FGM use.
- In this study, financial constraints were the main reason for stopping FSL-FGM.

How might these results change the focus of research or clinical practice?

- This study is one of the first to emphasize the valuable impact of FSL-FGM use in clinical practice over a longer period of time.

Introduction

During the last decades real-time Continuous Glucose Measurement (rt-CGM) has been introduced to measure glucose concentrations in the interstitial fluid. Flash glucose monitoring (FGM) is a variant of rt-CGM in which the user obtains results intermittently by using a reader. In 2014, Freestyle Libre flash glucose monitoring (FSL-FGM, Abbott) was introduced. In contrast to most CGM devices, the FSL-FGM is already factory calibrated with no need for daily calibration. Compared to fingerprick testing, FSL-FGM readings can be performed painless after insertion and provide additional information about trends in glucose levels during day and night.

In order to acquire evidence on the effects, efficacy and safety of use of FSL-FGM in the Netherlands, a nation-wide registry ("FLAsh monitor REgistry - NetherLands FLARE-NL) was established in 2016 [1]. The FLARE-NL-4 study demonstrated a decrease in HbA1c (from 64 to 60 mmol/mol) over an one-year study period and, importantly, improved quality of life, decreasing rates of work absenteeism and fewer diabetes related hospital admissions [1]. These results were confirmed by other studies that also demonstrated improved glycemic control and quality of life [2–6]. However, most of these studies are hampered by a limited study period (often < one year).

In order to provide insight in the long-term use of FSL-FGM, results of two-year follow-up measurements among persons who participated in the FLARE-NL-4 study are described in the current study. Next to glycemic control, outcomes concerning quality of life and disease burden are presented.

Methods

Study design, patient selection and aims

The FLARE-NL-4 register study had a prospective, observational design. The study protocol was approved by the Medical Ethical Committee of Isala (Zwolle, The Netherlands) (METC 16.0346). Detailed information concerning the FLARE-NL registry and the one-year outcomes have been published earlier [1,7]. The present study aims to describe the effects of FSL-FGM after two years follow-up. We invited patients that participated in the one-year FLARE-NL-4 study (n=1365) who had continued FSL-FGM for a minimum of one year (n=687). Invitations to participants were send by e-mail. A total of 342 patients agreed to participate in this two-year follow-up study.

Outcomes

Primary outcome was glycemic control over the two-year study period. Furthermore, changes in health-related quality of life and disease burden were investigated and comparisons were made between persons who continued FSL-FGM for at least two years versus persons who stopped FSL-FGM before the two-year follow-up was completed. Additionally, data were analyzed for persons with type 1 and type 2 diabetes mellitus separately.

Study procedures

After informed consent was obtained, study participants received a link to report their most recent HbA1c values and to fill out the online questionnaires regarding glycemic control, quality of life and disease burden. Glycemic control was assessed using self-reported most recent HbA1c values and the number of self-reported clinically significant hypoglycemias (defined as a glucose < 3 mmol/L [8]) in the past six months, measured with FSL-FGM or fingerprick testing. Additionally, participants were asked if they had experienced any hypoglycemic event during the past six months. Quality of life in the previous year was assessed by the 3-level version of EuroQol 5D (EQ-5D-3L) and the 12-Item Short Form Health Survey ^{v2} (SF-12^{v2}). The EuroQol is a generic measure developed by researchers from 5 European countries, including The Netherlands [9]. The EQ-5D-3L is one of the most widely used instruments for measuring health-related quality of life [10]. This questionnaire consists of two parts. First, a descriptive system which comprises the following five dimensions: mobility, self-care, usual activities, pain or discomfort and anxiety or depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. Second, the EQ-5D visual analogue scale (EQ-VAS) from which a single overall score for self-rated health status can be elicited, ranging from 0 to 100 [10,11]. The EQ-5D Dutch tariff is a valuation of all possible EQ-5D-3L health states, based on estimated regression coefficients. This score ranges from 0 to 1, where 1 refers to full health and 0 refers to death [12]. The SF-12 questionnaire measures eight health dimensions, amongst others general health, limitations in physical activities because of health problems, social functioning and vitality (energy/fatigue). The Physical Component Summary (PCS) and the Mental Component Summary (MCS) are two subscales derived from the SF-12 [13]. To investigate disease burden, the number of hospitalizations related to diabetes mellitus (DM) in the previous year and work absenteeism rate in the previous six months was measured using the questionnaire. In the FLARE-NL-4 study we strived for a more value-based healthcare approach. As such, the study also focused on patient reported outcome measures (PROMs), using a list compiled in collaboration with the Dutch Diabetes Patient Association (Diabetes Vereniging Nederland; DVN) to assess the degree of disease burden experienced by the study population in relation to their DM and the usefulness of FSL-FGM. This questionnaire has been described in more detail previously

and the questions as asked in the DVN-PROM can be found in the supplemental material attached to the FLARE-NL-4 paper [1].

Statistical analyses

Categorical data were expressed as n (%). To determine if variables were normally distributed, Q-Q plots and histograms were used. Normally distributed data were expressed as mean ± standard deviation (sd) and skewed distributed data as median with interquartile range [IQR]). The Fisher's exact test was used to analyse categorical variables. The Mann-Whitney U test was used to compare continuous variables if the data were distributed skewed. Linear mixed models with Bonferroni corrections were used to calculate estimated values (with 95% confidence intervals) and to test for differences between the 3 moments in time (t=0, t=1 and t=2 years) and between groups. In the model the fixed factors continued and stopped FSL-FGM were used as determinants. The difference in scores was determined based on the b-coefficient of each particular (continued or stopped FSL-FGM use) group. Significance of the b-coefficient was investigated with the Wald test based on a $p<0.05$. The quantity of the b-coefficient, with a 95% CI, gives the difference between both treatment modalities over the study period adjusted for baseline differences. Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.). A significance level of 5% (two-sided) was used.

Results

A total of 342 persons of the invited 687 (49.8%) agreed to participate in this follow-up study. As presented in Table 1, 178 (52.0%) of participants were men, mean age was 48.0 (±15.6) years, and the majority of the population (79.5%) had type 1 DM.

Changes over time among all participants are presented in Table 2. HbA1c decreased significantly from 60.7 (95% CI 59.1, 62.3) mmol/mol before the use of FSL-FGM to 57.3 (95% CI 55.8, 58.8) mmol/mol after one year and 57.8 (95% CI 56.0, 59.5) after two years.

Concerning quality of life, the SF-12 PCS increased during the study period. The number of working days lost and the hospital admission rate was not different as compared to baseline (Table 2).

Table 1. Baseline characteristics

	All (n=342)	Continued FSL-FGM (n=260)	Stopped FSL-FGM (n=82)
Male gender, n (%)	178 (52.0)	140 (53.8)	38 (46.3)
Age, years	48.0 (15.6)	47.7 (15.8)	49.0 (15.1)
HbA1c, mmol/mol	61.2 (12.9)	62.1 (13.3)	58.2 (11.4)*
HbA1c, %	7.8 (1.2)	7.8 (1.2)	7.5 (1.0)*
Type diabetes			
Type 1 diabetes, n (%)	272 (79.5)	214 (82.3)	58 (70.7)
Type 2 diabetes, n (%)	45 (13.2)	30 (11.5)	15 (18.3)
LADA, n (%)	16 (4.7)	10 (3.8)	6 (7.3)
MODY, n (%)	2 (0.6)	1 (0.4)	1 (1.2)
Other forms of diabetes, n (%)	7 (2.0)	5 (1.9)	2 (2.4)
Complications			
Microvascular complications, n (%)	121 (35.4)	89 (34.2)	32 (39.0)
Neuropathy, n (%)	71 (20.8)**	52 (20.0)	19 (23.2)
Albuminuria, n (%)	62 (18.1)	47 (18.1)	15 (18.3)
Retinopathy, n (%)	72 (21.1)	50 (19.2)	22 (26.8)
Macrovascular complications, n (%)	50 (14.6)	38 (14.6)	12 (14.6)

Data are presented as number (%) or mean (SD). *p<0.05 **Data available for n=108 (80 persons who continued and 28 who stopped FSL-FGM).

After two years, 260 (76.0%) persons still used FSL-FGM and 82 (24.0%) had stopped before the two-year follow-up was completed. Financial constraints (54.9%) and termination of the FLARE-NL4 study (13.4%) were the main reasons for stopping FSL-FGM (Table 3). Besides a higher baseline HbA1c among persons who continued FSL-FGM there were no significant differences between groups at baseline. Among persons who continued FSL-FGM, 114 (43.8%) had reimbursement of the FSL-FGM by their healthcare insurance and 146 (56.2%) paid for the FSL-FGM themselves.

Changes over time among persons who continued and stopped FSL-FGM use are presented in Table 4. HbA1c decreased significantly over the whole two-year study period among persons who continued FSL-CGM (mean difference -3.5 mmol/mol (95% CI -6.4, -0.7)) while this was -2.4 mmol/mol (95%CI -7.5, 2.7) mmol/mol for persons who stopped FSL-FGM. The overall difference between groups was 2.2 (95%CI -1.3, 5.8) mmol/mol.

Table 2. Changes in glycemic control, quality of life and disease burden among all participants

	Baseline (A)	One year (B)	Two years (C)	B vs. A.	C vs. A.	C vs. B.
Glycemia						
HbA1c	60.7 (59.1, 62.3)	57.3 (55.8, 58.8)	57.8 (56.0, 59.5)	-3.4 (-6.1, -0.7)	-2.9 (-5.9, -0.02)	0.5 (-2.4, 3.3)
N	341	253	342			
Hypoglycemic events past six months	64.7 (55.3, 74.0)	66.3 (55.0, 77.6)	51.0 (42.1, 59.9)	1.6 (-16.2, 19.5)	-13.6 (-29.4, 2.1)	-15.3 (-32.8, 2.3)
N	325	311	294			
Quality of life						
EQ-5D-3L Dutch tariff	0.8 (0.8, 0.9)	0.9 (0.8, 0.9)	0.8 (0.8, 0.9)	0.01 (-0.03, 0.05)	0.0 (-0.04, 0.04)	-0.01 (-0.05, 0.03)
N	342	342	336			
EQ-5D-3L VAS	69.8 (67.4, 72.2)	71.7 (69.0, 74.4)	73.9 (71.0, 76.9)	1.9 (-2.5, 6.3)	4.1 (-0.5, 8.7)	2.2 (-2.6, 7.1)
N	342	342	336			
SF-12^{v2} PCS	38.2 (37.4, 38.9)	47.2 (46.2, 48.2)	46.9 (45.9, 47.9)	9.1 (7.6, 10.6)	8.7 (7.2, 10.2)	-0.4 (-2.1, 1.4)
N	342	342	342			
SF-12^{v2} MCS	48.8 (47.6, 50.1)	49.4 (48.3, 50.5)	47.5 (46.4, 48.7)	0.6 (-1.5, 2.6)	-1.3 (-3.4, 0.8)	-1.9 (-3.8, 0.03)
N	342	333	333			
Disease burden						
Hospital admissions	0.1 (0.04, 0.2)	0.1 (-0.01, 0.1)	1.3 (-2.2, 4.8)	-0.1 (-0.2, 0.1)	1.2 (-3.1, 5.5)	1.3 (-3.0, 5.6)
N	342	342	341			
Lost working days	6.0 (2.7, 9.3)	5.1 (2.2, 8.0)	5.7 (1.5, 9.9)	-0.9 (-6.3, 4.5)	-0.3 (-6.8, 5.6)	0.6 (-5.6, 6.8)
N	342	342	339			

Data are presented as mean (difference) with 95% confidence interval. HbA1c concentrations are presented in mmol/mol. Abbreviations: EQ-5D-3L, 3-level version of EuroQol 5D; EQ-VAS, EQ-visual analogue scale; MCS, Mental Component Score; PCS, Physical Component Score; SF-12^{v2}, 12-Item Short Form Health Survey^{v2}.

Table 3. Reasons for discontinuing FSL-FGM

Reason for stopping FSL-FGM	Number
Financial constraints	45 (54.9)
End of the study	11 (13.4)
Unsatisfied with ease of use	3 (3.7)
Allergy to the adhesives	3 (3.7)
Use of an alternative to FSL-FGM	3 (3.7)
Inadequate glucose regulation despite FSL-FGM	1 (1.2)
FSL-FSG is regarded unreliable	1 (1.2)
Undefined	15 (18.3)
Total	82 (100)

Data are presented as number (%).

The number of hypoglycemic events was not different after two years of follow-up in both groups. At two years, the percentage of persons who reported at least one hypoglycemic event during the past 6 months was higher in the continued vs. stopped FSL-FGM use group (88.5% vs. 79.3%, p<0.05, Supplemental Table 4).

The SF-12 MCS remained stable among persons who continued FSL-FGM use over te two-year period. Over the whole study period, the difference in SF-12 MCS change, as well as the difference in change of the EQ-5D Dutch tariff score, was significantly better among persons who continued FSL-FGM use as compared to persons who stopped (difference: 5.0 (95% CI 2.7, 7.3) and 0.07 (95% CI 0.02, 0.1), respectively). The SF-12 PCS increased in both groups. After two years, the percentage of persons who reported work absenteeism and hospital admission was lower for persons who continued FSL-FGM as compared to persons who stopped FSL-FGM (5.0% vs 14.6%, p<0.01 and 5.4% vs. 12.2%, p<0.05, respectively, presented in Supplemental Table 4).

Supplemental Tables 2 and 3 show the effects of use of FSL-FGM on changes in glycemic control, quality of life and disease burden for persons with type 1 DM (n=272) and type 2 DM (n=45) separately. The significant changes described above concerning the SF-12 PCS, the SF-12 MCS and the EQ-5D Dutch tariff score among persons who continued FSL-FGM were also observed among persons with type 1 DM who continued FSL-FGM.

Table 4. Changes in glycemic control, quality of life and disease burden among persons who continued FSL-FGM for at least two years and persons who had stopped FSL-FGM before the two-year follow-up period was completed

	Baseline (A)		One year (B)		Two years (C)
	Continued FSL-FGM	**Stopped FSL-FGM**	**Continued FSL-FGM**	**Stopped FSL-FGM**	**Continued FSL-FGM**
Glycemia					
HbA1c	62.4 (60.8, 64.0)	59.0 (56.2, 61.8)	58.3 (56.8, 59.7)	56.4 (53.8, 58.9)	58.9 (57.2, 60.6)
N	259	82	191	62	260
Hypoglycemic events	61.8 (52.8, 70.8)	67.5 (51.1, 83.9)	60.3 (49.7, 70.9)	72.3 (52.4, 92.2)	51.3 (43.0, 59.7)
N	250	75	242	69	229
Quality of life					
EQ-5D-3L VAS	70.9 (69.5, 74.2)	67.7 (63.6, 71.9)	73.8 (71.2, 76.4)	69.6 (64.9, 74.2)	74.8 (71.9, 77.6)
N	260	82	260	82	265
EQ-5D Dutch tariff	0.85 (0.83, 0.87)	0.84 (0.80, 0.88)	0.87 (0.85, 0.90)	0.84 (0.80, 0.88)	0.88 (0.85, 0.90)
N	260	82	260	82	256
SF-12^{v2} PCS	37.6 (36.9, 38.3)	38.7 (37.5, 40.0)	47.4 (46.4, 48.4)	47.1 (45.3, 48.8)	47.2 (46.2, 48.2)
N	260	82	260	82	260
SF-12^{v2} MCS	50.1 (48.8, 51.3)	47.6 (45.4, 49.9)	51.1 (50.0, 52.1)	47.8 (45.9, 49.6)	50.0 (48.9, 51.1)
N	260	82	254	79	254
Disease burden					
Hospital admissions	0.1 (0.07, 0.2)	0.1 (-0.04, 0.2)	0.1 (0.03, 0.2)	0.02 (-1.0, 0.1)	2.1 (-1.4, 5.5)
N	260	82	260	82	259
Lost working days	4.9 (1.6, 8.1)	7.2 (1.4, 13.0)	2.2 (-0.7, 5.0)	8.0 (3.0, 13.1)	3.4 (-0.7, 7.5)
N	260	82	260	82	257

Data are presented as mean (difference) with 95% confidence interval. HbA1c concentrations are presented in mmol/mol. Abbreviations: EQ-5D-3L, 3-level version of EuroQol 5D; EQ-VAS, EQ-visual analogue scale; MCS, Mental Component Score; PCS, Physical Component Score; SF-12^{v2}, 12-Item Short Form Health Survey^{v2}.

As presented in Supplemental Table 5, when comparing outcomes of the DVN-PROM questionnaire after two-years of follow-up between persons who continued or stopped FSL-FGM, persons who continued FSL-FGM reported their hypoglycemic episodes were less severe (81.9% vs. 11.4%), performed more adjustments of insulin dose (81.9% vs. 30.4%), had a better understanding of glucose fluctuations (94.5% vs. 7.6%), more often measured their glucose levels prior to traffic participation (65.4% vs. 39.2%) and participated more frequent in sports activities (42.9% vs. 3.8%). Importantly, persons who used the FSL-CGM felt more secure (77.2% vs. 8.9%). Furthermore, people with whom they live together were less concerned about the glucose regulation of their partner (65.0% vs. 9.0%).

	C vs. A		C vs. B		Overall difference
Stopped FSL-FGM	Continued FSL-FGM	Stopped FSL-FGM	Continued FSL-FGM	Stopped FSL-FGM	between groups
56.7 (53.6, 59.8) 82	-3.5 (-6.4, -0.7)	-2.4 (-7.5, 2.7)	0.6 (-2.1, 3.4)	0.3 (-4.6, 5.2)	2.2 (-1.3, 5.8)
50.7 (35.0, 66.4) 65	-10.5 (-25.4, 4.5)	-16.8 (-44.5, 10-.9)	-9.0 (-25.5, 7.5)	-21.6 (-52.5, 9.4)	0.6 (-17.2, 18.4)
74.8 (71.9, 77.6) 80	2.9 (-1.7, 7.4)	5.3 (-2.8, 13.4)	0.9 (-3.8, 5.7)	3.5 (-5.0, 12.0)	1.7 (-4.2, 7.6)
0.81 (0.77, 0.85) 80	0.02 (-0.02, 0.06)	-0.03 (-0.10, 0.04)	0.002 (-0.04, 0.04)	-0.03 (-0.1, 0.04)	0.07 (0.02, 0.1)
46.5 (44.8, 48.3) 82	9.6 (8.1, 11.0)	7.8 (5.2, 11.5)	-0.2 (-1.9, 1.5)	-0.5 (-3.5, 2.5)	0.7 (-1.4, 2.7)
45.0 (43.1, 47.0) 79	-0.03 (-2.1, 2.0)	-2.6 (-6.2, 1.1)	-1.1 (-2.9, 0.8)	-2.7 (-6.1, 0.6)	5.0 (2.7, 7.3)
0.6 (-5.5, 6.7) 82	1.9 (-2.3, 6.1)	0.5 (-7.0, 8.0)	2.0 (-2.2, 6.2)	0.6 (-6.9, 8.1)	2.1 (-1.4, 5.5)
8.0 (3.0, 13.1) 82	-1.5 (-7.9, 4.9)	0.9 (-10.5, 12.2)	1.2 (-4.9, 7.3)	0.01 (-10.8, 10.8)	-4.6 (-13.0, 3.7)

Discussion

In the present study we describe follow-up data concerning FSL-FGM derived from a nationwide registry. HbA1c decreased significantly after two years of follow-up. Among persons who continued FSL-FGM during the whole two-year period there was a HbA1c reduction of -3.5 mmol/mol (95% CI -6.4, -0.7) mmol/mol while HbA1c remained unchanged among persons who stopped FSL-FGM. Importantly, we observed significant (sustained) improvements in read-outs of quality of life (SF-12 MCS, EQ-5D Dutch tariff score and levels of anxiety and depression) among persons who continued FSL-FGM compared to persons who stopped.

The observed association between HbA1c improvement and FSL-FGM use is in line with recent publications [1,2,5,14–16]. The current study adds by demonstrating a significant HbA1c improvement over a two-year period among FSL-FGM users. We were unable to demonstrate a difference in change of HbA1c over the two-year study period between persons who continued FSL-FGM and those who stopped before the two-year follow-up was completed. We hypothesize that this is related to the fact that the group of persons who stopped FSL-FGM had already used FSL-FGM for at least one year, which likely has provided them with more insight into their glucose regulation (and fluctuations) [14]. We expect this 'learning effect' to have a positive influence on glycemic control during the following months after discontinuation of FSL-FGM.

The number of reported hypoglycemic events after two years of FSL-FGM use was not different as compared to baseline. However, the percentage of persons who detected at least one episode of hypoglycemia was higher among FSL-FGM users, compared to persons who stopped. Importantly, in the DVN-PROM questionnaire FSL-FGM users reported their hypoglycemic episodes to be less severe. Charleer *et al*. found a higher number of perceived hypoglycemic episodes among FSL-FGM users as compared to the period when they used SMBG, possibly related to more detailed insight in glucose fluctuations with FSL-FGM, and a reduction of self-reported severe hypoglycemia [15].

Overall, continuing FSL-FGM was associated with improved quality of life, as compared to patients stopping FSL-FGM. Other studies have highlighted the positive influence of FSL-FGM on quality of life among persons with DM [4–6,15–19]. Overend *et al*. reported a positive impact of FSL-FGM on psychological wellbeing and self-esteem as patients with type 1 DM experienced more control over their blood glucose values. The authors attributed a reduction in frequency, severity and fear of hypoglycemia as the key positive impact on wellbeing [17]. In line with these observations, the current study showed an improvement in understanding of glucose fluctuations among FSL-FGM users, and possibly related to this enhancement, they felt more secure. The positive impact of FSL-FGM on quality of life is also supported by the results of the EQ-5D-3L questionnaire: among patients who continued use of FSL-FGM for two years, the reported level of anxiety and depression was significantly lower compared to patients who stopped FSL-FGM (Supplemental Table 3).

In the FLARE-NL-4 study a decrease in work absenteeism rate (within six months) and the annual diabetes-related hospital admission rate was observed. Previous studies also showed a decrease in diabetes-related work absenteeism and hospital admissions after initiation of FSL-FGM [5,15]. The current follow-up study showed that stopping FSL-FGM was associated with a deterioration in the percentage of persons who reported work absenteeism and diabetes-related hospital admissions, compared to persons who continued FSL-FGM.

Of note, during the one-year FLARE-NL4 study patients had to finance half of the cost of the FSL-FGM themselves if they did fulfill the Dutch criteria for FSL-FGM reimbursement, and during the second year of use this group (56% of persons) had to pay the full amount (approximately 120 euros per month) themselves. This study demonstrated that 24% of persons stopped FSL-FGM use after the first year. For these persons financial constraints were the main reason for stopping.

This study has several limitations. Data were obtained from a nationwide registry and follow-up questionnaires and, as such, lacked a comparator. As discussed, a considerable number of persons included in the original FLARE-NL4 study did not participate in the present follow-up study, potentially resulting in selection bias. Importantly, in this study we did not have access to FSL-FGM data, therefore information concerning glucose metrics such as time in range is not available. Furthermore, information about the frequency of glucose monitoring, known to be associated with better glycemic control [20], was not included in the database. As data were patient-reported, recall bias may be present. The exact time point when participants stopped using FSL-FGM is unknown.

Since the majority of participants had to finance the costs of the FSL-FGM themselves after one year, this inevitably will contribute to selection bias, since the actual participants probably will be more affluent than the average DM population, which may be related to a higher quality of life among FSL-FGM users. Patients used FSL-FGM for several indications, as described in the FLARE-NL4 study [1].

Finally, it should be mentioned that one of the questionnaires (the 'DVN-PROM') used in this study has not been validated yet. Although the DVN-PROM was non-validated, we still find the results valuable and useful as it represents the results of collaboration with a DM patient organization and FSL-FGM users, and the questions asked are very recognizable for both caregivers and patients.

Conclusion

Although a considerable number of persons from the original FLARE-NL4 study were unavailable for this follow-up study, the data suggest that FSL-FGM use by persons with DM for a two-year period was associated with sustained improvement of self-reported Hba1c compared to the period before FSL-FGM use. Aspects of experienced quality of life were higher among persons who continued FSL-FGM as compared to persons who discontinued FSL-FGM before the two-year follow-up period was completed. Financial motives were the main reason for discontinuing FSL-FGM.

Abbreviations

(DM) diabetes mellitus, (DVN-PROM) Diabetes Vereniging Nederland Patient Reported Outcome Measure, (EQ-5D-3L) The 3-level version of EuroQol 5D, (EQ-VAS) EQ-5D visual analogue scale, (FLARE-NL) FLAsh monitor Registry in The Netherlands, (FSL-FGM) FreeStyle Libre Flash Glucose Monitor, (HRQOL) health-related quality of life, (IQR) Interquartile Range, (PRO) patient-reported outcome, (SAG) Stichting Achmea Gezondheidszorg, (SF-12^{v2}) 12-Item Short Form Health Survey ^{v2}

Funding statement

The FLARE-NL registry was funded by an unconditional grant (number Z699) from the Stichting Achmea Gezondheidszorg (SAG). The SAG is an innovation fund of health insurance company Zilverenkruis. The manufacturer of the FreeStyle Libre (Abbott) did not provide any finances for the proposed study and did not have any influence on study design, nor on definition of the target groups or the study objectives.

References

1. Fokkert M, van Dijk P, Edens M, Barents E, Mollema J, Slingerland R, et al. Improved well-being and decreased disease burden after 1-year use of flash glucose monitoring (FLARE-NL4). BMJ Open Diabetes Res Care 2019;7. https://doi.org/10.1136/bmjdrc-2019-000809.
2. Castellana M, Parisi C, Di Molfetta S, Di Gioia L, Natalicchio A, Perrini S, et al. Efficacy and safety of flash glucose monitoring in patients with type 1 and type 2 diabetes: a systematic review and meta-analysis. BMJ Open Diabetes Res Care 2020;8. https://doi.org/10.1136/bmjdrc-2019-001092.
3. Mancini G, Berioli MG, Santi E, Rogari F, Toni G, Tascini G, et al. Flash Glucose Monitoring: A Review of the Literature with a Special Focus on Type 1 Diabetes. Nutrients 2018;10. https://doi.org/10.3390/nu10080992.
4. Rouhard S, Buysschaert M, Alexopoulou O, Preumont V. Impact of flash glucose monitoring on glycaemic control and quality of life in patients with type 1 diabetes: A 18-month follow-up in real life. Diabetes Metab Syndr 2020;14:65–9. https://doi.org/10.1016/j.dsx.2019.12.007.
5. Deshmukh H, Wilmot EG, Gregory R, Barnes D, Narendran P, Saunders S, et al. Effect of Flash Glucose Monitoring on Glycemic Control, Hypoglycemia, Diabetes-Related Distress, and Resource Utilization in the Association of British Clinical Diabetologists (ABCD) Nationwide Audit. Diabetes Care 2020:dc200738. https://doi.org/10.2337/dc20-0738.
6. Ang E, Lee ZX, Moore S, Nana M. Flash glucose monitoring (FGM): A clinical review on glycaemic outcomes and impact on quality of life. J Diabetes Complications 2020;34:107559. https://doi.org/10.1016/j.jdiacomp.2020.107559.
7. Fokkert MJ, Damman A, van Dijk PR, Edens MA, Abbes S, Braakman J, et al. Use of FreeStyle Libre Flash Monitor Register in the Netherlands (FLARE-NL1): Patient Experiences, Satisfaction, and Cost Analysis. Int J Endocrinol 2019;2019. https://doi.org/10.1155/2019/4649303.
8. Group IHS. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2017;40:155–7. https://doi.org/10.2337/dc16-2215.
9. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208. https://doi.org/10.1016/0168-8510(90)90421-9.
10. M. Van Reenen and B. Janssen, EQ-5D-3L User Guide: Basic Information on How to Use the EQ-5D-3L Instrument, EuroQol Research Foundation, Rotterdam, Netherlands, 2015. n.d.
11. L. M. Lammers, P. F. M Stalmeijer, J. McDonnell et al., “Kwaliteit van leven meten in economische evaluaties: het Nederlands EQ-5D-tarief,” Nederlands Tijdschrift Voor Geneeskunde, vol. 149, no. 28, pp. 1574–1578, 2005. n.d.
12. Lamers LM, Stalmeier PFM, McDonnell J, Krabbe PFM, van Busschbach JJ. [Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff]. Ned Tijdschr Geneeskd 2005;149:1574–8.
13. Ware J, Kosinski M, Keller S. A 12-Item Short-Form Health Survey: Construction of Scales and Preliminary Tests of Reliability and Validity. Med Care 1996;34:220–33.
14. Evans M, Welsh Z, Ells S, Seibold A. The Impact of Flash Glucose Monitoring on Glycaemic Control as Measured by HbA1c: A Meta-analysis of Clinical Trials and Real-World Observational Studies. Diabetes Ther 2020;11:83–95. https://doi.org/10.1007/s13300-019-00720-0.
15. Charleer S, De Block C, Van Huffel L, Broos B, Fieuws S, Nobels F, et al. Quality of Life and Glucose Control After 1 Year of Nationwide Reimbursement of Intermittently Scanned Continuous Glucose Monitoring in Adults Living With Type 1 Diabetes (FUTURE): A Prospective Observational Real-World Cohort Study. Diabetes Care 2020;43:389–97. https://doi.org/10.2337/dc19-1610.

16. Tyndall V, Stimson RH, Zammitt NN, Ritchie SA, McKnight JA, Dover AR, et al. Marked improvement in HbA1c following commencement of flash glucose monitoring in people with type 1 diabetes. Diabetologia 2019;62:1349–56. https://doi.org/10.1007/s00125-019-4894-1.

17. Overend L, Simpson E, Grimwood T. Qualitative analysis of patient responses to the ABCD FreeStyle Libre audit questionnaire. Pract Diabetes 2019;36:45–50. https://doi.org/10.1002/pdi.2213.

18. Kramer G, Michalak L, Müller UA, Kloos C, Werner C, Kuniss N. Association between Flash Glucose Monitoring and Metabolic Control as well as Treatment Satisfaction in Outpatients With Diabetes Type 1. Exp Clin Endocrinol Diabetes 2019:a-0875-3988. https://doi.org/10.1055/a-0875-3988.

19. Al Hayek AA, Al Dawish MA. The Potential Impact of the FreeStyle Libre Flash Glucose Monitoring System on Mental Well-Being and Treatment Satisfaction in Patients with Type 1 Diabetes: A Prospective Study. Diabetes Ther 2019;10:1239–48. https://doi.org/10.1007/s13300-019-0616-4.

20. Lameijer A, Lommerde N, Dunn TC, Fokkert MJ, Edens MA, Kao K, et al. Flash Glucose Monitoring in the Netherlands: increased monitoring frequency is associated with improvement of glycemic parameters. Diabetes Res Clin Pract 2021:108897. https://doi.org/10.1016/j.diabres.2021.108897.

Supplemental material

Supplemental Table 1. Changes in glycemic control, quality of life and disease burden among persons with type 1 DM who continued FSL-FGM for at least two years and persons who had stopped FSL-FGM before the two-year follow-up period was completed

	Baseline (A)		One year (B)		Two years (C)
	Continued FSL-FGM	**Stopped FSL-FGM**	**Continued FSL-FGM**	**Stopped FSL-FGM**	**Continued FSL-FGM**
Glycemia					
HbA1c	62.5 (60.8, 64.2)	58.9 (55.7, 62.2)	58.5 (57.0, 60.1)	56.0 (53.1, 59.0)	58.7 (56.8, 60.6)
N	213	58	156	43	214
Hypoglycemic events	66.1 (56.0, 76.3)	73.0 (53.6, 92.4)	60.5 (49.0, 72.0)	85.5 (63.0, 108.0)	52.7 (43.3, 62.2)
N	208	57	202	53	190
Quality of life					
EQ-5D-3L VAS	72.7 (70.3, 75.1)	70.4 (65.8, 75.0)	73.6 (70.7, 76.6)	70.8 (65.2, 76.5)	75.6 (72.4, 78.8)
N	214	58	214	58	211
EQ-5D Dutch tariff	0.85 (0.83, 0.88)	0.84 (0.80, 0.89)	0.88 (0.86, 0.90)	0.86 (0.81, 0.90)	0.88 (0.86, 0.91)
N	214	58	214	58	211
SF-12^{v2} PCS	37.8 (37.0, 38.6)	39.8 (38.2, 41.3)	48.0 (47.0, 49.0)	48.3 (46.3, 50.3)	47.7 (46.7, 48.8)
N	214	58	214	58	214
SF-12^{v2} MCS	50.2 (48.8, 51.6)	45.7 (43.0, 48.3)	51.4 (50.2, 52.5)	47.9 (45.6, 50.1)	50.2 (49.0, 51.4)
N	214	58	209	55	209
Disease burden					
Hospital admissions	0.1 (0.1, 0.2)	0.1 (-0.1, 0.2)	0.1 (-0.001, 0.1)	0.03 (-0.08, 0.2)	2.5 (-1.8, 6.7)
N	214	58	214	58	213
Lost working days	4.5 (1.2, 7.9)	5.9 (-0.6, 12.4)	1.6 (-1.6, 4.7)	11.3 (5.2, 17.4)	4.1 (-0.9, 9.2)
N	214	58	214	58	211

Data are presented as mean (difference) with 95% confidence interval. HbA1c concentrations are presented in mmol/mol. Abbreviations: EQ-5D-3L, 3-level version of EuroQol 5D; EQ-VAS, EQ-visual analogue scale; MCS, Mental Component Score; PCS, Physical Component Score; SF-12^{v2}, 12-Item Short Form Health Survey^{v2}.

	C vs. A		C vs. B		Overall difference
Stopped FSL-FGM	**Continued FSL-FGM**	**Stopped FSL-FGM**	**Continued FSL-FGM**	**Stopped FSL-FGM**	**between groups**
57.3 (53.6, 60.9)	-3.8 (-6.9, -0.7)	-1.7 (-7.6, 4.2)	0.1 (-2.8, 3.0)	1.2 (-4.5, 6.9)	1.4 (-2.7, 5.5)
58					
52.4 (33.8, 71.1)	-13.4 (-30.3, 3.5)	-20.6 (-53.4, 12.2)	-7.8 (-25.9, 10.4)	-33.1 (-68.7, 2.6)	0.3 (-20.6, 21.2)
49					
72.0 (65.9, 78.2)	2.9 (-2.0, 7.7)	1.6 (-7.7, 11.0)	2.0 (-3.3, 7.3)	1.2 (-9.0, 11.4)	3.6 (-3.3, 10.5)
56					
0.83 (0.79, 0.88)	0.03 (-0.01, 0.07)	-0.01 (-0.1, 0.1)	0.0 (-0.04, 0.04)	-0.02 (-0.1, 0.1)	0.05 (0.0, 0.1)
56					
47.1 (45.0, 49.1)	9.9 (8.3, 11.5)	7.3 (4.2, 10.4)	-0.3 (-2.1, 1.6)	-1.2 (-4.7, 2.3)	0.69 (-1.6, 3.0)
58					
44.4 (42.0, 46.7)	0.0 (-2.2, 2.3)	-1.3 (-5.6, 3.1)	-1.1 (-3.2, 0.9)	-3.5 (-7.5, 0.5)	5.8 (3.2, 8.5)
55					
0.2 (-8.0, 8.3)	2.4 (-2.8, 7.6)	0.1 (-9.9, 10.1)	2.4 (-2.8, 7.6)	0.1 (-9.8, 10.1)	2.3 (-6.9, 11.5)
58					
11.2 (1.5, 20.9)	-0.4 (-7.8, 7.0)	5.2 (-9.0, 19.5)	2.5 (-4.7, 9.8)	-0.1 (-14.1, 13.8)	-7.1 (-18.0, 3.9)
58					

Supplemental Table 2. Changes in glycemic control, quality of life and disease burden among persons with type 2 DM who continued FSL-FGM for at least two years and persons who had stopped FSL-FGM before the two-year follow-up period was completed

	Baseline (A)		One year (B)		Two years (C)
	Continued FSL-FGM	**Stopped FSL-FGM**	**Continued FSL-FGM**	**Stopped FSL-FGM**	**Continued FSL-FGM**
Glycemia					
HbA1c	65.2 (59.7, 70.6)	62.5 (54.8, 70.1)	59.4 (53.7, 65.1)	62.7 (54.1, 71.3)	62.6 (56.8, 68.5)
N	30	15	23	10	30
Hypoglycemic events	27.5 (15.3, 39.6)	36.3 (15.7, 57.0)	37.2 (26.2, 48.3)	22.1 (3.0, 41.2)	45.6 (18.9, 72.4)
N	26	9	27	9	25
Quality of life					
EQ-5D-3L VAS	67.4 (59.8, 75.0)	64.4 (53.6, 75.1)	72.3 (64.1, 80.5)	61.1 (49.5, 72.3)	66.5 (58.9, 75.2)
N	30	15	30	15	30
EQ-5D Dutch tariff	0.79 (-.72, 0.86)	0.77 (0.67, 0.87)	0.78 (0.68, 0.87)	0.72 (0.59, 0.85)	0.77 (0.69, 0.89)
N	30	15	30	15	30
SF-12^{v2} PCS	36.0 (34.0, 38.0)	35.7 (32.8, 38.5)	42.1 (38.8, 45.5)	41.1 (36.4, 45.8)	43.5 (39.2, 47.8)
N	30	15	30	15	30
SF-12^{v2} MCS	47.9 (44.1, 51.5)	51.2 (46.0, 56.)	49.4 (46.3, 52.5)	48.1 (43.7, 52.5)	48.8 (45.1, 52.5)
N	30	15	30	15	30
Disease burden					
Hospital admissions	0.1 (-.0.02, 0.3)	0.0 (-0.2, 0.2)	0.3 (-0.03, 0.7)	0.0 (-0.5, 0.5)	0.2 (-1.3, 1.7)
N	30	15	30	15	30
Lost working days	9.4 (-1.8, 20.6)	4.1 (-11.8, 19.9)	1.4 (-0.8, 3.6)	0.3 (-2.8, 3.3)	0.0 (-0.5, 0.5)
N	30	15	30	15	30

Data are presented as mean (difference) with 95% confidence interval. HbA1c concentrations are presented in mmol/mol. Abbreviations: EQ-5D-3L, 3-level version of EuroQol 5D; EQ-VAS, EQ-visual analogue scale; MCS, Mental Component Score; PCS, Physical Component Score; SF-12^{v2}, 12-Item Short Form Health Survey^{v2}.

	C vs. A		C vs. B		Overall difference
Stopped FSL-FGM	**Continued FSL-FGM**	**Stopped FSL-FGM**	**Continued FSL-FGM**	**Stopped FSL-FGM**	**between groups**
52.9 (44.7, 61.1)	-2.5 (-12.1, 7.1)	-9.6 (-23.2, 4.0)	3.3 (-6.6, 13.1)	-9.8 (-24.2, 4.6)	9.7 (-0.3, 19.8)
15					
40.1 (-7.2, 87.4)	18.1 (-17.8, 54.0)	3.8 (-59.3, 66.9)	8.4 (-27.0, 43.9)	18.0 (-44.5, 80.5)	5.5 (-48.8, 59.9)
8					
72.2 (59.9, 84.5)	-0.9 (-14.8, 13.1)	7.8 (-11.9, 27.5)	-5.7 (-20.2, 8.7)	11.1 (-9.4, 31.5)	-5.7 (-20.7, 9.4)
15					
0.69 (0.54, 0.83)	-0.01 (-0.2, 0.1)	-0.08 (-0.3, 0.1)	0.01 (-0.2, 0.2)	-0.03 (-0.3, 0.2)	0.1 (-0.07, 0.27)
15					
41.2 (38.2, 44.3)	5.2 (0.8, 9.7)	7.9 (1.6, 14.1)	-0.9 (-6.4, 4.6)	2.5 (-5.3, 10.2)	-2.3 (-7.5, 3.0)
15					
46.8 (41.6, 52.0)	0.9 (-5.4, 7.3)	-4.4 (-13.4, 4.5)	-0.5 (-6.4, 5.3)	-1.3 (-9.6, 7.0)	2.0 (-4.4, 8.4)
15	30				
2.5 (0.4, 4.6)	0.07 (-1.8, 1.9)	2.5 (-0.1, 5.2)	-0.1 (-2.0, 1.8)	2.5 (-0.1, 5.2)	-2.3 (-4.9, 0.3)
15					
0.7 (-0.1, 1.4)	-9.4 (-23.3, 4.4)	-3.4 (-23.0, 16.2)	-1.4 (-4.1, 1.3)	0.4 (-3.5, 4.3)	0.7 (-0.3, 1.6)
15					

Supplemental Table 3. EQ-5D-3L scores among persons who continued FSL-FGM for at least two years or had stopped before the two-year follow-up period was completed

	Baseline			Two years		
	All (n=342)	**Continued FSL-FGM (n=260)**	**Stopped FSL-FGM (n=82)**	**All (n=331)**	**Continued FSL-FGM (n=253)**	**Stopped FSL-FGM (n=78)**
Mobility						
No problems in walking about, n (%)	277 (81.0)	210 (80.8)	67 (81.7)	262 (79.2)	201 (79.4)	61 (78.2)
Some problems in walking about, n (%)	64 (18.7)	49 (18.8)	15 (18.3)	66 (19.9)	49 (19.4)	17 (21.8)
Confined to bed, n (%)	1 (0.3)	1 (0.4)	0 (0.0)	3 (0.9)	3 (1.2)	0 (0.0)
Self-care						
No problems with self-care, n (%)	328 (95.9)	249 (95.8)	79 (96.3)	320 (96.7)	246 (97.2)	74 (94.9)
Some problems with washing or dressing, n (%)	12 (3.5)	9 (3.5)	3 (3.7)	8 (2.4)	5 (2.0)	3 (3.8)
Unable to wash or dress myself, n (%)	2 (0.6)	2 (0.8)	0 (0.0)	3 (0.9)	2 (0.8)	1 (1.3)
Usual activities						
No problems with performing usual activities, n (%)	225 (65.8)	175 (67.3)	50 (61.0)	234 (70.7)	180 (71.5)	54 (69.2)
Some problems with performing usual activities, n (%)	115 (33.6)	84 (32.3)	31 (37.8)	95 (28.7)	72 (28.7)	23 (29.5)
Unable to perform usual activities, n (%)	2 (0.6)	1 (0.4)	1 (1.2)	2 (0.6)	1 (0.4)	1 (1.3)
Pain / discomfort						
No pain or discomfort, n (%)	206 (60.2)	159 (61.2)	47 (57.3)	202 (61.0)	161 (63.6)	41 (52.6)
Moderate pain or discomfort, n (%)	127 (37.1)	94 (36.2)	33 (40.2)	118 (35.6)	85 (33.6)	33 (42.3)
Extreme pain or discomfort, n (%)	9 (2.6)	7 (2.7)	2 (2.4)	11 (3.3)	7 (2.8)	4 (5.1)
Anxiety / depression						
Not anxious or depressed, n (%)	252 (73.7)	196 (75.4)	56 (68.3)	254 (76.7)	208 (82.2)	46 (59.0)
Moderately anxious or depressed, n (%)	86 (25.1)	61 (23.5)	25 (30.5)	75 (22.7)	44 (17.4)	**31 (39.7)***
Extremely anxious or depressed, n (%)	4 (1.2)	3 (1.2)	1 (1.2)	2 (0.6)	1 (0.4)	1 (1.3)

Data are presented as number (%). Abbreviations: IQR, Interquartile Range. Significant outcome presented in bold. * $p<0.001$ as compared to persons who continued FSL-FGM.

Supplemental Table 4. Changes in the percentage of persons who reported hypoglycemic events, hospital admissions and lost working days among persons who continued FSL-FGM for at least two years and persons who had stopped FSL-FGM before the two-year follow-up period was completed

	Baseline		One year		Two years	
	Continued FSL-FGM (n=260)	**Stopped FSL-FGM (n=82)**	**Continued FSL-FGM (n=260)**	**Stopped FSL-FGM (n=82)**	**Continued FSL-FGM (n=260)**	**Stopped FSL-FGM (n=82)**
Glycemia						
Presence of any hypoglycemic event past 6 months, yes, n (%)	250 (96.2)	75 (91.5)	242 (93.1)	**69 (84.1)***	230 (88.5)	**65 (79.3)***
Disease burden						
Hospital admission past 12 months, yes, n (%)	21 (8.1)	6 (7.3)	11 (4.2)	2 (2.4)	14 (5.4)	**10 (12.2)***
Work absenteeism past 6 months, yes, n (%)	39 (15.0)	16 (19.5)	11 (4.2)	8 (9.8)	13 (5.0)	**12 (14.6)****

Data are presented as number (%). Significant outcomes presented in bold. *p<0.05 as compared to persons who continued FSL-FGM. **p<0.001 as compared to persons who continued FSL-FGM.

Supplemental Table 5. Selected results of Diabetes Vereniging Nederland patient-reported outcome measures (DVN-PROM) questionnaire comparing persons who continued FSL-FGM and persons who had stopped FSL-FGM before the two-year follow-up period was completed

	Continued FSL-FGM (n=254)	**Stopped FSL-FGM (n=79)**
Hypoglycemic episodes are less severe, n (%)	208 (81.9)	9 (11.4)*
Better understanding of glucose fluctuations, n (%)	240 (94.5)	6 (7.6)*
Feeling more secure since using FSL-FGM (or stopping, respectively), n (%)	196 (77.2)	7 (8.9)*
Performing more frequent adjustments of insulin doses, n (%)	208 (81.9)	24 (30.4)*
Always measuring glucose before participating in traffic as a driver, n (%)	166 (65.4)	31 (39.2)*
Sporting and exercising more frequently, n (%)	109 (42.9)	3 (3.8)*
House mates and family members are less worried about their glucose regulation, n (%)	165 (65.0)	7 (9.0)*

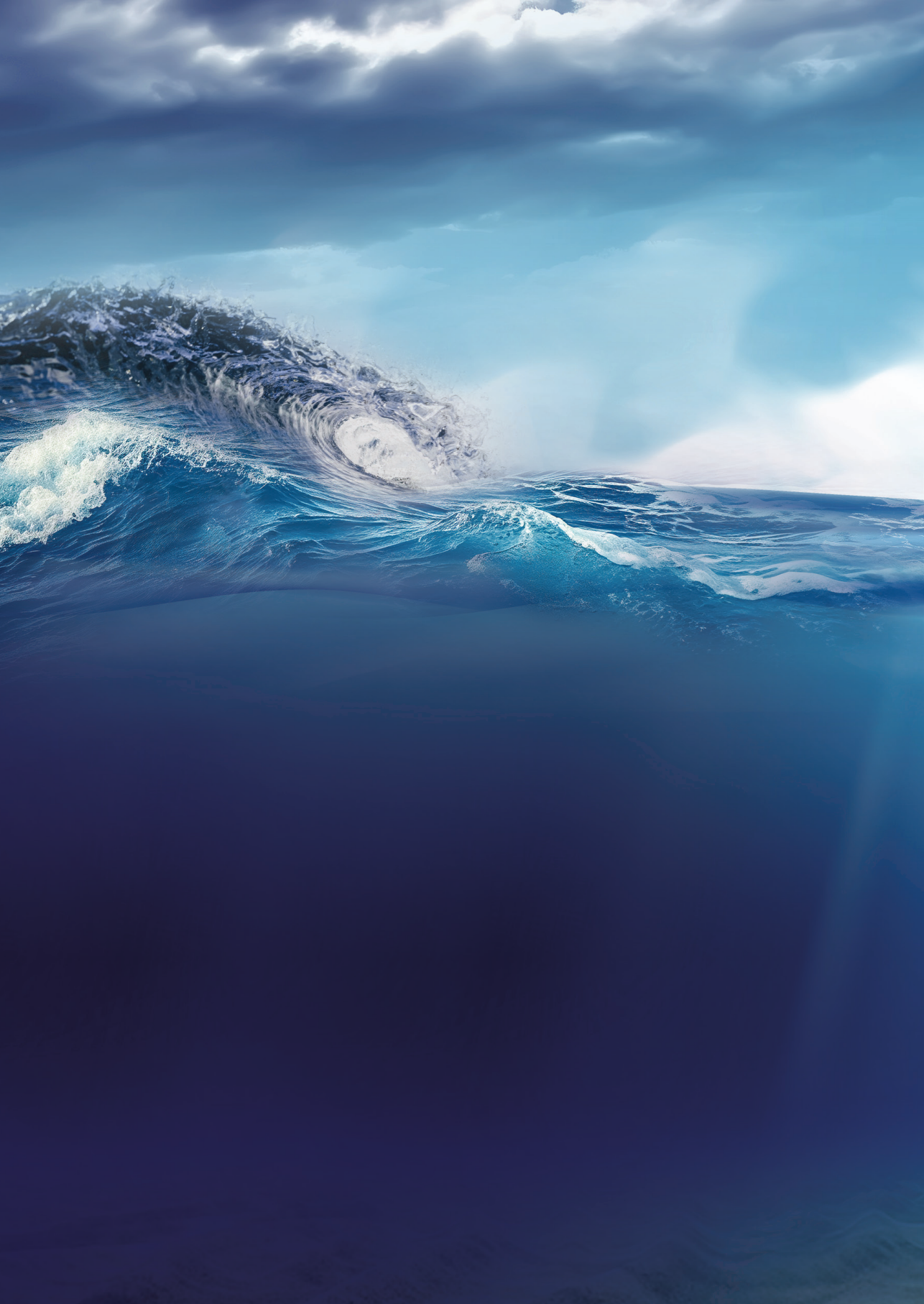
Data are presented as number (%).* p<0.0001 as compared to persons who continued FSL-FGM.

Supplemental Table 6. Changes in scores on the SF-12 subscales among persons who continued FSL-FGM for at least two years and persons who had stopped FSL-FGM before the two-year follow-up period was completed

	Baseline (A)		**One year (B)**		**Two years (C)**
	Continued FSL-FGM	**Stopped FSL-FGM**	**Continued FSL-FGM**	**Stopped FSL-FGM**	**Continued FSL-FGM**
Physical functioning	80.2 (77.0, 83.4)	84.2 (78.5, 89.9)	82.8 (79.6, 86.0)	83.5 (77.8, 89.3)	82.9 (79.8, 86.0)
N	254	79	254	79	254
Role physical	62.7 (60.0, 65.4)	59.8 (54.9, 64.7)	71.3 (68.5, 74.1)	62.0 (57.1, 67.0)	68.2 (65.4, 71.1)
N	254	79	254	79	254
Role emotional	75.0 (72.2, 77.8)	69.0 (64.0, 74.0)	80.3 (77.7, 83.0)	67.4 (62.6, 72.2)	77.7 (75.0, 80.4)
N	254	79	254	79	254
Mental health	69.1 (66.9, 71.3)	67.9 (64.0, 71.8)	75.8 (73.8, 77.8)	73.4 (69.8, 77.0)	74.7 (72.7, 76.7)
N	254	79	254	79	254
Bodily pain	83.3 (80.5, 86.0)	83.2 (78.3, 88.2)	14.2 (11.4, 16.9)	17.4 (12.5, 22.4)	85.7 (83.1, 88.3)
N	254	79	254	79	254
General health	47.1 (44.9, 49.4)	48.1 (44.1, 52.1)	52.1 (49.8, 54.3)	50.3 (46.3, 54.3)	51.0 (48.6, 53.4)
N	254	79	254	79	254
Vitality	59.2 (56.5, 61.8)	58.5 (53.7, 63.3)	64.6 (61.9, 67.2)	63.6 (58.9, 68.3)	63.4 (60.7, 66.1)
N	254	79	254	79	254
Social functioning	72.3 (69.3, 75.4)	69.3 (63.9, 74.7)	82.1 (79.3, 84.9)	75.9 (70.9, 81.0)	79.1 (76.1, 82.1)
N	254	79	254	79	254

Data are presented as mean (difference) with 95% confidence interval. SF-12^{v2}, 12-Item Short Form Health Survey^{v2}.

	C vs. A		C vs. B		Overall difference
Stopped FSL-FGM	**Continued FSL-FGM**	**Stopped FSL-FGM**	**Continued FSL-FGM**	**Stopped FSL-FGM**	**between groups**
82.3 (76.7, 87.9)	2.7 (-2.8, 8.1)	-1.9 (-11.7, 7.9)	0.1 (-5.3, 5.5)	-1.3 (-11.0, 8.5)	0.6 (-5.8, 7.0)
79					
59.5 (54.4, 64.6)	5.5 (0.7, 10.3)	-0.3 (-9.0, 8.3)	-3.1 (-8.0, 1.8)	-2.5 (-11.2, 6.2)	8.7 (2.9, 14.6)
79					
66.5 (61.6, 71.3)	2.7 (-2.0, 7.5)	-2.5 (-11.1, 6.0)	-2.6 (-7.2, 2.0)	-0.9 (-9.3, 7.4)	11.3 (5.7, 16.8)
79					
67.4 (63.7, 71.1)	5.6 (2.0, 9.3)	-0.5 (-7.0, 6.1)	-1.1 (-4.6, 2.3)	-6.0 (-12.3, 0.2)	7.3 (3.1, 11.5)
79					
81.0 (76.4, 85.7)	2.5 (-2.2, 7.1)	-2.2 (-10.5, 6.1)	71.6 (66.9, 76.2)	63.6 (55.3, 71.9)	4.7 (-0.6, 10.0)
79					
49.1 (44.8, 53.3)	3.8 (-0.1, 7.8)	0.9 (-6.1, 8.0)	-1.1 (-5.0, 2.9)	-1.3 (-8.4, 5.8)	1.9 (-2.9, 6.8)
79					
57.3 (52.5, 62.1)	4.2 (-0.4, 8.8)	-1.3 (-9.5, 7.0)	-1.2 (-5.7, 3.4)	-6.3 (-14.5, 1.9)	6.1 (0.6, 11.6)
79					
68.7 (63.3, 74.1)	6.8 (1.6, 12.0)	-0.6 (-10.0, 8.7)	-3.0 (-8.0, 2.1)	-7.3 (-16.3, 1.8)	10.5 (4.3, 16.7)
79					



Chapter 4

Commencement of Flash Glucose Monitoring is associated with a decreased rate of depressive disorders among persons with diabetes (FLARE-NL 7)

Julia J. Bakker [1], Annel Lameijer MD[1], Jose L. Flores-Guerrero MD PhD[2], Henk J.G. Bilo, MD PhD FRCP[3,4], Peter R. van Dijk, MD PhD[1]

1. University of Groningen, University Medical Center Groningen, Department of Endocrinology, Groningen, The Netherlands
2. University of Groningen, University Medical Center Groningen, Department of Nephrology, Groningen, The Netherlands
3. Isala, Diabetes Research Center, Zwolle, The Netherlands
4. University of Groningen, University Medical Center Groningen, Department of Internal Medicine, Groningen, The Netherlands

Abstract

Introduction

Depressive disorders are more common among persons with diabetes, as compared to persons without diabetes. The burden of glucose management is known to associate with depressive symptoms. This study aims to assess the effects of commencement of FreeStyle Libre Flash Glucose Monitoring (FSL-FGM) on the mental health status of persons with diabetes.

Research Design and Methods

Post-hoc analysis of data from a one-year prospective nation-wide FSL-FGM registry. Participants who used FSL-FGM for 12 months and completed the 12-Item Short Form Health Survey version 2 (SF-12^{v2}) questionnaires at baseline, 6 and 12 months were included. A SF-12^{v2} Mental Component Score (MCS) of ≤ 45 was used as cutoff to discriminate between persons with and without a depressive disorder.

Results

A total of 674 patients were included with a mean age of 48.2 (±15.8) years, 51.2% men, 78.2% type 1 diabetes (DM) and baseline HbA1c 62.8 (±13.4) mmol/mol (7.9 ± 1.2%). At baseline, 235 (34.9%) persons had a SF-12 MCS ≤ 45 while after 6 and 12 months these numbers decreased: 202 (30.0%, $p<0.01$) and 173 (25.7%, $p<0.01$). Overall MCS scores improved from 48.5 at baseline to 50.7 after 6 months and 51.3 after 12 months. In multivariable regression analysis age and MCS at baseline was associated with improvement of MCS after 12 months of FSL-FGM use.

Conclusions

This analyses suggests that use of FSL-FGM is associated with a decreased rate of depressive disorders among persons with diabetes. Future studies are needed to corroborate these findings.

Significance of the study

What is already known about this subject?

- Depressive disorders are more common among persons with diabetes, as compared to persons without diabetes.
- Use of FreeStyle Libre flash glucose monitoring (FSL-FGM) is associated with improvement of quality of life and reduced diabetes-related distress.

What are the new findings?

- This study suggests that commencement of FSL-FGM is associated with a decreased rate of depressive disorders among persons with diabetes.

How might these results change the focus of research or clinical practice?

- Persons with diabetes and comorbid depressive disorders could benefit from FSL-FGM initiation and subsequent long-term use, in terms of improvement of their mental health status.
- Future studies are needed to further evaluate the effects of FSL-FGM use on depressive disorder rates in persons with diabetes.

Introduction

With flash glucose monitoring (FGM) persons with diabetes mellitus (DM) can measure glucose concentrations in the interstitial fluid. The Free Style Libre (FSL; Abbott Diabetes Care) FGM is a factory calibrated FGM that replaces fingerprick testing by intermittent scanning of the sensor. The use of FSL-FGM results in positive effects on glycemic control and quality of life [1–5].

The prevalence of depression is reported to be 12% in persons with type 1 DM and 28% in persons with type 2 DM [6,7]. As compared to persons without diabetes this is threefold (for type 1 DM) and twofold (for type 2 DM) higher [6]. Adults with diabetes and comorbid depression have worse glycemic control and more micro- and macrovascular complications than those not diagnosed with a depressive disorder [8,9]. Intensive self-management, including (painful) fingerpricks, and insufficient insight in causes of variable glucose levels are determinants of depression in DM [10]. As FSL-FGM use alleviates the burden of diabetes self-management and provides insights in glucose excursions, its use may lead to improved mental wellbeing and lower rates of depressive disorders.

Longitudinal studies evaluating the effects of FSL-FGM initiation on depression and diabetes-related distress are scarce and show conflicting outcomes. Deshmukh et al. [11] showed reduced diabetes-related distress during 7 months of FSL-FGM use by persons with diabetes (97% type 1 DM). In another prospective cohort study, a decrease in diabetes-related distress after 12-weeks of use of FSL-FGM was described in youngsters with type 1 DM [12]. Tyndall et al. [13] demonstrated improvements with regards to total diabetes distress, regimen-related distress and emotional distress among persons with type 1 DM using FSL-FGM, although they paradoxically noticed an increase in depression and anxiety scores on the Hospital Anxiety and Depression Scale (HADS).

Given the negative impact of depression on quality of life, the potential beneficial effects of FSL-FGM on depressive disorders and conflicting (short-term) outcomes of studies evaluating the impact of FGM on mental health, the present study aims to provide more insight into the effects of long-term use of FSL-FGM on mental wellbeing and depressive disorder rates.

Methods

Study design and patient selection

This is a post-hoc analyses of data from the 'FLAsh monitor REgistry in the NetherLands' (FLARE-NL). The FLARE-NL registry had a prospective, observational design (study period June 2016 to July 2017) and aimed to assess the effects of FSL-FGM on daily life. The study protocol was approved by the Medical Ethical Committee of Isala (Zwolle, The Netherlands) (METC 16.0346). Detailed information concerning the one-year outcomes of the FLARE-NL registry have been published earlier [2,14]. In brief, adults (≥18 years) with DM using insulin were eligible for participation in the FLARE-NL registry); 1365 persons were included. For the present post-hoc analyses only persons who started FSL-FGM, continued to use it for 12 months and completed the 12-Item Short Form Health Survey version 2 (SF-12^{v2}) questionnaires at baseline, 6 and 12 months (n=674) were included. Based on previous studies, a MCS score of ≤ 45 was used as cutoff to indicate the presence of a depressive disorder [15,16].

Outcomes

Primary outcome was the difference in the rate of persons with a SF-12 MCS ≤ 45 (indicative of a depressive disorder) between baseline and 6 and 12 months after FSL-FGM initiation. Furthermore, changes in MCS over time were investigated for the total population as well as different subgroups. Finally, the association between the difference in MCS over the study period and other variables was assessed.

Study procedures

After informed consent was obtained, the healthcare provider filled out the data necessary for the registry and study participants filled out online questionnaires regarding quality of life and disease burden, including the SF-12^{v2} [17]. The SF-12^{v2} questionnaire measures eight health dimensions: physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. The Physical Component Summary (PCS) and the Mental Component Summary (MCS) are two subscales derived from the SF-12^{v2} [18]. Glycemic control during follow-up was assessed using self-reported most recent HbA1c values and the number of hypoglycemias (glucose < 3 mmol/L in the past six months).

Statistical analysis

To determine if variables were normally distributed, histograms and Q-Q plots were used. Categorical data were expressed as n (%), normally distributed data as mean ± SD and skewed distributed data as median with IQR. Pairwise t-test was used to compare the MCS after 6 and 12 months with baseline values. P-values were adjusted with the Holm method for multiple comparison. A two-sided p value < 0.05 was considered statistically significant. Univariable linear regression analyses were performed to investigate the association between the difference in MCS over the 12-month study period and other variables. Next, multivariable linear regression analysis was performed to investigate associations between the difference in MCS over the study period as dependent variable and multiple independent covariates (age, sex, baseline HbA1c, number of hypoglycemic episodes and micro- and macrovascular complications). Data were analyzed with R Statistical Software (version 4.0.3).

Results

A total of 674 persons were included in the study. As presented in Table 1, 345 (51.2%) were men and mean age was 48.2 (±15.8) years. Most persons (527 (78.2%)) had type 1 DM. Baseline HbA1c was 62.8 (±13.4) mmol/mol (7.9 ± 1.2%). Microvascular complications were present in 230 (34.1%) and macrovascular complications in 86 (12.8%) persons.

Changes in MCS are presented in Table 2. Baseline MCS was 48.5 and improved to 50.7 after 6 months and 51.3 after 12 months. Scores improved over time for both sexes, although baseline MCS was lower among women. At baseline, 235 (34.9%) participants had a SF-12 MCS ≤ 45, indicative for depressive disorder, which decreased to 202 (30.0%) after 6 months and 173 (25.7%) after 12 months ($p<0.01$). For men as well as women with a baseline MCS ≤ 45 scores improved after 6 and 12 months compared to baseline. The MCS scores after 12 months in these subgroups increased to 45.2 ± 9.2 and 43.6 ± 10.4 for men and women, respectively. Furthermore, improvement of MCS was observed in subgroups with type 1 DM and in all HbA1c subgroups (≤ 53, > 53 and > 64 mmol/mol).

Table 1. Baseline characteristics of all participants (n = 674)

Male sex, n (%)	345 (51.2)
Age, years	48.2 (15.8)
HbA1c, mmol/mol	62.8 (13.4)
HbA1c, %	7.9 (1.2)
Type of diabetes	
Type 1 DM, n (%)	527 (78.2)
Type 2 DM, n (%)	98 (14.5)
LADA, n (%)	37 (5.5)
MODY, n (%)	3 (0.4)
Other forms, n (%)	9 (1.3)
Complications	
Microvascular complications, n (%)	230 (34.1)
Neuropathy, n (%)	88 (13.1)
Albuminuria, n (%)	110 (16.3)
Retinopathy, n (%)	100 (14.8)
Macrovascular complications, n (%)	86 (12.8)
Angina pectoris, n (%)	15 (2.2)
Myocardial infarction, n (%)	22 (3.3)
PCI, n (%)	30 (4.5)
CABG, n (%)	23 (3.4)
TIA, n (%)	17 (2.5)
CVA, n (%)	14 (2.1)
Peripheral arterial disease, n (%)	32 (4.7)
Diabetes-related hospital admissions past 12 months, yes, n (%)	74 (11.0)
Diabetes-related work absenteeism past 6 months, yes, n (%)	25 (3.7)
Estimated strips use per day	2.0 [0-5.5]
Presence of any hypoglycemic events in past 6 months, n (%)	622 (92.3)
Estimated or measured number of hypoglycemic events in past 6 months	40.0 [15-80]
Therapy	
Insulin monotherapy, n (%)	575 (85.6)
OBGLD, n (%)	1 (0.1)
Insulin and OBGLD, n (%)	96 (14.3)

Data are presented as number (%), mean (SD) or median [25, 75th percentile]. Abbreviations: CABG, coronary artery bypass grafting; CVA, cerebral vascular event; DM, diabetes mellitus, LADA, latent autoimmune diabetes in adults; MODY, maturity-onset diabetes of the young; OBGLD, oral blood glucose lowering drugs; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Table 2. Changes in mental component score after 6 and 12 months of FSL-FGM use in different subgroups

	Baseline (A)	6 months (B)	12 months (C)	p-value A vs B	p-value A vs C
MCS	48.5 ± 10.2	50.7 ± 9.9	51.3 ± 9.9	<0.001	<0.001
n	674	674	674		
MCS in women	47.1 ± 10.4	48.9 ± 9.8	49.6 ± 10.2	0.03	0.003
n	329	329	329		
MCS in men	49.9 ± 9.9	52.4 ± 9.7	52.9 ± 9.2	0.001	<0.001
n	345	345	345		
MCS in persons with a baseline MCS ≤ 45	36.9 ± 6.0	43.4 ± 9.4	44.2 ± 9.9	<0.001	<0.001
n	235	235	235		
MCS in women with a baseline MCS ≤ 45	36.9 ± 6.0	42.9 ± 9.3	43.6 ± 10.4	<0.001	<0.001
n	137	137	137		
MCS in men with a baseline MCS ≤ 45	37.0 ± 6.0	44.0 ± 9.6	45.2 ± 9.2	<0.001	<0.001
n	98	98	98		
MCS in persons with a baseline MCS > 45	54.8 ± 5.5	54.6 ± 7.6	55.1 ± 7.4	0.87	0.87
n	439	439	439		
MCS in persons with type 1 DM	48.3±10.3	50.6 ± 10.0	51.5 ± 9.9	<0.001	<0.001
n	527	527	527		
MCS in persons with type 2 DM	48.5 ± 10.2	50.4 ± 9.7	50.5 ± 9.4	0.49	0.46
n	98	98	98		
MCS in persons with a HbA1c ≤ 53 mmol/mol	48.4± 10.5	51.7 ± 10.0	51.9 ± 9.9	0.005	0.004
n	176	176	176		
MCS in persons with a HbA1c > 53 mmol/mol	48.6 ± 10.1	50.4 ± 9.8	51.2 ± 9.8	0.01	0.001
n	497	497	497		
MCS in persons with HbA1c > 64 mmol/mol	48.9 ± 10.2	50.1 ± 9.9	51.1 ± 10.3	0.36	0.04
n	251	251	251		

Data are presented as mean ± standard deviation.

In multivariable regression model (R^2= 0.14, p-value= 0.001) with age, sex, baseline HbA1c, baseline number of hypoglycemic episodes, the presence of micro and macrovascular complications, delta HbA1c and baseline MCS only age (St. Beta -0.17, 95%CI -0.29, -0.07) and baseline MCS (St. Beta -0.50, 95% CI -0.60, -0.39) were significantly associated with improvements in MCS scores over 12 months (Table 3).

Table 3. Multivariable analysis for change in MCS

	Standardized beta	p-value
Age	-0.17 (-0.29, -0.07)	0.001
Male sex	-0.02 (-0.31, 0.29)	0.51
Baseline HbA1c, mmol/mol	0.02 (-0.11, 0.14)	0.80
Number of hypoglycemic events past 6 months	-0.11 (-0.23, 0.01)	0.08
Macrovascular complications	-0.08 (-0.42, 0.27)	0.66
Microvascular complications	-0.10 (-0.43, 0.13)	0.38
Delta of HbA1c, mmol/mol	-0.01 (-0.15, 0.12)	0.86
Baseline MCS	-0.50 (-0.60, -0.39)	<0.001

Standardized beta regression coefficients are presented with 95% confidence intervals.

Discussion

This study describes the effect of FSL-FGM initiation on the prevalence rate of depressive disorders in persons with diabetes, estimated by the number of SF-12^{v2} MCS scores ≤ 45. After 6 and 12 months of FSL-FGM use less persons had a MCS score indicative of a depressive disorder as compared to baseline. The over-all MCS also improved during follow-up, demonstrating improved mental wellbeing among FSL-FGM users.

Factors associated with depression and depressive disorders in persons with diabetes are female sex, higher HbA1c, nonwhite ethnicity, lower income, lower education level, a more sedentary lifestyle and presence of micro- and macrovascular complications [8,9,19]. In the present study, the depressive disorder rate was higher among women. Importantly, for men as well as women the proportion of persons with a depressive disorder improved after FSL-FGM initiation. In contrast to our findings, Tyndall *et al.* [13] observed that initiation of FSL-FGM in persons with type 1 DM was associated with worsening of depression scores, measured by the Hospital Anxiety and Depression Scale (HADS), although total diabetes distress levels were reduced. Of notice, newly elevated HADS depression scores after FSL-FGM commencement were related to greater social deprivation and lower income categories, a risk factor for depression and depressive disorders by itself [13]. Our study population may be wealthier, since participants had to finance half of the costs of the FSL-FGM themselves, and - although hypothetical - this might account for the differences in study outcomes.

The observed improvement in mental health was associated with baseline MCS scores. Although the change in mental health was not significantly associated with the baseline number of hypoglycemic events, the link between both has been described in previous studies.

Diabetes distress is associated with fear of hypoglycemia in persons with type 1 diabetes [11]. Overend *et al.* [20] attributed a lower hypoglycemia frequency, a decrease in hypoglycemia severity and less fear of hypoglycemia among persons who initiated FSL-FGM as a key positive impact on well-being [20]. Improvement of diabetes distress after FSL-FGM initiation correlated with improvement of glycemic control and hypoglycemia unawareness [11]. These observations suggest that the negative impact of (fear of) hypoglycemias on mental health could be modified by FSL-FGM initiation, although it definitely is possible to hypothesize another explanation.

This study has limitations. First and foremost, a considerable number of persons included in the original FLARE-NL registry dropped out after 6 and 12 months, without reporting a reason for discontinuation. We hypothesize that the voluntary nature of participation in this registry and the longer duration of follow-up (as compared to other studies) might be of influence here. Post-hoc analysis of baseline characteristics between persons with and without available data during of follow-up demonstrated that persons without available data were more often male (57.4 vs. 50.2%, p=0.017) significantly younger (44.2 (± 16.1) vs. 48.2 (± 15.8), p<0.001) and had a higher HbA1c (66.1 (± 15.1) vs 62.1 (± 13.0), p<0.001). Given, the number of participants that not filled in the questionnaires and the fact that data were patient reported, recall bias may be present. Since participants had to finance half of the costs of the FSL-FGM themselves, this will contribute to selection bias, as the selected participants probably will be more affluent than the average DM population. We did not have access to FSL-FGM data (as data were gathered from 2016-2017) and therefore information such as time in range and other glycemic metrics is not available. Although the SF-12^{v2} MCS is not a regular screening tool for depression and depressive disorders in persons with diabetes, the SF-12^{v2} is a considered as a valid generic instrument for measuring quality of life in this population [17]. As data on depression and depressive disorders in adults using FSL-FGM is lacking to date, this study provides some information to fill this gap. Nevertheless, our findings should be interpreted with caution and its clinical relevance has to be proven in future studies.

Conclusions

The observed outcomes suggest that the depressive disorder rate among persons with diabetes is reduced after longer term FSL-FGM use, as compared to the period preceding FSL-FGM commencement.

Abbreviations

(CABG) coronary artery bypass grafting, (CVA), cerebral vascular event, (DM) diabetes mellitus, (FLARE-NL) FLAsh monitor Registry in The Netherlands, (FSL-FGM) FreeStyle Libre Flash Glucose Monitor, (IQR) Interquartile Range, (LADA), latent autoimmune diabetes in adults, (MCS), Mental Component Score, (MODY), maturity-onset diabetes of the young, (OBGLD), oral blood glucose lowering drugs, (PCI), percutaneous coronary intervention, (SF-12^{v2}) 12-Item Short Form Health Survey ^{v2}, (SAG) Stichting Achmea Gezondheidszorg, (TIA), transient ischemic attack.

Funding Statement

The FLARE-NL registry was funded by an unconditional grant (number Z699) from the Stichting Achmea Gezondheidszorg (SAG). The SAG is an innovation fund of health insurance company Zilverenkruis. The manufacturer of the FreeStyle Libre (Abbott) did not provide any finances for the proposed study and did not have any influence on study design, nor on definition of the target groups or the study objectives.

References

1. Ang E, Lee ZX, Moore S, Nana M. Flash glucose monitoring (FGM): A clinical review on glycaemic outcomes and impact on quality of life. Journal of Diabetes and Its Complications 2020;34:107559. https://doi.org/10.1016/j.jdiacomp.2020.107559.
2. Fokkert M, Dijk P van, Edens M, Barents E, Mollema J, Slingerland R, et al. Improved well-being and decreased disease burden after 1-year use of flash glucose monitoring (FLARE-NL4). BMJ Open Diabetes Research and Care 2019;7. https://doi.org/10.1136/bmjdrc-2019-000809.
3. Lameijer A, Fokkert MJ, Edens MA, Gans ROB, Bilo HJG, Dijk PR van. Two-year use of flash glucose monitoring is associated with sustained improvement of glycemic control and quality of life (FLARE-NL-6). BMJ Open Diabetes Research and Care 2021;9:e002124. https://doi.org/10.1136/bmjdrc-2021-002124.
4. Evans M, Welsh Z, Ells S, Seibold A. The Impact of Flash Glucose Monitoring on Glycaemic Control as Measured by HbA1c: A Meta-analysis of Clinical Trials and Real-World Observational Studies. Diabetes Ther 2020;11:83–95. https://doi.org/10.1007/s13300-019-00720-0.
5. Deshmukh H, Wilmot EG, Gregory R, Barnes D, Narendran P, Saunders S, et al. Effect of Flash Glucose Monitoring on Glycemic Control, Hypoglycemia, Diabetes-Related Distress, and Resource Utilization in the Association of British Clinical Diabetologists (ABCD) Nationwide Audit. Dia Care 2020:dc200738. https://doi.org/10.2337/dc20-0738.
6. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. J Affect Disord 2012;142 Suppl:S8-21. https://doi.org/10.1016/S0165-0327(12)70004-6.
7. Khaledi M, Haghighatdoost F, Feizi A, Aminorroaya A. The prevalence of comorbid depression in patients with type 2 diabetes: an updated systematic review and meta-analysis on huge number of observational studies. Acta Diabetol 2019;56:631–50. https://doi.org/10.1007/s00592-019-01295-9.
8. Trief PM, Xing D, Foster NC, Maahs DM, Kittelsrud JM, Olson BA, et al. Depression in Adults in the T1D Exchange Clinic Registry. Diabetes Care 2014;37:1563–72. https://doi.org/10.2337/dc13-1867.
9. Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care 2000;23:934–42. https://doi.org/10.2337/diacare.23.7.934.
10. Holt RIG, de Groot M, Golden SH. Diabetes and Depression. Curr Diab Rep 2014;14:491. https://doi.org/10.1007/s11892-014-0491-3.
11. Deshmukh H, Wilmot EG, Gregory R, Barnes D, Narendran P, Saunders S, et al. Predictors of diabetes-related distress before and after FreeStyle Libre-1 use: Lessons from the Association of British Clinical Diabetologists nationwide study. Diabetes Obes Metab 2021. https://doi.org/10.1111/dom.14467.
12. Al Hayek AA, Robert AA, Al Dawish MA. Effectiveness of the Freestyle Libre Flash Glucose Monitoring System on Diabetes Distress Among Individuals with Type 1 Diabetes: A Prospective Study. Diabetes Ther 2020;11:927–37. https://doi.org/10.1007/s13300-020-00793-2.
13. Tyndall V, Stimson RH, Zammitt NN, Ritchie SA, McKnight JA, Dover AR, et al. Marked improvement in HbA1c following commencement of flash glucose monitoring in people with type 1 diabetes. Diabetologia 2019;62:1349–56. https://doi.org/10.1007/s00125-019-4894-1.
14. Fokkert MJ, Damman A, van Dijk PR, Edens MA, Abbes S, Braakman J, et al. Use of FreeStyle Libre Flash Monitor Register in the Netherlands (FLARE-NL1): Patient Experiences, Satisfaction, and Cost Analysis. Int J Endocrinol 2019;2019. https://doi.org/10.1155/2019/4649303.

15. Vilagut G, Forero CG, Pinto-Meza A, Haro JM, de Graaf R, Bruffaerts R, et al. The mental component of the short-form 12 health survey (SF-12) as a measure of depressive disorders in the general population: results with three alternative scoring methods. Value Health 2013;16:564–73. https://doi.org/10.1016/j.jval.2013.01.006.

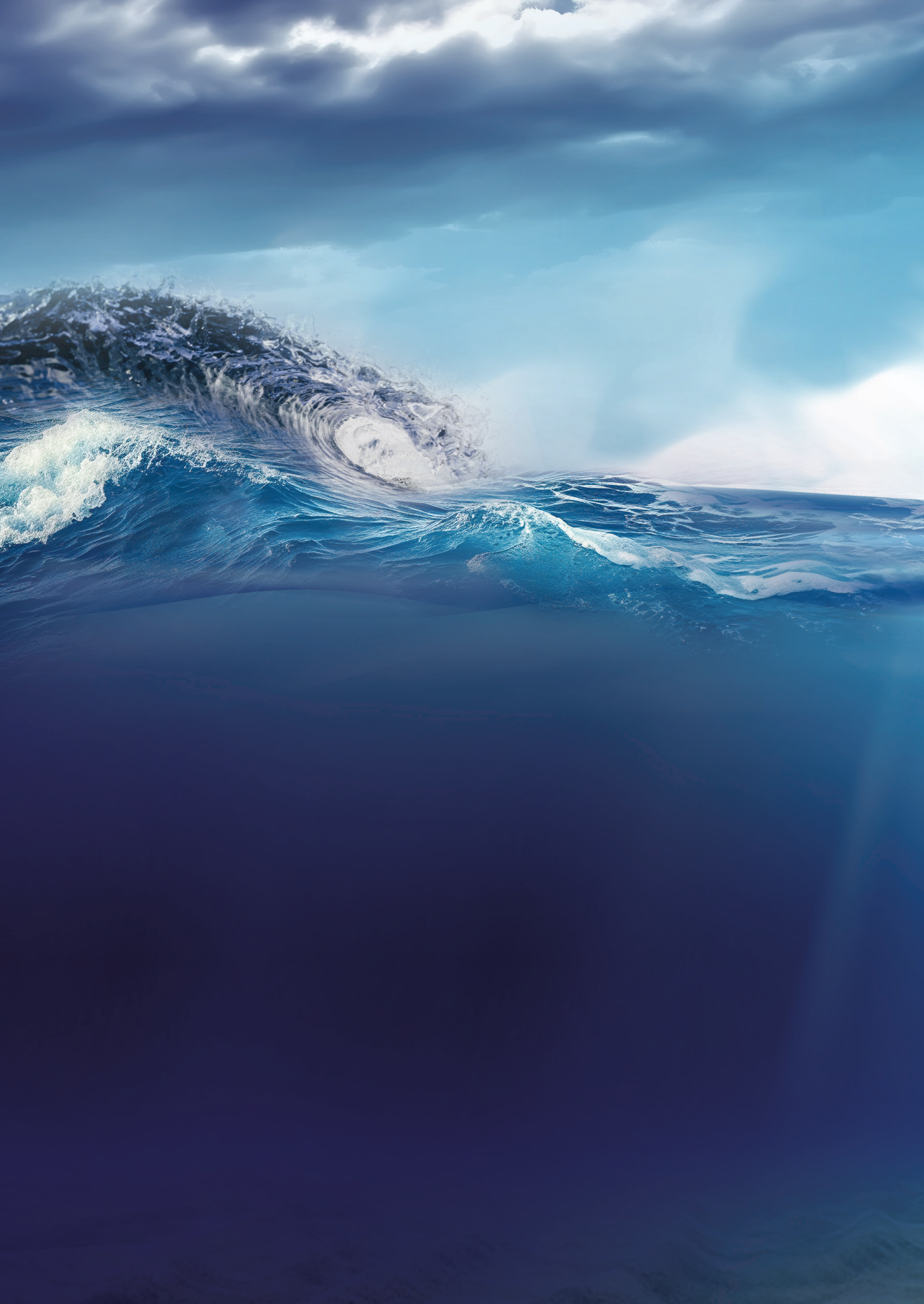
16. Gill SC, Butterworth P, Rodgers B, Mackinnon A. Validity of the mental health component scale of the 12-item Short-Form Health Survey (MCS-12) as measure of common mental disorders in the general population. Psychiatry Res 2007;152:63–71. https://doi.org/10.1016/j.psychres.2006.11.005.

17. Kathe N, Hayes CJ, Bhandari NR, Payakachat N. Assessment of Reliability and Validity of SF-12v2 among a Diabetic Population. Value in Health 2018;21:432–40. https://doi.org/10.1016/j.jval.2017.09.007.

18. Ware J, Kosinski M, Keller S. A 12-Item Short-Form Health Survey: Construction of Scales and Preliminary Tests of Reliability and Validity. Medical Care 1996;34:220–33.

19. Rajput R, Gehlawat P, Gehlan D, Gupta R, Rajput M. Prevalence and predictors of depression and anxiety in patients of diabetes mellitus in a tertiary care center. Indian J Endocrinol Metab 2016;20:746–51. https://doi.org/10.4103/2230-8210.192924.

20. Overend L, Simpson E, Grimwood T. Qualitative analysis of patient responses to the ABCD FreeStyle Libre audit questionnaire. Practical Diabetes 2019;36:45–50. https://doi.org/10.1002/pdi.2213.



Chapter 5

Flash Glucose Monitoring in the Netherlands: increased monitoring frequency is associated with improvement of glycemic parameters

Annel Lameijer[1], Nicole Lommerde[2], Timothy C. Dunn[3], Marion J. Fokkert[4], Mireille A. Edens[5], Kalvin Kao[3], Yongjin Xu[3], R.O.B. Gans[2], Henk J.G. Bilo[2,6], Peter R. van Dijk[1,6]

1. University of Groningen, University Medical Center Groningen, Department of Endocrinology, Groningen, The Netherlands;
2. University of Groningen, University Medical Center Groningen, Department of Internal Medicine, Groningen, The Netherlands;
3. Abbott Diabetes Care, Alameda, CA USA;
4. Isala, Department of Clinical Chemistry, Zwolle, The Netherlands;
5. Isala, Department of Innovation and Science, Zwolle, The Netherlands;
6. Isala, Diabetes Research Center, Zwolle, The Netherlands.

Abstract

Aims

To evaluate the association between flash glucose monitoring (FLASH) frequency and glycemic parameters during real-life circumstances in the Netherlands.

Methods

Obtained glucose readings were de-identified and uploaded to a dedicated database when FLASH reading devices were connected to internet. Data between September 2014 and March 2020, comprising 16,331 analyzable readers (163,762 sensors) were analyzed. Scan rate per reader was determined and each reader was sorted into 20 equally sized rank ordered groups (n=817 each).

Results

Users performed a median of 11.5 [IQR 7.7-16.7] scans per day. Those in the lowest and highest ventiles scanned on average 3.7 and 40.0 times per day and had an eHbA1c of 8.6% (71 mmol/mol) and 6.9% (52 mmol/mol), respectively. Increasing scan rates were associated with more time in target range (3.9-10 mmol/L), less time in hyperglycemia (>10 mmol/L), and a lower standard deviation of glucose. An eHbA1c of 7.0% (53 mmol/mol) translated in approximately 65% time in target range, 30% time in hyperglycemia and 5% time in hypoglycemia (<3.9 mmol/L).

Conclusions

These outcomes among Dutch FLASH users suggest that with higher scan rate glycemic control improves.

Introduction

Adequate and timely glucose level assessment is indispensable for patients with diabetes mellitus (DM) treated with multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) when aiming for adequate glycemic control. Glucose measurements enable patients and caregivers to make insulin dose adjustments and to aim for changes in lifestyle and dietary habits, which will help to improve metabolic control. Ultimately, with optimized glycemic control micro- and macrovascular complications can be delayed or prevented (1–3).

The opportunity to quickly assess capillary glucose concentrations with finger pricks has been a major breakthrough since the 1980's. Nevertheless, finger prick testing has several limitations. Since they are point measurements, information on glucose trends is limited. Many patients feel reluctant to perform finger pricks many times daily, since it can be disruptive to daily activities and painful. Continuous glucose monitoring (CGM), either by real time Continuous Glucose Monitoring (rt-CGM) or by Flash Glucose Monitoring (FLASH), allows a more frequent assessment of glucose concentrations in the interstitial fluid and also provides information on glucose trends. CGM is changing diabetes management and often contributes to increased quality of life, treatment satisfaction, better and more stable glycemic control and improved short term outcomes (4–11).

In 2014, the first version of the FreeStyle Libre® Flash Glucose Monitoring System (Abbott Diabetes Care, Witney, UK) system was introduced in the Netherlands and from December 2019 the FLASH is reimbursed for patients with DM using MDI or CSII. The FLASH performs on partially different principles than earlier CGMs. The user must proactively obtain the results by using a reader instead of data being relayed automatically to a receiver. Furthermore, the FLASH is already factory calibrated with no need for daily calibration by the patient during the 14-day sensor wear, and is meant to be inserted in the upper arm only. Several studies demonstrated better glycemic control, improved quality of life and lower disease burden among persons with DM using FLASH (4–7,12–15).

With increasing possibilities to use FLASH, there is a clear need for information on the effects of its use under real life circumstances by larger groups of patients with DM. The aim of the present study was to evaluate the use of FLASH under real-life circumstances in the Netherlands and to assess the effects on glycemic parameters.

Patients and methods

Study design and aims

This is a nationwide study with a cross-sectional design. The aim was to investigate the magnitude of FLASH reader use in the Netherlands during the period September 2014 to March 2020 and to examine associations between FLASH scan frequency and glycemic parameters under real life circumstances.

Data collection

The FLASH monitors glucose levels in interstitial fluid for up to 14 days. A dedicated reader or a smartphone app is used to scan the FLASH sensor to collect the current glucose, the last 8 hours history and glucose trend. Up to 8 hours of glucose readings are automatically stored every 15 minutes on the sensor. This study only included data collected via the specific reading devices, but not with the smartphone app. When a reader was connected to personal computer-based software with an internet connection, the reader's 90-day memory was de-identified and uploaded to a database. The report software, available for free download, includes an agreement that de-identified data will be collected at each internet-connected use of the software (16).

Analyses

Within this database, completely anonymized information on the use of scanning devices and connected sensors was accumulated. The available data also contained information of the country in which the scanning device was registered. In addition to data from Dutch users, data from users from other countries were retrieved from the database for comparisons. The duration of FLASH monitoring, the number of readers and sensors and the scanning frequency per sensor and individual scanning device could be determined. The scanning frequency for each sensor was calculated by the number of scans divided by the duration of sensor use according to recorded start and end times. Scanning frequency per reader was assessed by calculating the mean scan rate of all its sensors, followed by determining the cumulative frequency distribution and summary metrics (mean, median and interquartile range (IQR)). To investigate patterns of scanning, frequency of scanning per day and per hour was collected.

Furthermore, analyses of glycemia were performed based on all the data that were uploaded. To be included in these analyses it was required for each sensor to have at least 120 operational hours to ensure reliable glucose control measures. Data from all sensors belonging to the same reader were combined and calculated as the mean of all

sensor measures. The cumulative frequency of scan rates, as well as the mean eHbA1c, was calculated for each five percent of available readers to stratify the readers into 20 equally sized groups (bins), and descriptive statistics were calculated. The frequency distribution of scans by hour of the day was assessed for scanning patterns across the day. Several measures of glycemia were used including mean glucose, time in target range (defined as glucose between 3.9 and 10 mmol/L), time in hyperglycemia (>10 mmol/L and >13.9 mmol/L) and time in hypoglycemia (<3.9 mmol/L and <3.0 mmol/L) (17).

The available information on glucose per scanner was converted into eHbA1c using an algorithm (eHbA1c (%) = (mean glucose in mmol/L + 2.59)/1.59) (18). eHbA1c is presented in IFCC (mmol/mol) and DCCT/NGSP units (%).

Outcomes

Primary outcome was the association between FLASH (scan) frequency and glycemic parameters (estimated HbA1c (eHbA1c), time in target range, time in hyper- and hypoglycemia, and standard deviation of glucose). As secondary outcome, scan frequency during time in target range and time in hypo- and hyperglycemia was assessed for persons with lower and higher eHbA1c values. In addition, the number of obtained glucose readings in the Netherlands, their pattern across the day and comparisons with worldwide data were assessed.

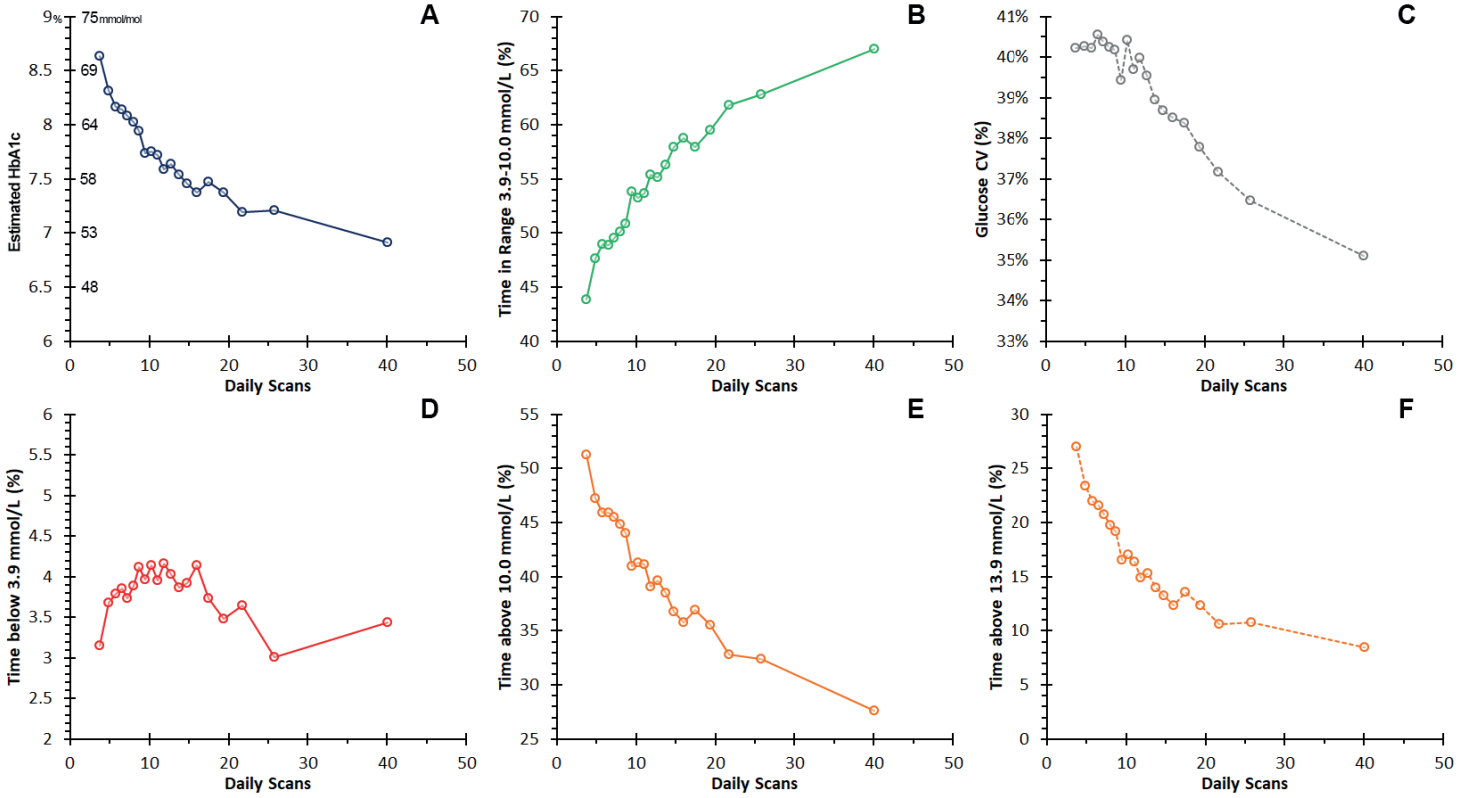
Statistical analysis

The span of glycemic measures and relative changes were reported from the lowest to highest scan rate groups. The database was analyzed by structured query language routines, and further summarized by KNIME (www.knime.org), the Python programming language (www.python.org), and the R statistical package (www.r-project.org).

Results

Up to March 2020, there were 16,331 analyzable readers (163,762 sensors) from the Netherlands, out of a total of 932,793 (10,348,827 sensors) across all countries (Supplemental Table S1). There were 27.9 million glucose scans performed by the users in the Netherlands, and the sensors provided 48.7 million hours of glucose monitoring data. The median [IQR] number of daily scans in the Netherlands was 11.5 [7.7, 16.7] (Figure 1, panel A.). During day hours (6 AM to 10 PM) this number was 8.9 [5.9, 13.2] and during night hours (10 PM to 6 AM) 2.4 [1.6, 3.6]. There were no significant differences in scan frequency between the different days of the week (data not shown).

Figure 1. Daily scan rate with the FLASH and associations with glycemia per bin of scan frequency



Daily scans (20 equally sized groups, n=817 each) versus A. Mean estimated HbA1c; B. Mean time in target range (glucose 3.9-10.0mmol/L); C. Mean coefficient of variation; D. Median time in hypoglycemia (<3.9 mmol/L); E. Mean time in level 1 hyperglycemia (>10.0 mmol/L); F. Mean time in level 2 hyperglycemia (>13.9 mmol/L).

Table 1. Twenty bins ordered by scan rate, comprising 817 readers each, with associated indices of glycemia

Scan rate per day	Estimated HbA1c (%)	Estimated HbA1c (mmol/mol)	Glucose < 2.5 mmol/L (min/day)	Glucose < 3.0 mmol/L (min/day)	Glucose < 3.9 mmol/L (min/day)	Glucose 3.9-10.0 mmol/L (hours/day)	Glucose > 10.0 mmol/L (hours/day)	Glucose > 13.9 mmol/L (hours/day)
3.7	8.6	71	4.1	12.0	45.4	10.5	12.3	6.5
4.9	8.3	67	5.2	14.3	53.0	11.4	11.3	5.6
5.7	8.2	66	5.3	14.3	54.5	11.7	11.0	5.3
6.5	8.1	65	5.5	15.9	55.5	11.7	11.0	5.2
7.3	8.1	65	5.1	13.8	53.8	11.9	10.9	5.0
8.0	8.0	64	5.0	14.1	55.9	12.0	10.8	4.7
8.7	7.9	63	5.2	13.9	59.4	12.2	10.6	4.6
9.4	7.7	61	4.9	14.2	57.1	12.9	9.8	4.0
10.2	7.8	61	5.4	14.6	59.6	12.8	9.9	4.1
11.0	7.7	61	5.0	13.9	57.0	12.9	9.9	3.9
11.9	7.6	59	5.6	15.8	60.0	13.3	9.4	3.6
12.7	7.6	60	4.6	13.0	58.1	13.2	9.5	3.7
13.7	7.5	59	4.7	13.1	55.7	13.5	9.2	3.4
14.8	7.5	58	5.3	14.1	56.5	13.9	8.8	3.2
16.0	7.4	57	5.0	14.2	59.6	14.1	8.6	3.0
17.5	7.5	58	4.2	12.1	53.8	13.9	8.9	3.3
19.3	7.4	57	4.1	11.2	50.1	14.3	8.5	3.0
21.8	7.2	55	4.0	11.8	52.5	14.8	7.9	2.6
25.8	7.2	55	3.1	9.1	43.3	15.1	7.8	2.6
40.0	6.9	52	2.9	8.7	49.5	16.1	6.6	2.0

Data are presented as means, except for time below 2.5, 3.0 and 3.9 mmol/L; these are medians

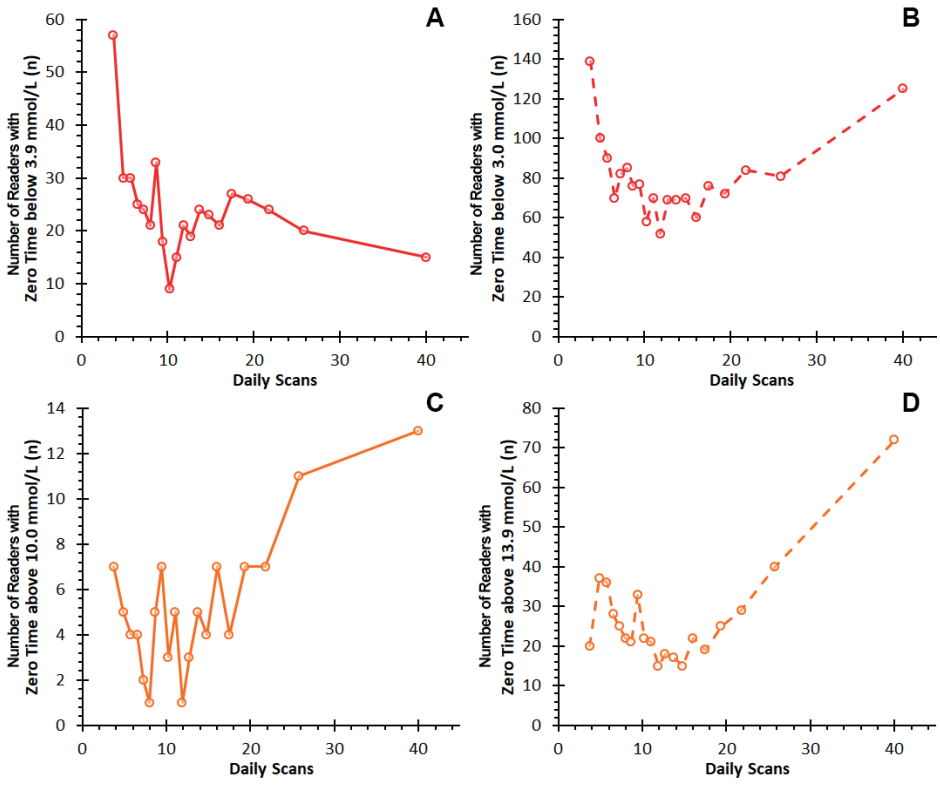
The 20 bins stratified by mean daily scan rate were analyzed for the associated glycemic metrics (Table 1). The lowest 5% of readers (n=817) had a mean scan rate of 3.7 scans per day, with a mean eHbA1c of 8.6% (71 mmol/mol), while the 5% of readers with the highest scan frequency had a mean scan rate of 40.0 scans per day and a mean eHbA1c of 6.9% (52 mmol/mol). Indices of glycemia are also presented in Supplemental Figure S1 (panel B. to G.).

Associations of scan rate with eHbA1c, time in range, time in hyper- and hypoglycemia, and coefficient of variation are presented in Figure 1. Overall, per bin with increasing scan frequency an association with lower eHbA1c levels, less time in hyperglycemia and improved glucose variability (expressed as a lower standard deviation) was observed. Within the bin that represents persons who scanned more than 40 times per day an eHbA1c below 7.0% (53 mmol/mol) has been achieved. The association of scanning frequency with time in hypoglycemia was less pronounced (Figure 1. panel D).

Additionally, the number of readers in each bin with zero time in hypo- and hyperglycemia was evaluated (Figure 2). At hypoglycemia with a glucose level <3.0 mmol/L (54 mg/dl) (Figure 2, panel B.), there was a decrease followed by an increase in the number of readers with zero exposure to this level of hypoglycemia across the scan groups. For zero exposure to hyperglycemia, the association was clearer; persons with higher scan rates were more likely to have zero time in hyperglycemia. Concerning hyperglycemia above 13.9 mmol/L (250 mg/dl), at the highest scan group of 40 scans per day, 72 of 817 (8.8%) readers had no exposure to this level of hyperglycemia.

When grouping the readers into 20 equal bins defined by eHbA1c, the highest eHbA1c bin performed just under 10 scans per day, while the lowest bin had a daily scan rate of 18 per day (Figure 3). The association with the other glucose metrics was also evident; those with the lowest eHbA1c had the highest time in range and in hypoglycemia, and the lowest time in hyperglycemia. For glucose variability, there is an increasing relationship between eHbA1c and standard deviation of glucose levels. Of notice, an eHbA1c of 7.0% (53 mmol/mol) corresponded with a scan frequency of 15 scans per day and translated in approximately 65% time in target range, 30% time in hyperglycemia (>10 mmol/L) and 5% time in hypoglycemia (below 3.9 mmol/L) (see Figure 3).

Figure 2. Daily scan rate with the FLASH and associations with zero time in hypo- and hyperglycemia

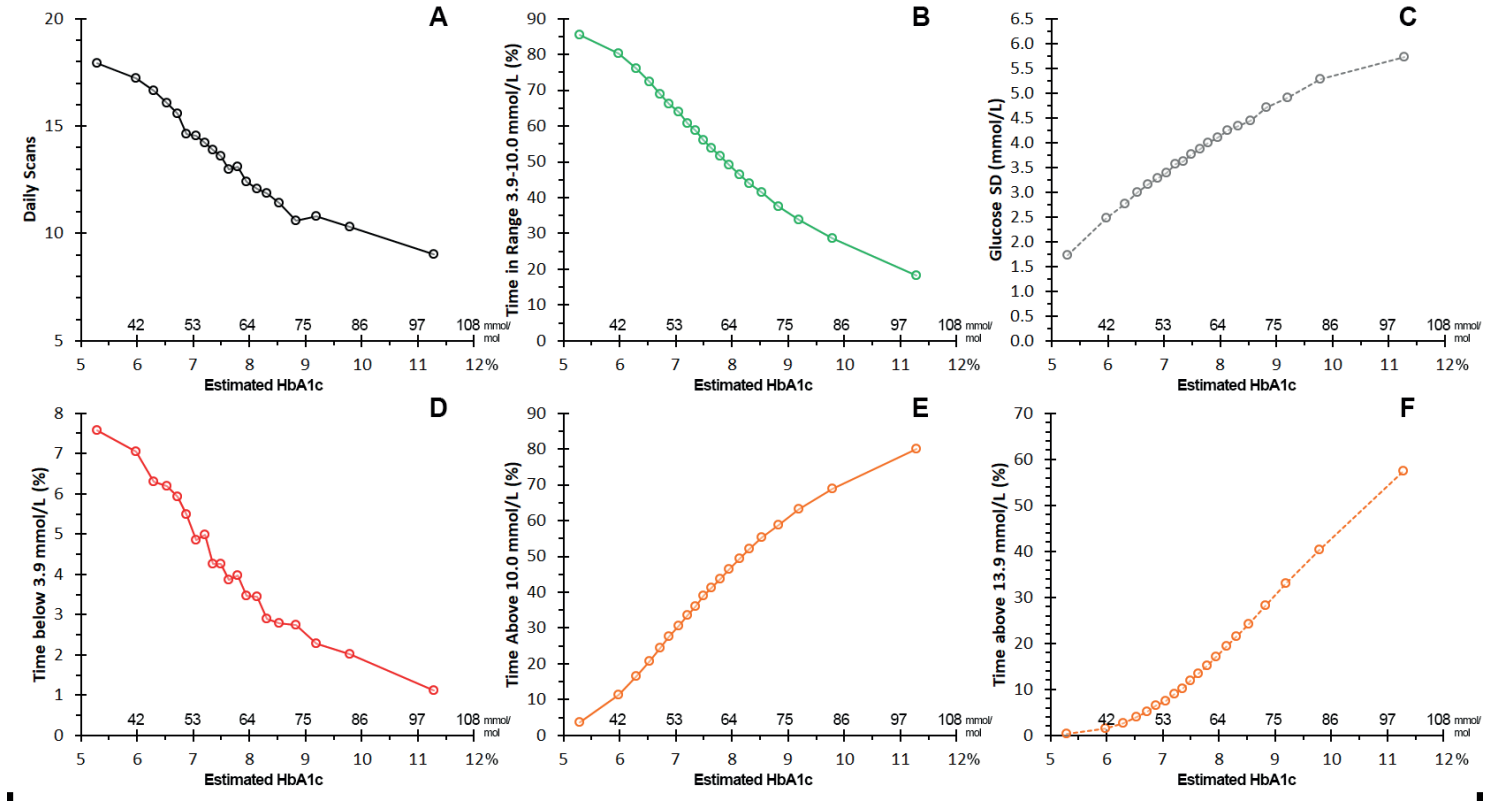


Daily scan rate versus number of readers with A. Zero time a glucose below 3.9 mmol/L. B. Zero time a glucose below 3.0 mmol/L. C. Zero time a glucose above 10.0 mmol/L. D. Zero time a glucose above 13.9 mmol/L.

To evaluate the scan behavior between eHbA1c groups in more detail, the scan rates (scaled to units of scans per day) during each glucose range was determined for each bin (Figure 4). During glucose levels within the target range or in hyperglycemia persons with lower average estimated HbA1c values tend to scan more frequently as compared to those with higher estimated HbA1c values, whereas the scan frequency in hypoglycemia tends to stay relative stable over the different average eHbA1c levels.

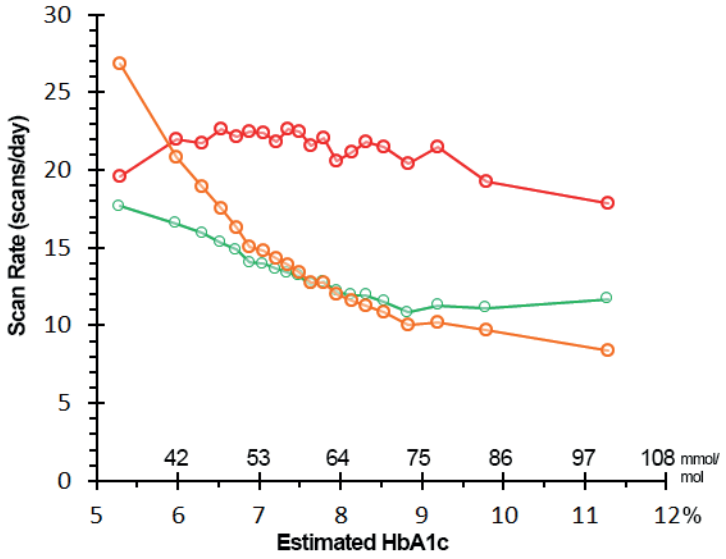
Comparison of data from the Netherlands with the worldwide data is presented in Supplemental Table S1 and Figure S2. Overall, there was a - virtually - similar daily scan rate (mean 13.4 vs. 13.2) and parameters of glycemia demonstrate a slightly higher HbA1c 7.7 (1.4)% (61 (15.3) mmol/mol) vs. 7.5 (1.5)% (58 (16.4) mmol/mol) and less time in target range (13.1 (4.5) vs. 13.9 (4.9) hours per day) in the Dutch population.

Figure 3. Daily scan rate with the FLASH and indices of glycemia per bin of eHbA1c



Estimated HbA1c (20 equally sized groups, n=817 each) versus A. Daily Scans; B. Mean time in target range (glucose 3.9-10.0mmol/L). C. Mean standard deviation of glucose; D. Median time in hypoglycemia (<3.9 mmol/L); E. Mean time in level 1 hyperglycemia (>10.0 mmol/L); F. Mean time in level 2 hyperglycemia (>13.9 mmol/L).

Figure 4. Scan frequency during time in range, hypo- and hyperglycemia according to average estimated HbA1c



The red line represents the scan rate during hypoglycemia (<3.9 mmol/L), the green line the scan rate during target range (3.9-10.0 mmol/L) and the orange line the scan rate during hyperglycemia (>10.0 mmol/L). Dots correspond to the 20 bins of eHbA1c .

Discussion

This study describes the impact of FLASH use in the Netherlands up to March 2020. Although one should be careful to not draw too firm conclusions from cross-sectional data as analyzed in the present study, the findings definitely allow some tentative clinically meaningful interpretations.

First and foremost, there is an association between increasing scan frequency with better glycemic control. In general, a scanning frequency of > 20 times per day is associated with an eHbA1c level close to 7.0% (53 mmol/mol), in line with previous results presented by Dunn et al. (19). The other way around: the lower the daily scan frequency, the higher the associated eHbA1c. Therefore, we hypothesize that advising users who scan with a low frequency to scan more often may result in better glycemic control. Furthermore, persons who scan with low frequency tend to concentrate scanning in the hypoglycemic range and tend to disregard scanning in the hyperglycemic range. This suggests that users with a low scan rate potentially do not reap the benefits of FLASH compared to users who scan more frequently.

Of notice, a scanning frequency to reach an eHbA1c level of < 7.0% (53 mmol/mol) - currently the most often used target for HbA1c levels - corresponds with a time in target range (glucose 3.9-10.0 mmol/L) of 65% in our analysis. This percentage of time is less than current guidelines advice as ideal time in range (< 70%) for most people with type 1 and type 2 diabetes (17). This finding emphasizes the difference between eHbA1c (more stable) and time in range as (more dynamic) outcome parameter. When educating healthcare professionals and FLASH users, these findings can be incorporated, aiming for a more satisfactory use of FLASH. In contrast to more recent CGM devices, the FLASH we analyzed has no alarm function for (predicted) hypo- or hyperglycemia. The upcoming use of (FLASH) CGM devices with alarm function will possibly have an additional positive effect on the ability to reach glycemic targets (20).

Data as acquired from Dutch users are mostly in line with the worldwide data. On average, users scan about 13 times daily. The eHbA1c in the Netherlands tends to be somewhat higher as well as the amount of time spent in hyperglycemia. It should be mentioned that comparisons are hampered by the lack of information concerning the population, including indication for FLASH use. Until December 2019, the use of FLASH in the Netherlands was mainly restricted to persons who failed to reach adequate glycemic control. This selection, in contrast to the more heterogeneous worldwide population with regards to diabetes management, could well account for the current findings. The considerable number of scans (> 30) needed to achieve the internationally defined target glycemic variability of ≤ 36% is presumably also related to the expected high amount of FLASH users with inadequate glycemic control in this study, related to the reimbursement criteria in The Netherlands until December 2019.

Limitations of this study should be acknowledged. As mentioned before, the cross-sectional design of this study precludes conclusions concerning causality. As a consequence of the anonymous nature of the database used for this study, detailed information concerning characteristics of FLASH users was unavailable. Ideally, users' characteristics and longitudinal analyses should be included in future analyses. In addition, the lack of information concerning carbohydrate intake and exercise patterns during FLASH should also be taken into account. As there is a heterogeneous population with various indications for FLASH use, we were unable to define specific subgroups who might benefit the most from FLASH. As parameter of glycemic variability, the coefficient of variation of glucose concentrations was used. It should be noted that outcomes for the standard deviation of glucose levels (data presented in Supplemental Figure S3) were in line with the coefficient of variation (the ratio of the standard deviation divided by the mean, Figure 1C). Lastly, it should be noted that eHbA1c does not always closely approximates a laboratory measured HbA1c (21). After this study ended, the term eHbA1c has been changed to Glucose Management Indicator (GMI) in the Netherlands.

Conclusions

The observed outcomes suggest that with increasing FLASH scan rate glycemic parameters improve, including eHbA1c, time in range, time in hyperglycemia and standard deviation of glucose. Although causality between scan rate and described outcomes is not proven, both users and health care professionals have to be aware of this probable relationship.

Abbreviations

(CSII) continuous subcutaneous insulin infusion, (DM) diabetes mellitus, (eHbA1C) estimated HbA1c, (FLASH) Flash Glucose Monitor, (IQR) Interquartile Range, (MDI) multiple daily injections, (rt-CGM) real time Continuous Glucose Monitoring.

Funding statement

This work was partly funded by the University Medical Center Groningen (Department of Internal Medicine) and partly by Abbott Diabetes Care (the last part being in the form of an unconditional research grant).

References

1. Nathan DM, Cleary PA, Backlund J-YC, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005 Dec 22;353(25):2643–53.
2. Bebu I, Schade D, Braffett B, Kosiborod M, Lopes-Virella M, Soliman EZ, et al. Risk Factors for First and Subsequent CVD Events in Type 1 Diabetes: The DCCT/EDIC Study. Diabetes Care [Internet]. 2020 Apr 1 [cited 2020 Dec 20];43(4):867–74. Available from: https://care.diabetesjournals.org/content/43/4/867
3. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet Lond Engl. 1998 Sep 12;352(9131):854–65.
4. Deshmukh H, Wilmot EG, Gregory R, Barnes D, Narendran P, Saunders S, et al. Effect of Flash Glucose Monitoring on Glycemic Control, Hypoglycemia, Diabetes-Related Distress, and Resource Utilization in the Association of British Clinical Diabetologists (ABCD) Nationwide Audit. Diabetes Care [Internet]. 2020 Jul 15 [cited 2020 Jul 20];dc200738. Available from: http://care.diabetesjournals.org/lookup/doi/10.2337/dc20-0738
5. Ang E, Lee ZX, Moore S, Nana M. Flash glucose monitoring (FGM): A clinical review on glycaemic outcomes and impact on quality of life. J Diabetes Complications [Internet]. 2020 Jun [cited 2020 Jul 22];34(6):107559. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1056872719313418
6. Charleer S, Mathieu C, Nobels F, De Block C, Radermecker RP, Hermans MP, et al. Effect of Continuous Glucose Monitoring on Glycemic Control, Acute Admissions, and Quality of Life: A Real-World Study. J Clin Endocrinol Metab. 2018 01;103(3):1224–32.
7. Fokkert M, van Dijk P, Edens M, Barents E, Mollema J, Slingerland R, et al. Improved well-being and decreased disease burden after 1-year use of flash glucose monitoring (FLARE-NL4). BMJ Open Diabetes Res Care. 2019 Dec 9;7(1):e000809.
8. Lind M, Ólafsdóttir AF, Hirsch IB, Bolinder J, Dahlqvist S, Pivodic A, et al. Sustained Intensive Treatment and Long-term Effects on HbA $_{1c}$ Reduction (SILVER Study) by CGM in People With Type 1 Diabetes Treated With MDI. Diabetes Care [Internet]. 2020 Nov 15 [cited 2020 Nov 17];dc201468. Available from: http://care.diabetesjournals.org/lookup/doi/10.2337/dc20-1468
9. Thabit H, Prabhu JN, Mubita W, Fullwood C, Azmi S, Urwin A, et al. Use of Factory-Calibrated Real-time Continuous Glucose Monitoring Improves Time in Target and HbA1c in a Multiethnic Cohort of Adolescents and Young Adults With Type 1 Diabetes: The MILLENNIAL Study. Diabetes Care [Internet]. 2020 Jul 28 [cited 2020 Nov 18]; Available from: https://care.diabetesjournals.org/content/early/2020/07/27/dc20-0736
10. Rodbard D. Continuous Glucose Monitoring: A Review of Recent Studies Demonstrating Improved Glycemic Outcomes. Diabetes Technol Ther [Internet]. 2017 Jun [cited 2020 Nov 20];19(S3):S-25-S-37. Available from: http://www.liebertpub.com/doi/10.1089/dia.2017.0035
11. Stone JY, Bailey TS. Benefits and limitations of continuous glucose monitoring in type 1 diabetes. Expert Rev Endocrinol Metab. 2020;15(1):41–9.
12. Tyndall V, Stimson RH, Zammitt NN, Ritchie SA, McKnight JA, Dover AR, et al. Marked improvement in HbA1c following commencement of flash glucose monitoring in people with type 1 diabetes. Diabetologia [Internet]. 2019 [cited 2020 Jan 13];62(8):1349–56. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6647076/

13. Evans M, Welsh Z, Ells S, Seibold A. The Impact of Flash Glucose Monitoring on Glycaemic Control as Measured by HbA1c: A Meta-analysis of Clinical Trials and Real-World Observational Studies. Diabetes Ther [Internet]. 2020 Jan [cited 2020 Sep 20];11(1):83–95. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6965602/

14. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. The Lancet [Internet]. 2016 Nov 5 [cited 2020 Jun 17];388(10057):2254–63. Available from: http://www.sciencedirect.com/science/article/pii/S0140673616315355

15. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline J-P, Rayman G. Use of Flash Glucose-Sensing Technology for 12 months as a Replacement for Blood Glucose Monitoring in Insulin-treated Type 2 Diabetes. Diabetes Ther [Internet]. 2017 Jun [cited 2020 Sep 21];8(3):573–86. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5446381/

16. Freestyle Libre | Software Disclaimer | Abbott [Internet]. [cited 2020 Dec 31]. Available from: https://www.freestyle.abbott/ca/en/products/libre/software/disclaimer.html

17. 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 [Internet]. 2019 Jun 7 [cited 2020 Apr 15]; Available from: https://care.diabetesjournals.org/content/early/2019/06/07/dci19-0028

18. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. Translating the A1C Assay Into Estimated Average Glucose Values. Diabetes Care [Internet]. 2008 Aug [cited 2020 Nov 20];31(8):1473–8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2742903/

19. Dunn TC, Xu Y, Hayter G, Ajjan RA. Real-world flash glucose monitoring patterns and associations between self-monitoring frequency and glycaemic measures: A European analysis of over 60 million glucose tests. Diabetes Res Clin Pract. 2018 Mar;137:37–46.

20. Cappon G, Vettoretti M, Sparacino G, Facchinetti A. Continuous Glucose Monitoring Sensors for Diabetes Management: A Review of Technologies and Applications. Diabetes Metab J [Internet]. 2019 Aug [cited 2020 Nov 23];43(4):383–97. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6712232/

21. Bergenstal RM, Beck RW, Close KL, Grunberger G, Sacks DB, Kowalski A, et al. Glucose Management Indicator (GMI): A New Term for Estimating A1C From Continuous Glucose Monitoring. Diabetes Care [Internet]. 2018 Nov [cited 2020 Nov 19];41(11):2275–80. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6196826/

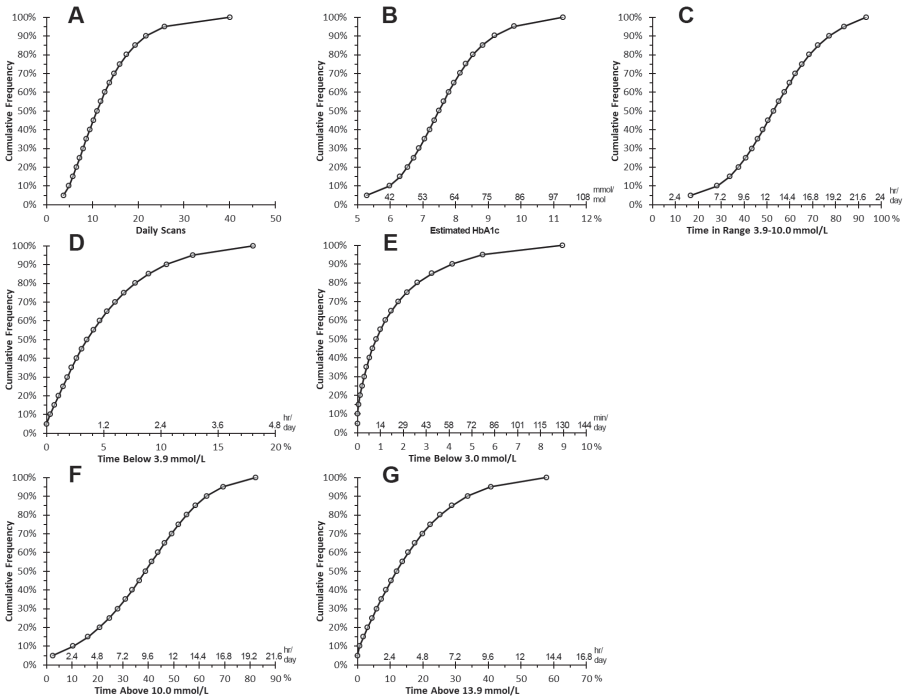
Supplemental material

Supplemental Table S1. Reader and sensor metrics for The Netherlands and worldwide

	The Netherlands	**All countries**
Readers	16,331	932,793
Days of sensor data in analysis	79 (144)	85 (143)
Sensors	163,762	10,348,827
Duration of sensors in analysis (days)	13.9 (0.2)	13.9 (0.5)
Glucose scans	27.9 million	1.61 billion
Monitoring hours	48.7 million	3.02 billion
Automatically recorded glucose readings	195 million	12.1 billion
Number of readers	16,331	932,793
Daily scans	13.4 (8.9)	13.2 (10.7)
eHbA1c (%)	7.7 (1.4)	7.5 (1.5)
eHbA1c (mmol/mol)	61 (15.3)	58 (16.4)
Hours per day glucose > 10.0 mmol/L	9.6 (4.7)	8.8 (5.1)
Hours per day glucose 3.9 to 10.0 mmol/L	13.1 (4.5)	13.9 (4.9)
Minutes per day glucose < 3.9 mmol/L	54.6 (80.3)	51.7 (88.6)
Minutes per day glucose < 3.0 mmol/L	13.1 (30.5)	12.0 (32.8)
Minutes per day glucose < 2.5 mmol/L	4.7 (14.3)	4.5 (15.6)

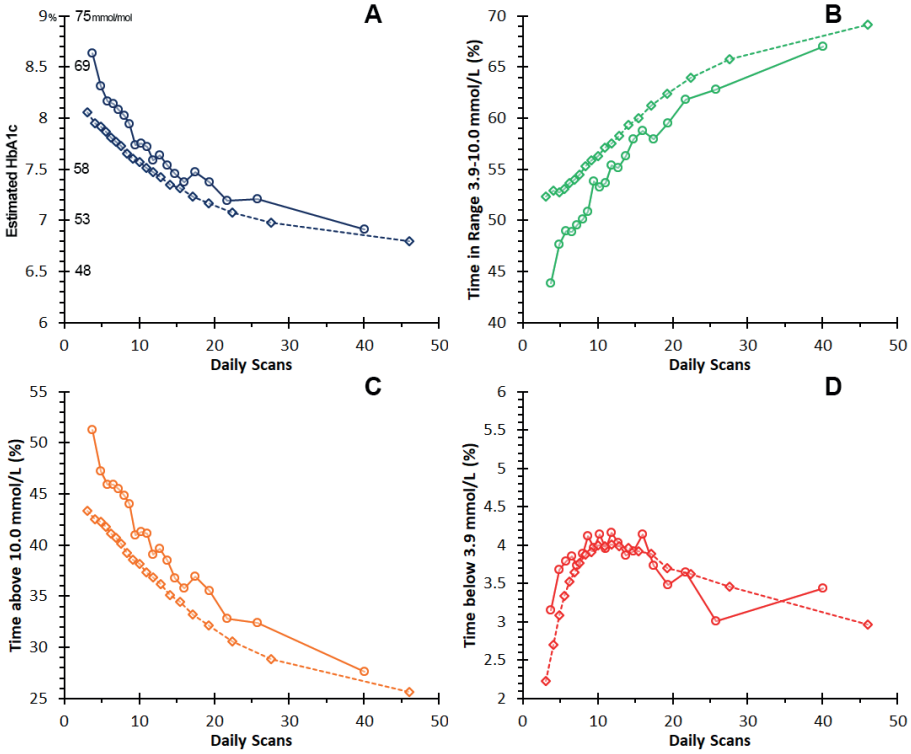
Data collected between September 2014 and March 2020, presented as numbers and means (standard deviation), except for time below 2.5, 3.0 and 3.9 mmol/L, days of sensor data in analysis, and duration of sensors in analysis; these are medians (IQR). Abbreviations: eHbA1c, estimated HbA1c.

Supplemental Figure S1. Cumulative frequency for 20 equally sized groups (n=817 each) of the number of daily scans with FLASH (panel A.) and indices of glycemic control (panel B. to G.)



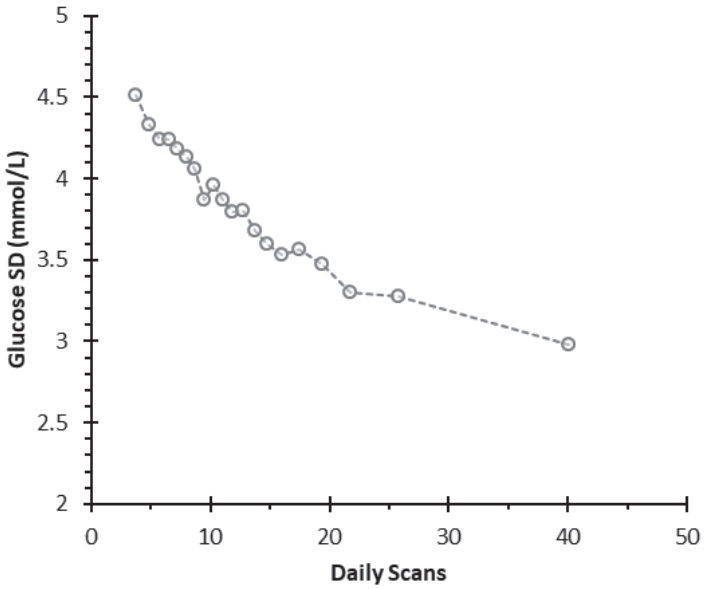
Cumulative frequency for 20 equally sized groups (n=817 each) of A. Mean daily scans B. Mean estimated HbA1c; C. Mean time in range (glucose 3.9-10.0 mmol/L); D. Median time in level 1 hypoglycemia (glucose <3.9 mmol/L); E. Median time in level 2 hypoglycemia (glucose <3.0 mmol/L); F. Mean time in level 1 hyperglycemia (glucose >10 mmol/L); G. Mean time in level 2 hyperglycemia (glucose >13.9 mmol/L).

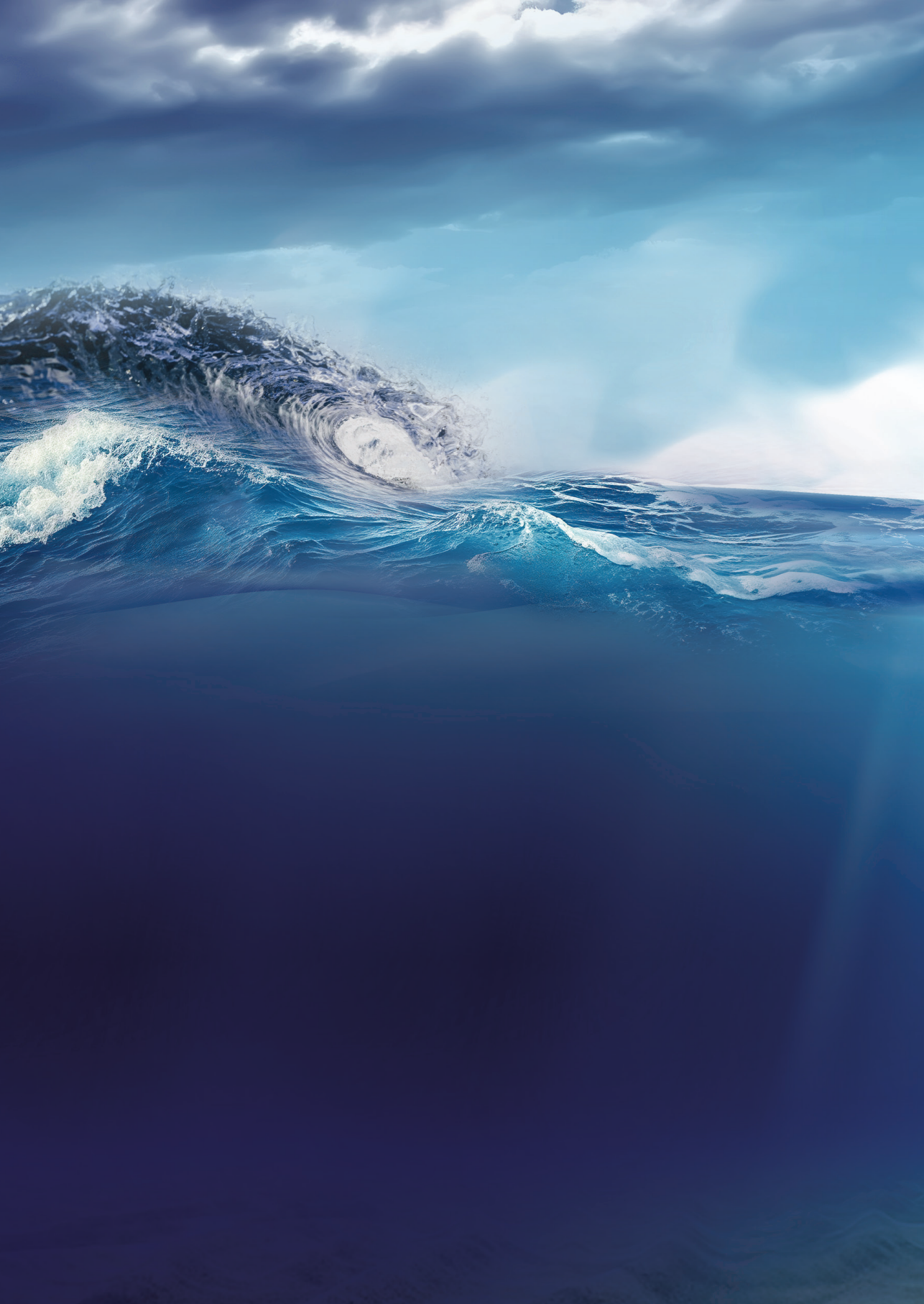
Supplemental Figure S2. Daily scan rate with the FLASH and associations with indices of glycemia per bin of scan rate. Comparison between the Netherlands (solid line) and other countries (dashed line)



Daily scans (n) versus A. estimated HbA1c. B. Time in target range (glucose 3.9-10.0mmol/L). C. Time in hyperglycemia (>10.0 mmol/L). D. Time in hypoglycemia (<3.9 mmol/L).

Supplemental Figure S3. Daily scan rate with the FLASH and association with glucose standard deviation per bin of scan frequency.





Chapter 6

Real-life 24-week changes in glycemic parameters among European users of flash glucose monitoring with type 1 and 2 diabetes and different levels of glycemic control

Annel Lameijer MD[1], Julia J. Bakker BSc[1], Kalvin Kao MSc[2], Yongjin Xu PhD[2], Rijk O.B. Gans MD PhD[3], Henk J.G. Bilo MD PhD FRCP[3,4], Timothy C. Dunn PhD[2], Peter R. van Dijk MD PhD[1,4]

1. University of Groningen, University Medical Center Groningen, Department of Endocrinology, Groningen, The Netherlands
2. Abbott Diabetes Care, Alameda, CA USA
3. University of Groningen, University Medical Center Groningen, Department of Internal Medicine, Groningen, The Netherlands
4. Isala, Diabetes Research Center, Zwolle, The Netherlands

Abstract

Aim

To evaluate real-life changes of glycemic parameters among flash glucose monitoring (FLASH) users who do not meet glycemic targets.

Methods

De-identified data were obtained between 2014 and 2021 from patients using FLASH uninterrupted for a 24-week period. Glycemic parameters during first and last sensor use were examined in four identifiable groups: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM) on basal-bolus insulin, T2DM on basal insulin, and T2DM without insulin treatment. Within each group, subgroup analyses were performed in persons with initial suboptimal glycemic regulation (time in range (TIR; 3.9-10 mmol/L) <70%, time above range (TAR; >10 mmol/L) >25%, or time below range (TBR; <3.9 mmol/L) >4%).

Results

Data were obtained from 1,909 persons with T1DM and 1,813 persons with T2DM (1,499 basal-bolus insulin, 189 basal insulin, and 125 non-insulin users). In most of the performed analyses, both overall and in the various subgroups, significant improvements were observed in virtually all predefined primary (TIR) and secondary endpoints (eHbA1c, TAR, TBR and glucose variability).

Conclusions

24-weeks FLASH use in real life by persons with T1DM and T2DM with suboptimal glycemic regulation is associated with improvement of glycemic parameters, irrespective of pre-use regulation or treatment modality.

Introduction

The possibility to continuously monitor glucose values in the interstitial fluid, either by real time Continuous Glucose Monitoring (rtCGM) or flash glucose monitoring (FLASH) devices has changed diabetes management. Besides information on actual glucose levels and glucose trends rt-CGM and FLASH devices nowadays offer alarm features and allow assessment of other aspects of glucose regulations such as time in range (TIR), time above range (TAR), and time below range (TBR) [1]. Several studies demonstrated improvement of HbA1c among persons with type 1 and type 2 diabetes (T1DM and T2DM) after initiation of FLASH, as compared to conventional fingerstick blood glucose monitoring [2–5], with the most pronounced HbA1c decline in patients with suboptimal glycemic regulation prior to FLASH initiation [2,3,6]. Next to glycemic regulation [7], FLASH initiation has been associated with improved quality of life [2,8,9], less diabetes-distress [3,10], less diabetes-related work absenteeism [9], fewer hospital admissions [9,11,12] and reduced hypoglycemic unawareness [3].

As adjunct to HbA1c, evaluation of glycemic regulation in clinical practice is increasingly based on times spent in different CGM-based glycemic target ranges [13,14]. There is growing evidence relating time in range (TIR, the percentage of time with glucose values between 3.9 and 10 mmol/L) to diabetes-related long-term micro- and macrovascular complications in T1DM and T2DM [15–18]. Improvements in TIR and reduced times spent above and below target ranges have been observed in FLASH and rt-CGM users with T1DM and T2DM [5,19–21].

To date, real-life data about the longer-term effects of FLASH use on glycemic regulation based on times spent in CGM-based glycemic target ranges [13] in persons with T1DM and T2DM with a glycemic regulation outside the internationally defined glycemic target ranges is lacking. The present study aims to evaluate real-life 24-week changes of glycemic metrics among European FLASH users, comparing groups of persons with T1DM and T2DM with different treatment modalities who do not meet the internationally defined glycemic targets [13].

Materials and Methods

Study design and aims

This is a retrospective longitudinal analysis of data from European FLASH users (mostly living in Germany, Supplemental Table S3), obtained in the period 2014 to 2021. The aim was to evaluate the baseline glycemic parameters among four groups: persons with (I) T1DM on basal-bolus insulin (combined data of multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII)), (II) T2DM on basal-bolus insulin (ibid), (III) T2DM with

basal insulin only, and (IV) T2DM with no insulin treatment. Next, in these four different treatment groups, subgroup analyses of 24-week changes were performed in persons with initial suboptimal glycemic regulation (time in range (TIR, 3.9-10 mmol/L) <70%, time above range (TAR, >10 mmol/L) >25%, or time below range (TBR, <3.9 mmol/L) >4%) at FLASH initiation (i.e., during use of the first sensor). Due to the subgroup definition as described above, it should be noted that in the subgroup analyses FLASH users could be included more than once in the analyses (e.g., when showing both a TIR <70% and a TAR > 25%).

Data collection

In 2014 the FreeStyle Libre® Flash Glucose Monitoring System (Abbott Diabetes Care, Witney, UK) was introduced. The sensor is placed on the back of the upper arm and can be worn for 14 days. A dedicated reader or a smartphone app is used to scan the sensor to collect the current glucose level, the trend in glucose levels, and the last 8 hours history of glucose levels. Every 15 minutes glucose readings are automatically stored on the sensor. The mean absolute relative difference (MARD), a measure of accuracy, of the FreeStyle Libre 2 system is 9.2% [22]. This study only included data collected via the sensor-specific reading device, not via the smartphone app. When a reader was connected to personal computer-based software with an internet connection, the 90-day memory of the reader was de-identified and uploaded to a database. The report software, that is available as a free download, includes an agreement that de-identified data will be collected at each internet-connected use of the software [23].

Within this database, anonymized information on the use of scanning devices, connected sensors and the country-level IP address was accumulated. In 2019 additional information about the age category (reported in 10-year batches and only including subjects 18 years and older), gender, type of diabetes, diabetes duration, diabetes treatment and micro- and macrovascular complications was obtained via a voluntary online questionnaire. All users of the desktop reporting software were invited to fill out this questionnaire via a notification. Only persons ≥ 18 years old who completed this questionnaire were included in this study. Further inclusion criteria were: persons with T1DM using basal-bolus insulin therapy (either MDI or CSII), as well as persons with T2DM using basal-bolus insulin therapy (either MDI or CSII), basal insulin or a non-insulin treatment, who consecutively had used 12 sensors paired with one reading device. There were no specific exclusion criteria.

Analyses of glycemia were performed based on all the data that were uploaded. To be included in the longitudinal analyses it was required for each sensor to have had at least 120 operational hours. Data from all sensors belonging to the same reader were combined. The following measures of glycemia were used: mean glucose, eHbA1c, TIR (glucose

between 3.9 and 10 mmol/L), TAR (glucose >10 mmol/L), time in level 2 hyperglycemia (glucose >13.9 mmol/L), TBR (glucose <3.9 mmol/L), time in level 2 hypoglycemia (glucose <3.0 mmol/L), coefficient of variation (CV) and standard deviation (SD) of glucose [13]. eHbA1c is presented in NGSP units (%) and IFCC [mmol/mol]. The scanning frequency for each sensor was calculated by the number of scans divided by the duration of sensor use and expressed as numbers per day. Scanning frequency per reader was assessed by calculating the mean scan rate of all 12 sensors, followed by determining the cumulative frequency distribution and summary metrics (mean, median and interquartile range (IQR)).

Outcomes

Primary outcome was the difference in TIR between the first sensor (first 2 weeks of FLASH) and the twelfth sensor (week 22 to 24). As secondary outcomes the 24-week change in eHbA1c, TAR, time in level 2 hyperglycemia, TBR, time in level 2 hypoglycemia, glucose CV, glucose SD and the FLASH monitoring frequency was analyzed. The 24-week changes in these glycemic parameters were analyzed in the above-defined subgroups in the four treatment groups of persons with T1DM and T2DM with initial suboptimal glycemic regulation.

Statistical analysis

The database was analyzed by structured query language routines, the Python programming language (www.python.org), and the R statistical package (www.r-project.org). Normally distributed data were expressed as means and skewed distributed data as medians. For all data, the paired mean differences with 95% confidence intervals are provided since all paired differences were normally distributed. For analysis of the achievement rates, e.g. the percentage of FLASH users with a TIR >70%, the 95% confidence interval of the difference was calculated with a t-distribution. A correction for regression to the mean was applied to each subject. The regression to mean corrections were determined by simulating the expected measurement errors and applying them to the first sensor results [24]. The measurement errors were estimated by calculating the standard deviations of residuals from a regression trend during sensors 2 through 12 for each subject.

Results

Out of 13,734 FLASH users (7,505 T1DM and 6,229 T2DM) who completed the questionnaires and were eligible for inclusion, a total of 3,722 (1,909 T1DM and 1,813 T2DM) continued to have FLASH data available for at least 24 consecutive weeks. Baseline characteristics are presented in Table 1.

Table 1. Characteristics of FLASH users in Europe with type 1 or type 2 diabetes

	Type 1 diabetes		Type 2 diabetes					
	Basal-bolus & CSII		Basal-bolus & CSII		Basal		Non-insulin	
	All	FLASH users with 12 sensors	All	FLASH users with 12 sensors	All	FLASH users with 12 sensors	All	FLASH users with 12 sensors
Number	7,505	1,909	4,983	1,499	726	189	520	125
Most prevalent age category (years)	55-64	55-64	65-74	65-74	65-74	65-74	55-64	55-64
18-24 years	359 (4.8%)	46 (2.4%)	3 (0.1%)	0	2 (0.3%)	0	0	0
25-34 years	699 (9.3%)	123 (6.4%)	27 (0.5%)	6 (0.4%)	6 (0.8%)	2 (1.1%)	5 (1.0%)	0
35-44 years	1,018 (13.6%)	183 (9.6%)	121 (2.4%)	21 (1.4%)	16 (2.2%)	2 (1.1%)	24 (4.6%)	6 (4.8%)
45-54 years	1,647 (21.9%)	394 (20.6%)	548 (11.0%)	157 (10.5%)	90 (12.4%)	17 (9.0%)	81 (15.6%)	12 (9.6%)
55-64 years	2,099 (28.0%)	596 (31.2%)	1,627 (32.7%)	426 (28.4%)	236 (32.5%)	61 (32.3%)	189 (36.3%)	46 (36.8%)
65-74 years	1,296 (17.3%)	436 (22.8%)	1,863 (37.4%)	611 (40.8%)	259 (35.7%)	66 (34.9%)	166 (31.9%)	41 (32.8%)
75+ years	387 (5.2%)	131 (6.9%)	794 (15.9%)	278 (18.5%)	117 (16.1%)	41 (21.7%)	55 (10.6%)	20 (16.0%)
Male (%)	65.1	68.5	85.0	87.5	83.3	87.8	89.6	88.8
Diabetes diagnosis past 5 years (%)	13.1	14.6	9.3	7.9	11.4	11.1	31.7	34.4
Diabetes diagnosed <1 year ago	165 (2.2%)	50 (2.6%)	60 (1.2%)	15 (1.0%)	17 (2.3%)	5 (2.6%)	35 (6.7%)	7 (5.6%)
Diabetes diagnosed 1-5 years ago	821 (10.9%)	228 (11.9%)	403 (8.1%)	103 (6.9%)	66 (9.1%)	16 (8.5%)	130 (25.0%)	36 (28.8%)
Diabetes diagnosed 6-10 years ago	647 (8.6%)	143 (7.5%)	818 (16.4%)	243 (16.2%)	157 (21.6%)	32 (16.9%)	125 (24.0%)	28 (22.4%)
Diabetes diagnosed 11-15 years ago	717 (9.6%)	152 (8.0%)	1,045 (21.0%)	298 (19.9%)	171 (23.6%)	45 (23.8%)	109 (21.0%)	21 (16.8%)
Diabetes diagnosed 16-20 years ago	727 (9.7%)	137 (7.2%)	965 (19.4%)	291 (19.4%)	115 (15.8%)	27 (14.3%)	62 (11.9%)	16 (12.8%)
Diabetes diagnosed > 20 years ago	4,405 (58.7%)	1,196 (62.7%)	1,656 (33.2%)	540 (36.0%)	195 (26.9%)	64 (33.9%)	55 (10.6%)	17 (13.6%)
Unknown	23 (0.3%)	3 (0.2%)	36 (0.7%)	9 (0.6%)	5 (0.7%)	0	4 (0.8%)	0
≥1 micro- or macrovascular complication(s) (%)	36.4	40.4	62.6	64.7	61.2	61.9	45.7	48.2
Less than daily SMBG prior to FLASH (%)	4.0	5.2	4.8	4.8	13.9	15.3	36.2	47.2
Mean sensor use (days)		13.4		13.3		13.5		13.5

Abbreviations: CSII, continuous subcutaneous insulin infusion, SMBG, self-monitoring of blood glucose

Type 1 diabetes

The 24-week changes in glycemic parameters during FLASH use by persons with T1DM, comparing the first and last FLASH sensor, are presented in Table 2. A TIR <70% at initiation was observed in 63% of persons with T1DM. In this subgroup, improvements in eHbA1c (7.6% (59.2 mmol/mol) to 7.4% (57.3 mmol/mol), p<0.0001), TIR (54% to 57%, p<0.0001), TAR (41% to 37%, p<0.0001), time in level 2 hyperglycemia (14% to 12%, p<0.0001), TBR (4.1% to 3.7%, p<0.0001), time in level 2 hypoglycemia (1.2% to 0.7%, p<0.0001) and CV (38.9% to 37.7%, p<0.0001) were observed over time. The FLASH daily scan frequency decreased from 14 to 12 times (p<0.0001).

A TAR > 25% at initiation was observed in 59% of persons. In these patients improvements in eHbA1c (7.7% (61.0 mmol/mol) to 7.5% (58.5 mmol/mol), p<0.0001), TIR (53% to 57%, p<0.0001), TAR (43% to 39%, p<0.0001), time in level 2 hyperglycemia (15% to 12%, p<0.0001), time in level 2 hypoglycemia (0.9% to 0.5%, p=0.003) and CV (37.7% to 36.8%, p<0.0001) were observed over time (Table 2).

More than 4% time in hypoglycemia was observed in 46% of persons at initiation of FLASH monitoring. In these patients improvements in TIR (65% to 66%, p=0.003), TBR (8.5% to 6.6%, p<0.0001), time in level 2 hypoglycemia (2.6% to 1.8%, p<0.0001), and time in level 2 hyperglycemia (7.5% to 6.8%, p=0.0006) were observed, whereas eHbA1c slightly increased from 6.6% (49.1 mmol/mol) to 6.7% (49.8 mmol/mol) (p=0.006).

The 24-week changes in glycemic parameters in persons with T1DM on CSII versus MDI are presented in Supplemental Tables S1 and S2. The observed improvements in glycemic metrics were comparable to the overall group of persons with T1DM, except for the smaller group on CSII (n=190) with > 4% TBR where no improvement in TIR, TAR or TBR was observed.

Table 2. Changes in glycemic parameters among persons with type 1 diabetes after 24 weeks of FLASH use by starting glycemic levels

		Sensor 1 TIR <70%		Sensor 1 TAR (>10 mmol/L) >25%			Sensor 1 TBR (<3.9 mmol/L) >4%		
	Sensor 1	Sensor 12	Difference; p-value (95% CI)	Sensor 1	Sensor 12	Difference; p-value (95% CI)	Sensor 1	Sensor 12	Difference; p-value (95% CI)
Number of subjects	**1,195**	1,195		1,122	1,122		880	880	
Mean glucose (mmol/L)	9.5	9.2	**-0.3; p<0.0001 (-0.36 to -0.2)**	9.7	9.4	**-0.4; p<0.0001 (-0.44 to -0.28)**	8.0	8.1	**0.1; p=0.006 (0.029 to 0.17)**
eHbA1c (%)	7.6	7.4	**-0.2; p<0.0001 (-0.23 to -0.13)**	7.7	7.5	**-0.2; p<0.0001 (-0.28 to -0.17)**	6.6	6.7	**0.1; p=0.006 (0.02 to 0.11)**
eHbA1c (mmol/mol)	59.2	57.3	**-1.9; p<0.0001 (-2.5 to -1.4)**	61.0	58.5	**-2.5; p<0.0001 (-3.01 to -1.9)**	49.1	49.8	**0.7; p=0.006 (0.2 to 1.2)**
TIR 3.9-10.0 mmol/L (%)	53.5	57.3	**3.8; p<0.0001 (3.09 to 4.52)**	53.3	57.1	**3.9; p<0.0001 (3.12 to 4.61)**	64.7	65.7	**0.9; p=0.003 (0.29 to 1.54)**
CV (%)	38.9	37.7	**-1.3; p<0.0001 (-1.59 to -0.93)**	37.7	36.8	**-1; p<0.0001 (-1.28 to -0.62)**	41.0	38.8	**-2.2; p<0.0001 (-2.54 to -1.8)**
Glucose SD (mmol/L)	65.5	61.9	**-3.7; p<0.0001 (-4.3 to -3.02)**	65.6	61.8	**-3.8; p<0.0001 (-4.5 to -3.13)**	59.6	56.9	**-2.7; p<0.0001 (-3.4 to -2)**
Time <3.0 mmol/L (%)	1.2	0.7	**-0.4; p<0.0001 (-0.57 to -0.231)**	0.9	0.5	**-0.2; p=0.003 (-0.34 to -0.07)**	2.6	1.8	**-0.64; p<0.0001 (-0.88 to -0.41)**
Time <3.9 mmol/L (%)	4.1	3.7	**-0.5; p<0.0001 (-0.8 to -0.22)**	3.2	2.9	-0.04; p=0.73 (-0.28 to 0.2)	8.5	6.6	**-1.4; p<0.0001 (-1.84 to -1.01)**
Time >10.0 mmol/L (%)	40.6	37.1	**-3.5; p<0.0001 (-4.3 to -2.7)**	42.6	38.5	**-4.1; p<0.0001 (-4.9 to -3.2)**	25.4	25.8	0.4; p=0.30 (-0.3 to 1.1)
Time >13.9 mmol/L (%)	13.8	11.6	**-2.2; p<0.0001 (-2.8 to -1.7)**	14.5	12.0	**-2.4; p<0.0001 (-3.01 to -1.9)**	7.5	6.8	**-0.7; p=0.0006 (-1.1 to -0.3)**
Subjects with TIR >70% (%)	8.5	17.2	**8.6; p<0.0001 (8.6 to 8.7)**	10.0	17.6	**7.6; p<0.0001 (7.6 to 7.7)**	36.6	39.1	**2.5; p<0.0001 (2.5 to 2.5)**

		Sensor 1 TIR <70%		Sensor 1 TAR (>10 mmol/L) >25%			Sensor 1 TBR (<3.9 mmol/L) >4%		
	Sensor 1	Sensor 12	Difference; p-value (95% CI)	Sensor 1	Sensor 12	Difference; p-value (95% CI)	Sensor 1	Sensor 12	Difference; p-value (95% CI)
Subjects with time <3.0 mmol/L <1% (%)	46.1	57.2	**11.1; p<0.0001 (11.1 to 11.2)**	53.6	64.4	**10.9; p<0.0001 (10.9 to 10.9)**	21.5	36.3	**14.7; p<0.0001 (14.7 to 14.8)**
Subjects with time <3.9 mmol/L <4% (%)	48.9	52.6	**3.7; p<0.0001 (3.7 to 3.7)**	57.6	60.2	**2.6; p<0.0001 (2.5 to 2.6)**	11.9	26.0	**14.1; p<0.0001 (14.1 to 14.1)**
Subjects with time >10 mmol/L <25% (%)	15.9	23.3	**7.5; p<0.0001 (7.5 to 7.5)**	9.5	19.5	**10; p<0.0001 (9.98 to 10.03)**	51.1	51.0	**-0.1; p=0.0007 (-0.1 to -0.1)**
Subjects with time >13.9 mmol/L <5% (%)	20.4	31.0	**10.5; p<0.0001 (10.5 to 10.55)**	17.3	29.1	**11.8; p<0.0001 (11.8 to 11.83)**	47.2	54.2	**7; p<0.0001 (7 to 7.05)**
Daily scans (number/day)	14.0	12.4	**-1.6; p<0.0001 (-1.9 to -1.3)**	14.2	12.6	**-1.6; p<0.0001 (-2 to -1.3)**	14.9	13.3	**-1.6; p<0.0001 (-2 to -1.2)**

Data are presented as means, except for time < 3.0 and 3.9 mmol/L, these are medians. For all data the mean difference with 95% CI are provided.
Significant outcome presented in bold (p<0.05).
Abbreviations: CV, coefficient of variation; eHbA1c, estimated HbA1c;TIR, time in range; SD, standard deviation.

Type 2 diabetes

Changes over time in persons with T2DM subdivided by treatment modality are presented in Tables 3 and 4. A TIR <70% at initiation was observed among 39% persons on basal-bolus insulin, 37% on basal insulin, and 17% non-insulin users (Table 3). Within the basal-bolus group improvements of eHbA1c (7.9% (63.4 mmol/mol) to 7.5% (58.6 mmol/mol), p<0.0001), TIR (52% to 61%, p<0.0001), TAR (46% to 37%, p<0.0001), TBR (0.9% to 0.7%, p=0.006) and CV (31% to 30%, p<0.0001) were observed. In the basal insulin group, improvement of eHbA1c (8.2% (65.7 mmol/mol) to 7.6% (59.7 mmol/mol), p=0.007), TIR (49% to 61%, p<0.0001) and TAR (50% to 38%, p<0.0001) was seen. In the small group of non-insulin users (n=21) improvements of eHbA1c (7.9% (62.4 mmol/mol) to 7.1% (54.0 mmol/mol), p=0.02), TIR (53% to 72%, p=0.003) and TAR (45% to 27%, p=0.006) were observed.

A TAR >25% at initiation was observed among 44% of persons with T2DM on basal-bolus insulin, 43% on basal insulin, and 25% non-insulin users (Table 4). In patients with T2DM on basal-bolus insulin improvements of eHbA1c (7.9% (62.7 mmol/mol) to 7.5% (58.1 mmol/mol), p<0.0001), TIR (54% to 63%, p<0.0001) and TAR (44% to 36%, p<0.0001) were observed. In the basal insulin group improvement of eHbA1c (8.0% (64.2 mmol/mol) to 7.6% (59.1 mmol/mol), p=0.001), TIR (52% to 62%, p=0.0002) and TAR (47% to 36%, p=0.0002) was seen. In the non-insulin group improvements of TIR (59% to 71%, p=0.03) and TAR (40% to 29%, p=0.03) were observed. The mean scan frequency declined from 12 to 10 times daily in the basal-bolus insulin group (p<0.0001), and from 10 to 9 times daily in the basal insulin group (p=0.02).

Table 3. Changes in glycemic parameters after 24 weeks of FLASH use among persons with type 2 diabetes with different treatment modalities who started with a TIR <70% during sensor 1

	Basal-bolus			Basal			Non-insulin		
	Sensor 1	**Sensor 12**	**Difference; p-value (95% CI)**	**Sensor 1**	**Sensor 12**	**Difference; p-value (95% CI)**	**Sensor 1**	**Sensor 12**	**Difference; p-value (95% CI)**
Number of subjects	588	588		70	70		21	21	
Mean glucose (mmol/L)	10.1	9.4	**-0.7; p<0.0001 (-0.83 to -0.57)**	10.4	9.5	**-0.9; p=0.0007 (-1.38 to -0.39)**	9.9	8.7	**-1.2; p=0.02 (-2.21 to -0.24)**
eHbA1c (%)	7.9	7.5	**-0.4; p<0.0001 (-0.52 to -0.36)**	8.2	7.6	**-0.55; p=0.0007 (-0.87 to -0.24)**	7.9	7.1	**-0.77; p=0.02 (-1.39 to -0.15)**
eHbA1c (mmol/mol)	63.4	58.6	**-4.8; p<0.0001 (-5.66 to -3.9)**	65.7	59.7	**-6.1; p=0.0007 (-9.46 to -2.66)**	62.4	54.0	**-8.41; p=0.02 (-15.19 to -1.64)**
TIR 3.9-10.0 mmol/L (%)	51.7	61.0	**9.3; p<0.0001 (7.84 to 10.77)**	48.6	60.7	**12.1; p<0.0001 (6.63 to 17.5)**	52.7	72.2	**19.5; p=0.003 (7.62 to 31.47)**
CV (%)	31.0	30.0	**-1; p<0.0001 (-1.39 to -0.54)**	30.3	29.2	-1.09; p=0.11 (-2.44 to 0.25)	29.0	25.5	**-3.5; p=0.03 (-6.71 to -0.31)**
Glucose SD (mmol/L)	55.6	50.5	**-5.1; p<0.0001 (-6 to -4.16)**	55.7	50.1	**-5.6; p=0.001 (-9.02 to -2.27)**	50.6	39.9	**-10.7; p=0.003 (-17.21 to -4.2)**
Time <3.0 mmol/L (%)	0.2	0.0	**-0.27; p=0.0006 (-0.43 to -0.12)**	0.2	0.0	-0.3; p=0.07 (-0.56 to 0.02)	0.1	0.0	-0.6; p=0.13 (-1.33 to 0.19)
Time <3.9 mmol/L (%)	0.9	0.7	**-0.4; p=0.006 (-0.76 to -0.13)**	0.8	0.4	-0.5; p=0.10 (-1.04 to 0.09)	0.7	0.0	-1.7; p=0.13 (-3.99 to 0.55)
Time >10.0 mmol/L (%)	46.3	37.2	**-9.2; p<0.0001 (-10.7 to -7.6)**	49.7	37.6	**-12.1; p<0.0001 (-17.6 to -6.6)**	45.3	27.0	**-18.3; p=0.006 (-30.7 to -5.9)**
Time >13.9 mmol/L (%)	13.6	9.4	**-4.2; p<0.0001 (-5.1 to -3.2)**	16.0	10.1	**-5.9; p=0.008 (-10.2 to -1.6)**	10.7	4.5	**-6.2; p=0.04 (-12.1 to -0.3)**
Subjects with TIR >70% (%)	10.6	33.7	**23.1; p<0.0001 (23.1 to 23.1)**	10.3	34.3	**24; p<0.0001 (23.9 to 24.1)**	9.3	66.7	**57.3; p<0.0001 (57.1 to 57.5)**

	Basal-bolus			Basal			Non-insulin		
	Sensor 1	**Sensor 12**	**Difference; p-value (95% CI)**	**Sensor 1**	**Sensor 12**	**Difference; p-value (95% CI)**	**Sensor 1**	**Sensor 12**	**Difference; p-value (95% CI)**
Subjects with time <3.0 mmol/L <1% (%)	82.9	88.6	**5.7; p<0.0001 (5.7 to 5.8)**	83.3	90.0	**6.7; p<0.0001 (6.7 to 6.8)**	85.0	100.0	**15; p<0.0001 (14.8 to 15.2)**
Subjects with time <3.9 mmol/L <4% (%)	85.4	87.9	**2.5; p<0.0001 (2.5 to 2.6)**	83.4	88.6	**5.1; p<0.0001 (5.1 to 5.2)**	84.7	90.5	**5.8; p<0.0001 (5.6 to 6)**
Subjects with time >10.0 mmol/L <25% (%)	8.4	28.1	**19.6; p<0.0001 (19.6 to 19.7)**	7.5	30.0	**22.5; p<0.0001 (22.4 to 22.6)**	9.4	57.1	**47.7; p<0.0001 (47.5 to 48)**
Subjects with time >13.9 mmol/L <5% (%)	24.2	44.9	**20.7; p<0.0001 (20.7 to 20.7)**	20.6	45.7	**25.16; p<0.0001 (25 to 25.3)**	29.0	66.7	**37.6; p<0.0001 (37.3 to 38)**
Daily scans (number/day)	12.0	10.3	**-1.7; p<0.0001 (-2.2 to -1.2)**	9.5	8.5	-1; p=0.13 (-2.2 to 0.3)	13.0	10.6	-2.5; p=0.15 (-5.9 to 1)

Data are presented as means, except for time < 3.0 and 3.9 mmol/L, these are medians. For all data the mean difference with 95% CI are provided.
Significant outcome presented in bold (p<0.05).
Abbreviations: CV, coefficient of variation; eHbA1c, estimated HbA1c; TIR, time in range; SD, standard deviation.

Table 4. Changes in glycemic parameters after 24 weeks of FLASH use among persons with type 2 diabetes with different treatment modalities who started with a TAR (>10 mmol/L) >25%

	Basal-bolus			Basal			Non-insulin		
	Sensor 1	**Sensor 12**	**Difference; p-value (95% CI)**	**Sensor 1**	**Sensor 12**	**Difference; p-value (95% CI)**	**Sensor 1**	**Sensor 12**	**Difference; p-value (95% CI)**
Number of subjects	667	667		82	82		31	31	
Mean glucose (mmol/L)	10.0	9.3	**-0.7; p<0.0001 (-0.78 to -0.55)**	10.2	9.4	**-0.7; p=0.001 (-1.2 to -0.29)**	9.7	8.9	-0.7; p=0.08 (-1.55 to 0.08)
eHbA1c (%)	7.9	7.5	**-0.4; p<0.0001 (-0.49 to -0.35)**	8.0	7.6	**-0.5; p=0.001 (-0.76 to -0.18)**	7.7	7.2	-0.46; p=0.08 (-0.98 to 0.05)
eHbA1c (mmol/mol)	62.7	58.1	**-4.6; p<0.0001 (-5.38 to -3.79)**	64.2	59.1	**-5.1; p=0.001 (-8.25 to -2.02)**	60.7	55.6	-5.05; p=0.08 (-10.66 to 0.55)
TIR 3.9-10.0 mmol/L (%)	54.4	62.6	**8.2; p<0.0001 (6.82 to 9.53)**	52.2	62.2	**10; p=0.0002 (4.84 to 15.1)**	59.1	70.6	**11.4; p=0.03 (1.4 to 21.5)**
CV (%)	30.2	29.4	**-0.8; p<0.0001 (-1.15 to -0.4)**	29.5	28.6	-0.93; p=0.13 (-2.15 to 0.29)	26.7	25.3	-1.4; p=0.20 (-3.64 to 0.84)
Glucose SD (mmol/L)	54.0	49.2	**-4.7; p<0.0001 (-5.55 to -3.88)**	53.5	48.6	**-4.9; p=0.001 (-7.82 to -1.93)**	46.2	41.1	-5; p=0.10 (-11.12 to 1.03)
Time <3.0 mmol/L (%)	0.1	0.0	**-0.09; p=0.03 (-0.18 to -0.01)**	0.1	0.0	-0.2; p=0.06 (-0.49 to 0.003)	0.1	0.0	**-0.2; p=0.02 (-0.34 to -0.04)**
Time <3.9 mmol/L (%)	0.8	0.5	0; p=0.68 (-0.23 to 0.15)	0.7	0.2	-0.4; p=0.08 (-0.89 to 0.05)	0.5	0.0	-0.8; p=0.13 (-1.82 to 0.25)
Time >10.0 mmol/L (%)	44.4	35.9	**-8.5; p<0.0001 (-9.9 to -7)**	46.5	36.4	**-10; p=0.0002 (-15.2 to -4.9)**	40.0	28.8	**-11.3; p=0.03 (-21.5 to -1.1)**
Time >13.9 mmol/L (%)	12.4	8.8	**-3.7; p<0.0001 (-4.5 to -2.8)**	14.1	9.5	**-4.6; p=0.02 (-8.4 to -0.7)**	8.0	5.9	-2.1; p=0.41 (-7.3 to 3.04)
Subjects with TIR >70% (%)	17.9	38.2	**20.3; p<0.0001 (20.3 to 20.4)**	18.4	36.6	**18.2; p<0.0001 (18.1 to 18.4)**	27.1	64.5	**37.4; p<0.0001 (37.2 to 37.7)**

	Basal-bolus			Basal			Non-insulin		
	Sensor 1	**Sensor 12**	**Difference; p-value (95% CI)**	**Sensor 1**	**Sensor 12**	**Difference; p-value (95% CI)**	**Sensor 1**	**Sensor 12**	**Difference; p-value (95% CI)**
Subjects with time <3.0 mmol/L <1% (%)	87.8	91.2	**3.4; p<0.0001 (3.4 to 3.4)**	86.5	92.7	**6.2; p<0.0001 (6.1 to 6.3)**	92.5	100.0	**7.5; p<0.0001 (7.5 to 7.6)**
Subjects with time <3.9 mmol/L <4% (%)	90.4	90.1	**-0.3; p<0.0001 (-0.3 to -0.3)**	86.9	91.5	**4.6; p<0.0001 (4.5 to 4.6)**	91.8	93.5	**1.7; p<0.0001 (1.6 to 1.8)**
Subjects with time >10.0 mmol/L <25% (%)	10.6	31.5	**20.9; p<0.0001 (20.8 to 20.9)**	11.8	32.9	**21.2; p<0.0001 (21.1 to 21.3)**	16.1	54.8	**38.8; p<0.0001 (38.6 to 39)**
Subjects with time >13.9 mmol/L <5% (%)	29.5	48.3	**18.7; p<0.0001 (18.7 to 18.79)**	28.3	48.8	**20.45; p<0.0001 (20.3 to 20.6)**	45.7	67.7	**22; p<0.0001 (21.8 to 22.3)**
Daily scans (number/day)	12.0	10.3	**-1.7; p<0.0001 (-2.2 to -1.3)**	10.0	8.6	**-1.3; p=0.02 (-2.4 to -0.2)**	12.1	9.8	-2.3; p=0.07 (-4.7 to 0.2)

Data are presented as means, except for time < 3.0 and 3.9 mmol/L, these are medians. For all data the mean difference with 95% CI are provided.
Significant outcome presented in bold (p<0.05).
Abbreviations: CV, coefficient of variation; eHbA1c, estimated HbA1c; TIR, time in range; SD, standard deviation.

Discussion

Overall, these real-life data indicate that continuous FLASH use is associated with improvement of glycemic parameters in most of the users. Improvements were observed in both type 1 and type 2 diabetes in the subgroups with different types of suboptimal glycemic regulation.

An important observation with regards to the subgroup with T1DM and a TIR <70% is the concurrent improvement of TIR, time in hyperglycemia, time in hypoglycemia, and CV. This indicates more stable glucose levels after 24 weeks of FLASH. In the T1DM subgroup with >4% TBR, the initial eHbA1c was much lower (49.1 mmol/L (6.6%)) compared to the other subgroups (<70% TIR and >25% TAR). After 24 weeks of FLASH, less time in hypoglycemia and level 2 hyperglycemia but a small increase in eHbA1c and decrease in TIR was observed. To the best of our knowledge, these are the first real-life data that confirm that FLASH leads to significant reduction of time spent in hypoglycemia without clinically relevant worsening of (e)HbA1c in T1DM [25,26]. As spending time in hypoglycemia is associated with many risks, a diminished quality of life, and adverse clinical outcomes, the observed decrease of time in hypoglycemia is of relevance for patients with T1DM [27,28]. In the recently published FLASH-UK randomized controlled trial among persons with T1DM and a higher HbA1c at baseline (mean 8.7%±0.9% (72±10 mmol/mol), 24-weeks (second generation) FLASH use was associated with improvement of HbA1c, TIR, TAR, TBR and CV, compared to fingerstick testing [5]. The improvements in TIR (43% to 52%) and TAR (50% to 45%) were more pronounced in their study, presumably because of the higher baseline values, as compared to the subgroup with T1DM and TAR > 25% in our study. Further, due to the real-life nature of our data, the magnitude of changes in glycemic parameters could well be diminished compared to changes observed in clinical trial settings since the present study lacks a pre-utilization comparison to establish baseline measures.

Concerning T2DM, there are several observations noteworthy. First, in persons on basal-bolus insulin with an initial TIR <70% time in hypoglycemia decreased while improvements in eHbA1c, TIR, and time in hyperglycemia were observed. In a previous RCT setting FLASH initiation in T2DM patients using basal-bolus insulin led to less time in hypoglycemia but no significant change in TIR, time in hyperglycemia and HbA1c after a 12 month period [29]. Differences in study results may be explained by a higher number of participants in the present study and by differences in study design. Also, subgroup analyses in the RCT might have identified subgroups with different patterns of improvement in glycemic parameters.

Second, in previous studies among persons using basal insulin [30,31] HbA1c improvement after FLASH initiation was observed. The present study adds to these studies by demonstrating improvements in different sensor-derived glycemic target ranges. Third, in the subgroup

of persons with T2DM without insulin treatment and suboptimal glycemic regulation (TIR <70%, n=21; or TAR >25%, n=31, with overlap) significant improvement of eHbA1c, TIR and TAR was observed. Although these findings should be interpreted with caution given the small number of patients, we suggest that FLASH use may be of benefit for persons with T2DM without insulin treatment for those with suboptimal glucose regulation. Apparently, FLASH contributes to a greater understanding of how food, physical activity and stress affect blood glucose levels which in turn may lead to improved self-care behavior, quality of life and adequate lifestyle measures to improve glycemic metrics [32] [33].

The highest scanning frequency in our study was observed among the subgroup of persons with T1DM and >4% TBR, who had the highest TIR and an eHbA1c <7% (<53 mmol/mol). Previous research also showed an association between higher glucose monitoring frequency with FLASH and improvement of eHbA1c, TIR, time in hyperglycemia and a lower glycemic variability in patients with diabetes [34,35]. At this stage we cannot add much to these observations, except that the occurrence of hypoglycemia is associated with a higher monitoring frequency. Whether this higher frequency is associated with a proactive stance (i.e., frequent checks to prevent or diminish hypoglycemic episodes) or a reactive stance (i.e. frequent checks as soon as hypoglycemia is present) is unknown.

In addition to the existing literature, the present study provides information about the impact of FLASH use in groups with different treatment modalities and different types of suboptimal glycemic regulation. Whether the observed improvements in glycemic metrics eventually translate into relevant differences in outcomes merits further study. In the present work there is – in line with other reports on CGM metrics – focus on TIR as measure of glycemic control. Recent work by Rodbard et al. [36] suggests that TAR (instead of TIR) is more valuable as a substitute for glucose control. In the present study TAR also improved in all subgroups.

Limitations include the real-life observational nature of the study with the lack of a comparator group, but strengths include having a greater number of patients. In total 3,722 out of 13,734 persons (27%) continuously used FLASH for 24 weeks, as was recorded by sequential use of 12 sensors paired with the same reader. Information about the reasons for lack of continued data uploading, discontinuation of FLASH use or the lack of consistent use of FLASH could not be obtained, because of the anonymous nature of the data. Hypothetically, persons who continued FLASH for 24 weeks might be more motivated to make thorough use of the system because of the experienced benefits and this potentially resulted in selection bias. Also, differences in reimbursement for FLASH between healthcare systems in Europe should be taken into account: as FLASH use is not reimbursed for non-insulin users in Europe, this group of FLASH users must have paid the costs of FLASH themselves, which likely have led to selection of persons with type 2 diabetes and a high motivation to make optimal

use the device including more frequent glucose checks. Another notable observation is the high percentage of male FLASH users with T2DM. Although T2DM is more common among middle aged men than women, this percentage was higher than might be expected [37,38], possibly because men had more resources to start FLASH (on their own costs) [39]. Due to the anonymous nature of the database used for this study, detailed information concerning characteristics of FLASH users, including socioeconomic factors, available income, lifestyle data (e.g., carbohydrate intake and exercise patterns) and BMI was unavailable. Information about use of oral glucose lowering medication is lacking, as it was not included in the questionnaire. Furthermore, we do not have information on aspects of the health status of persons with diabetes that are relevant to their quality of life, in terms of patient-reported outcome measures (PROMs) or patient-reported experience measures (PREMs) [40]. Lastly, it should be noted that sensor derived estimates of the eHbA1c does not always closely approximate a laboratory measured HbA1c [41]. eHbA1c was calculated using the linear regression formula presented by the ADAG Study group [42].

Conclusions

The findings of this study extends existing literature about the effects of FLASH use on various measures of glycemic regulation, by providing data regarding the effects of FLASH use among groups with different treatment modalities and subgroups with different types of glycemic dysregulation. The findings suggest that use of FLASH for 24 weeks by persons with T1DM and T2DM is associated with an improvement of glycemic parameters in the majority of analyses. More data is needed on persons with T2DM without insulin use to allow firmer conclusions for that specific group.

Abbreviations

(CSII) continuous subcutaneous insulin infusion, (CV) coefficient of variation, (eHbA1c) estimated HbA1c, (FLASH) flash glucose monitoring, (IQR) Interquartile Range, (MDI) multiple daily injections, (rt-CGM) real time Continuous Glucose Monitoring, (SMBG) self-monitoring of blood glucose, (SD) standard deviation, (TAR) time above range, (TBR) time below range, (TIR) time in range.

Funding statement

This work was partly funded by the University Medical Center Groningen (Department of Internal Medicine) and partly by Abbott Diabetes Care (in the form of an unconditional research grant).

References

1. Cappon G, Vettoretti M, Sparacino G, Facchinetti A. Continuous Glucose Monitoring Sensors for Diabetes Management: A Review of Technologies and Applications. Diabetes Metab J 2019;43:383–97. https://doi.org/10.4093/dmj.2019.0121.
2. Ang E, Lee ZX, Moore S, Nana M. Flash glucose monitoring (FGM): A clinical review on glycaemic outcomes and impact on quality of life. J Diabetes Complications 2020;34:107559. https://doi.org/10.1016/j.jdiacomp.2020.107559.
3. Deshmukh H, Wilmot EG, Gregory R, Barnes D, Narendran P, Saunders S, et al. Effect of Flash Glucose Monitoring on Glycemic Control, Hypoglycemia, Diabetes-Related Distress, and Resource Utilization in the Association of British Clinical Diabetologists (ABCD) Nationwide Audit. Diabetes Care 2020:dc200738. https://doi.org/10.2337/dc20-0738.
4. Evans M, Welsh Z, Ells S, Seibold A. The Impact of Flash Glucose Monitoring on Glycaemic Control as Measured by HbA1c: A Meta-analysis of Clinical Trials and Real-World Observational Studies. Diabetes Ther 2020;11:83–95. https://doi.org/10.1007/s13300-019-00720-0.
5. Leelarathna L, Evans ML, Neupane S, Rayman G, Lumley S, Cranston I, et al. Intermittently Scanned Continuous Glucose Monitoring for Type 1 Diabetes. N Engl J Med 2022;387:1477–87. https://doi.org/10.1056/NEJMoa2205650.
6. Lameijer A, Fokkert MJ, Edens MA, Slingerland RJ, Bilo HJG, van Dijk PR. Determinants of HbA1c reduction with FreeStyle Libre flash glucose monitoring (FLARE-NL 5). J Clin Transl Endocrinol 2020;22:100237. https://doi.org/10.1016/j.jcte.2020.100237.
7. Dickinson JK, Guzman SJ, Maryniuk MD, O'Brian CA, Kadohiro JK, Jackson RA, et al. The Use of Language in Diabetes Care and Education. Diabetes Care 2017;40:1790–9. https://doi.org/10.2337/dci17-0041.
8. Lameijer A, Fokkert MJ, Edens MA, Gans ROB, Bilo HJG, Dijk PR van. Two-year use of flash glucose monitoring is associated with sustained improvement of glycemic control and quality of life (FLARE-NL-6). BMJ Open Diabetes Res Care 2021;9:e002124. https://doi.org/10.1136/bmjdrc-2021-002124.
9. Fokkert M, Dijk P van, Edens M, Barents E, Mollema J, Slingerland R, et al. Improved well-being and decreased disease burden after 1-year use of flash glucose monitoring (FLARE-NL4). BMJ Open Diabetes Res Care 2019;7. https://doi.org/10.1136/bmjdrc-2019-000809.
10. Al Hayek AA, Robert AA, Al Dawish MA. Effectiveness of the Freestyle Libre Flash Glucose Monitoring System on Diabetes Distress Among Individuals with Type 1 Diabetes: A Prospective Study. Diabetes Ther Res Treat Educ Diabetes Relat Disord 2020;11:927–37. https://doi.org/10.1007/s13300-020-00793-2.
11. Roussel R, Riveline J-P, Vicaut E, de Pouvourville G, Detournay B, Emery C, et al. Important Drop in Rate of Acute Diabetes Complications in People With Type 1 or Type 2 Diabetes After Initiation of Flash Glucose Monitoring in France: The RELIEF Study. Diabetes Care 2021;44:1368–76. https://doi.org/10.2337/dc20-1690.
12. Riveline J-P, Roussel R, Vicaut E, de Pouvourville G, Detournay B, Emery C, et al. Reduced Rate of Acute Diabetes Events with Flash Glucose Monitoring Is Sustained for 2 Years After Initiation: Extended Outcomes from the RELIEF Study. Diabetes Technol Ther 2022;24:611–8. https://doi.org/10.1089/dia.2022.0085.
13. 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. https://doi.org/10.2337/dci19-0028.
14. Advani A. Positioning time in range in diabetes management. Diabetologia 2020;63:242–52. https://doi.org/10.1007/s00125-019-05027-0.

15. Lu J, Wang C, Shen Y, Chen L, Zhang L, Cai J, et al. Time in Range in Relation to All-Cause and Cardiovascular Mortality in Patients With Type 2 Diabetes: A Prospective Cohort Study. Diabetes Care 2021;44:549–55. https://doi.org/10.2337/dc20-1862.

16. Beck RW, Bergenstal RM, Riddlesworth TD, Kollman C, Li Z, Brown AS, et al. Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials. Diabetes Care 2019;42:400–5. https://doi.org/10.2337/dc18-1444.

17. Raj R, Mishra R, Jha N, Joshi V, Correa R, Kern PA. Time in range, as measured by continuous glucose monitor, as a predictor of microvascular complications in type 2 diabetes: a systematic review. BMJ Open Diabetes Res Care 2022;10:e002573. https://doi.org/10.1136/bmjdrc-2021-002573.

18. El Malahi A, Van Elsen M, Charleer S, Dirinck E, Ledeganck K, Keymeulen B, et al. Relationship Between Time in Range, Glycemic Variability, HbA1c, and Complications in Adults With Type 1 Diabetes Mellitus. J Clin Endocrinol Metab 2022;107:e570–81. https://doi.org/10.1210/clinem/dgab688.

19. Elbalshy M, Haszard J, Smith H, Kuroko S, Galland B, Oliver N, et al. Effect of divergent continuous glucose monitoring technologies on glycaemic control in type 1 diabetes mellitus: A systematic review and meta-analysis of randomised controlled trials. Diabet Med 2022;39:e14854. https://doi.org/10.1111/dme.14854.

20. Visser MM, Charleer S, Fieuws S, De Block C, Hilbrands R, Van Huffel L, et al. Effect of switching from intermittently scanned to real-time continuous glucose monitoring in adults with type 1 diabetes: 24-month results from the randomised ALERTT1 trial. Lancet Diabetes Endocrinol 2023;11:96–108. https://doi.org/10.1016/S2213-8587(22)00352-7.

21. Krakauer M, Botero JF, Lavalle-González FJ, Proietti A, Barbieri DE. A review of flash glucose monitoring in type 2 diabetes. Diabetol Metab Syndr 2021;13:42. https://doi.org/10.1186/s13098-021-00654-3.

22. Alva S, Bailey T, Brazg R, Budiman ES, Castorino K, Christiansen MP, et al. Accuracy of a 14-Day Factory-Calibrated Continuous Glucose Monitoring System With Advanced Algorithm in Pediatric and Adult Population With Diabetes. J Diabetes Sci Technol 2022;16:70–7. https://doi.org/10.1177/1932296820958754.

23. Freestyle Libre | Software Disclaimer | Abbott n.d. https://www.freestyle.abbott/ca/en/products/libre/software/disclaimer.html (accessed December 31, 2020).

24. Jangam S, Dunn T, Xu Y, Hayter G, Ajjan RA. Flash glucose monitoring improves glycemia in higher risk patients: a longitudinal, observational study under real-life settings. BMJ Open Diabetes Res Care 2019;7:e000611. https://doi.org/10.1136/bmjdrc-2018-000611.

25. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. The Lancet 2016;388:2254–63. https://doi.org/10.1016/S0140-6736(16)31535-5.

26. Charleer S, De Block C, Van Huffel L, Broos B, Fieuws S, Nobels F, et al. Quality of Life and Glucose Control After 1 Year of Nationwide Reimbursement of Intermittently Scanned Continuous Glucose Monitoring in Adults Living With Type 1 Diabetes (FUTURE): A Prospective Observational Real-World Cohort Study. Diabetes Care 2020;43:389–97. https://doi.org/10.2337/dc19-1610.

27. Kalra S, Mukherjee JJ, Venkataraman S, Bantwal G, Shaikh S, Saboo B, et al. Hypoglycemia: The neglected complication. Indian J Endocrinol Metab 2013;17:819–34. https://doi.org/10.4103/2230-8210.117219.

28. Zhou Z, Sun B, Huang S, Zhu C, Bian M. Glycemic variability: adverse clinical outcomes and how to improve it? Cardiovasc Diabetol 2020;19:102. https://doi.org/10.1186/s12933-020-01085-6.

29. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline J-P, Rayman G. Use of Flash Glucose-Sensing Technology for 12 months as a Replacement for Blood Glucose Monitoring in Insulin-treated Type 2 Diabetes. Diabetes Ther 2017;8:573–86. https://doi.org/10.1007/s13300-017-0255-6.

30. Carlson AL, Daniel TD, DeSantis A, Jabbour S, Karslioglu French E, Kruger D, et al. Flash glucose monitoring in type 2 diabetes managed with basal insulin in the USA: a retrospective real-world chart review study and meta-analysis. BMJ Open Diabetes Res Care 2022;10:e002590. https://doi.org/10.1136/bmjdrc-2021-002590.

31. Elliott T, Beca S, Beharry R, Tsoukas MA, Zarruk A, Abitbol A. The impact of flash glucose monitoring on glycated hemoglobin in type 2 diabetes managed with basal insulin in Canada: A retrospective real-world chart review study. Diab Vasc Dis Res 2021;18:14791641211021374. https://doi.org/10.1177/14791641211021374.

32. White ND, Knezevich E. Flash Glucose Monitoring Technology Impact on Diabetes Self-Care Behavior. Am J Lifestyle Med 2019;14:130–2. https://doi.org/10.1177/1559827619890955.

33. Wada E, Onoue T, Kobayashi T, Handa T, Hayase A, Ito M, et al. Flash glucose monitoring helps achieve better glycemic control than conventional self-monitoring of blood glucose in non-insulin-treated type 2 diabetes: a randomized controlled trial. BMJ Open Diabetes Res Care 2020;8:e001115. https://doi.org/10.1136/bmjdrc-2019-001115.

34. Lameijer A, Lommerde N, Dunn TC, Fokkert MJ, Edens MA, Kao K, et al. Flash Glucose Monitoring in the Netherlands: increased monitoring frequency is associated with improvement of glycemic parameters. Diabetes Res Clin Pract 2021:108897. https://doi.org/10.1016/j.diabres.2021.108897.

35. Dunn TC, Xu Y, Hayter G, Ajjan RA. Real-world flash glucose monitoring patterns and associations between self-monitoring frequency and glycaemic measures: A European analysis of over 60 million glucose tests. Diabetes Res Clin Pract 2018;137:37–46. https://doi.org/10.1016/j.diabres.2017.12.015.

36. Rodbard D. Continuous glucose monitoring metrics (Mean Glucose, time above range and time in range) are superior to glycated haemoglobin for assessment of therapeutic efficacy. Diabetes Obes Metab 2023;25:596–601. https://doi.org/10.1111/dom.14906.

37. on behalf of The Scottish Diabetes Research Network Epidemiology Group, Logue J, Walker JJ, Colhoun HM, Leese GP, Lindsay RS, et al. Do men develop type 2 diabetes at lower body mass indices than women? Diabetologia 2011;54:3003–6. https://doi.org/10.1007/s00125-011-2313-3.

38. Nordström A, Hadrévi J, Olsson T, Franks PW, Nordström P. Higher Prevalence of Type 2 Diabetes in Men Than in Women Is Associated With Differences in Visceral Fat Mass. J Clin Endocrinol Metab 2016;101:3740–6. https://doi.org/10.1210/jc.2016-1915.

39. The gender pay gap situation in the EU. Eur Comm - Eur Comm n.d. https://ec.europa.eu/info/policies/justice-and-fundamental-rights/gender-equality/equal-pay/gender-pay-gap-situation-eu_en (accessed September 11, 2022).

40. Wu Z, Bandini A, Brazeau A-S, Rabasa-Lhoret R. Patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs), it's time to give more credits to patients' voice in research: the example of assessing hypoglycemia burden. Diabetes Metab 2023;49:101417. https://doi.org/10.1016/j.diabet.2022.101417.

41. Bergenstal RM, Beck RW, Close KL, Grunberger G, Sacks DB, Kowalski A, et al. Glucose Management Indicator (GMI): A New Term for Estimating A1C From Continuous Glucose Monitoring. Diabetes Care 2018;41:2275–80. https://doi.org/10.2337/dc18-1581.

42. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ, et al. Translating the A1C Assay Into Estimated Average Glucose Values. Diabetes Care 2008;31:1473–8. https://doi.org/10.2337/dc08-0545.

Supplemental material

Supplemental Table S1. Changes in glycemic parameters among persons with type 1 diabetes using CSII after 24 weeks of FLASH use by starting glycemic levels

	Sensor 1 TIR <70%			**Sensor 1 TAR (>10 mmol/L) >25%**			**Sensor 1 TBR (<3.9 mmol/L) >4%**		
	Sensor 1	**Sensor 12**	**Difference; p-value (95% CI)**	**Sensor 1**	**Sensor 12**	**Difference; p-value (95% CI)**	**Sensor 1**	**Sensor 12**	**Difference; p-value (95% CI)**
Number of subjects	277	277		262	262		190	190	
Mean glucose (mmol/L)	9.4	9.1	**-0.3; p=0.0004 (-0.40 to -0.11)**	9.6	9.3	**-0.3; p<0.0001 (-0.44 to -0.16)**	7.9	8.0	0.1; p=0.18 (-0.05 to 0.25)
eHbA1c (%)	7.5	7.4	**-0.2; p=0.0004 (-0.25 to -0.07)**	7.7	7.5	**-0.2; p<0.0001 (-0.28 to -0.10)**	6.6	6.6	0.1; p=0.18 (-0.03 to 0.16)
eHbA1c (mmol/mol)	58.8	57.0	**-1.8; p=0.0004 (-2.72 to -0.79)**	60.2	58.2	**-2.1; p<0.0001 (-3.04 to -1.13)**	48.4	49.1	0.7; p=0.18 (-0.32 to 1.72)
TIR 3.9-10.0 mmol/L (%)	55.6	58.6	**3.0; p<0.0001 (1.74 to 4.27)**	55.5	58.7	**3.1; p<0.0001 (1.83 to 4.43)**	67.3	66.9	-0.4; p=0.55 (-1.73 to 0.92)
CV (%)	38.3	37.6	**-0.6; p=0.04 (-1.28 to -0.02)**	37.0	36.4	-0.5; p=0.10 (-1.19 to 0.10)	40.4	39.2	**-1.2; p=0.002 (-2.01 to -0.45)**
Glucose SD (mmol/L)	3.6	3.4	**-0.1; p<0.0001 (-0.21 to -0.07)**	3.5	3.4	**-0.2; p<0.0001 (-0.23 to -0.08)**	3.2	3.1	**-0.1; p=0.006 (-0.15 to 0.01)**
Time <3.0 mmol/L (%)	0.9	0.5	-0.1; p=0.68 (-0.37 to 0.24)	0.6	0.3	0.0; p=0.95 (-0.23 to 0.25)	2.4	2.0	-0.1; p=0.55 (-0.62 to 0.33)
Time <3.9 mmol/L (%)	3.5	3.0	-0.1; p=0.75 (-0.62 to 0.44)	2.7	2.3	0.1; p=0.54 (-0.30 to 0.57)	8.0	7.4	-0.5; p=0.20 (-1.34 to 0.28)
Time >10.0 mmol/L (%)	39.5	36.4	**-3.2; p<0.0001 (-4.59 to -1.75)**	41.2	37.6	**-3.5; p<0.0001 (-4.98 to -2.11)**	23.6	24.4	0.8; p=0.31 (-0.74 to 2.32)
Time >13.9 mmol/L (%)	12.6	10.8	**-1.8; p=0.0002 (-2.76 to -0.86)**	13.1	11.1	**-2.1; p<0.0001 (-3.04 to -1.09)**	6.4	6.6	0.2; p=0.68 (-0.63 to 0.96)
Subjects with TIR >70% (%)	10.9	16.6	**5.7; p<0.0001 (5.66 to 5.74)**	13.1	17.9	**4.9; p<0.0001 (4.82 to 4.91)**	42.2	41.6	**-0.6; p<0.0001 (-0.69 to -0.56)**
Subjects with time <3.0 mmol/L <1% (%)	52.1	60.6	**8.6; p<0.0001 (8.50 to 8.61)**	60.9	70.6	**9.7; p<0.0001 (9.67 to 9.78)**	23.3	32.6	**9.3; p<0.0001 (9.26 to 9.41)**

	Sensor 1 TIR <70%			Sensor 1 TAR (>10 mmol/L) >25%			Sensor 1 TBR (<3.9 mmol/L) >4%		
	Sensor 1	Sensor 12	Difference; p-value (95% CI)	Sensor 1	Sensor 12	Difference; p-value (95% CI)	Sensor 1	Sensor 12	Difference; p-value (95% CI)
Subjects with time <3.9 mmol/L <4% (%)	54.4	57.4	**3.0; p<0.0001 (2.99 to 3.10)**	64.5	67.2	**2.6; p<0.0001 (2.58 to 2.70)**	12.9	25.3	**12.4; p<0.0001 (12.31 to 12.44)**
Subjects with time >10 mmol/L <25% (%)	16.5	22.7	**6.2; p<0.0001 (6.18 to 6.28)**	10.5	17.9	**7.4; p<0.0001 (7.38 to 7.48)**	56.1	55.3	**-0.9; p<0.0001 (-0.93 to -0.79)**
Subjects with time >13.9 mmol/L <5% (%)	21.3	30.0	**8.7; p<0.0001 (8.64 to 8.76)**	19.0	28.2	**9.3; p<0.0001 (9.19 to 9.31)**	50.0	54.2	**4.2; p<0.0001 (4.10 to 4.25)**
Daily scans (number/day)	14.0	12.5	**-1.5; p<0.0001 (-2.09 to -0.89)**	14.2	12.6	**-1.6; p<0.0001 (-2.22 to -0.99)**	15.1	13.0	**-2.1; p<0.0001 (-3.01 to -1.22)**

Data are presented as means, except for time < 3.0 and 3.9 mmol/L, these are medians. For all data the mean difference with 95% CI are provided. Significant outcome presented in bold (p<0.05). Abbreviations: CV, coefficient of variation; eHbA1c, estimated HbA1c;TIR, time in range; SD, standard deviation.

Supplemental Table S2. Changes in glycemic parameters among persons with type 1 diabetes using MDI after 24 weeks of FLASH use by starting glycemic levels

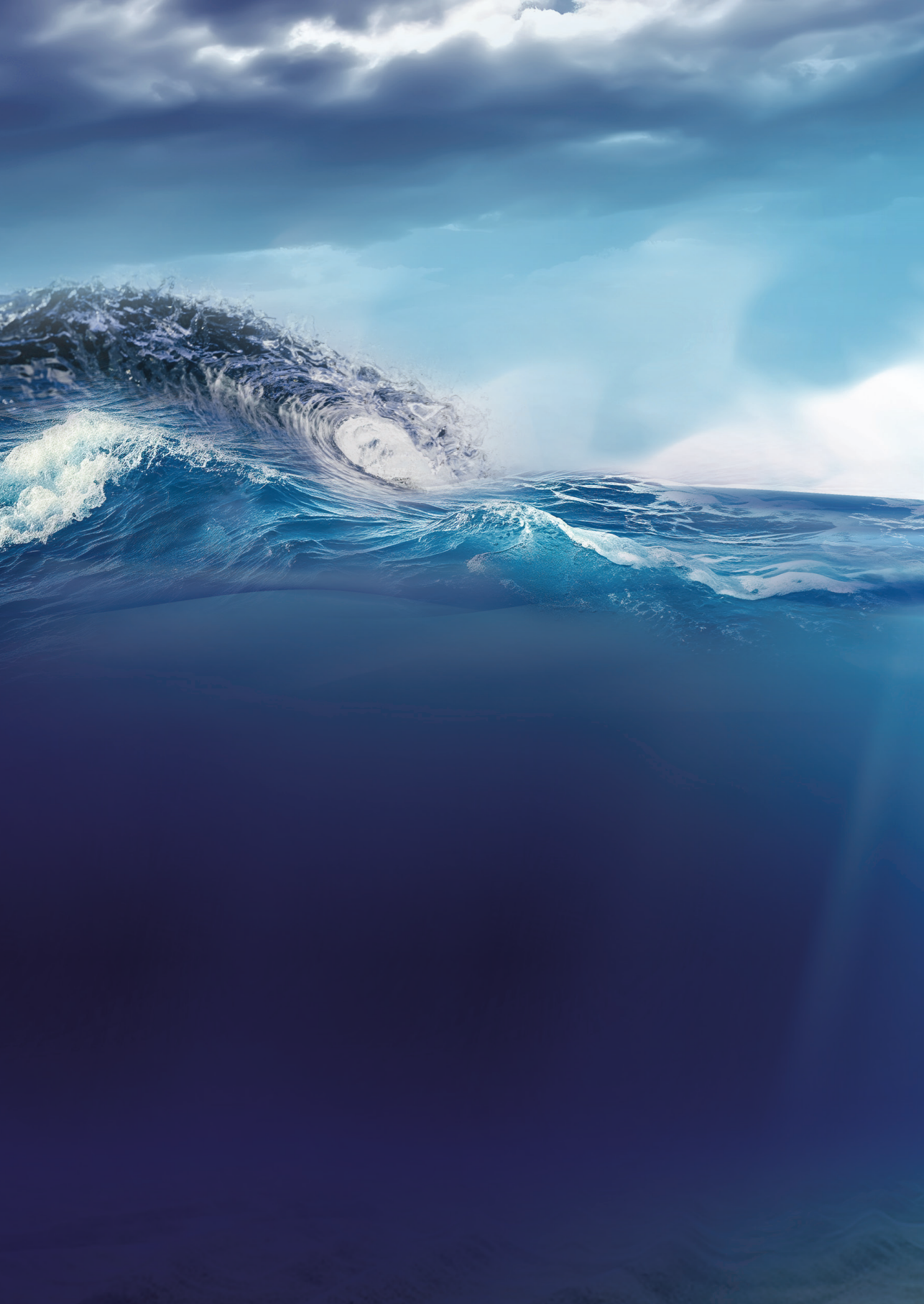
	Sensor 1 TIR <70%			Sensor 1 TAR (>10 mmol/L) >25%			Sensor 1 TBR (<3.9 mmol/L) >4%		
	Sensor 1	Sensor 12	Difference; p-value (95% CI)	Sensor 1	Sensor 12	Difference; p-value (95% CI)	Sensor 1	Sensor 12	Difference; p-value (95% CI)
Number of subjects	868	868		812	812		660	660	
Mean glucose (mmol/L)	9.5	9.2	**-0.3; p<0.0001 (-0.39 to -0.20)**	9.7	9.3	**-0.4; p<0.0001 (-0.48 to -0.28)**	8.0	8.1	**0.1; p=0.02 (0.02 to 0.18)**
eHbA1c (%)	7.6	7.4	**-0.2; p<0.0001 (-0.25 to -0.12)**	7.7	7.5	**-0.2; p<0.0001 (-0.30 to -0.18)**	6.7	6.7	**0.1; p=0.02 (0.01 to 0.11)**
eHbA1c (mmol/mol)	59.2	57.2	**-2.0; p<0.0001 (-2.69 to -1.37)**	61.0	58.4	**-2.6; p<0.0001 (-3.31 to -1.94)**	49.3	50.0	**0.7; p=0.02 (0.12 to 1.25)**
TIR 3.9-10.0 mmol/L (%)	53.1	57.2	**4.0; p<0.0001 (3.17 to 4.90)**	52.8	56.9	**4.1; p<0.0001 (3.18 to 5.01)**	64.1	65.3	**1.2; p=0.0009 (0.50 to 1.93)**

	Sensor 1 TIR <70%			Sensor 1 TAR (>10 mmol/L) >25%			Sensor 1 TBR (<3.9 mmol/L) >4%		
	Sensor 1	Sensor 12	Difference; p-value (95% CI)	Sensor 1	Sensor 12	Difference; p-value (95% CI)	Sensor 1	Sensor 12	Difference; p-value (95% CI)
CV (%)	39.1	37.7	**-1.4; p<0.0001 (-1.80 to -1.01)**	37.9	36.9	**-1.0; p<0.0001 (-1.41 to -0.64)**	41.1	38.8	**-2.3; p<0.0001 (-2.77 to -1.91)**
Glucose SD (mmol/L)	3.7	3.4	**-0.2; p<0.0001 (-0.26 to -0.18)**	3.7	3.4	**-0.2; p<0.0001 (-0.27 to -0.18)**	3.3	3.2	**-0.2; p<0.0001 (-0.21 to -0.12)**
Time <3.0 mmol/L (%)	1.3	0.8	**-0.5; p<0.0001 (-0.69 to -0.27)**	0.9	0.6	**-0.2; p=0.005 (-0.40 to -0.07)**	2.7	1.7	**-0.7; p<0.0001 (-1.00 to -0.45)**
Time <3.9 mmol/L (%)	4.4	4.0	**-0.6; p=0.0007 (-0.96 to -0.26)**	3.4	3.3	-0.1; p=0.67 (-0.36 to 0.23)	8.5	6.4	**-1.6; p<0.0001 (-2.06 to -1.10)**
Time >10.0 mmol/L (%)	40.7	37.0	**-3.6; p<0.0001 (-4.59 to -2.67)**	42.7	38.5	**-4.3; p<0.0001 (-5.28 to -3.27)**	25.9	26.2	0.3; p=0.54 (-0.56 to 1.06)
Time >13.9 mmol/L (%)	14.0	11.6	**-2.4; p<0.0001 (-3.06 to -1.74)**	14.7	12.1	**-2.6; p<0.0001 (-3.32 to -1.91)**	7.7	6.9	**-0.9; p=0.0003 (-1.31 to -0.40)**
Subjects with TIR >70% (%)	8.0	17.4	**9.4; p<0.0001 (9.37 to 9.42)**	9.3	17.6	**8.3; p<0.0001 (8.31 to 8.36)**	35.1	38.3	**3.3; p<0.0001 (3.23 to 3.30)**
Subjects with time <3.0 mmol/L <1% (%)	44.0	55.8	**11.8; p<0.0001 (11.74 to 11.81)**	51.3	62.1	**10.8; p<0.0001 (10.75 to 10.82)**	21.2	37.3	**16.0; p<0.0001 (16.00 to 16.08)**
Subjects with time <3.9 mmol/L <4% (%)	46.8	50.7	**3.9; p<0.0001 (3.83 to 3.90)**	55.3	57.8	**2.4; p<0.0001 (2.41 to 2.48)**	11.8	26.4	**14.6; p<0.0001 (14.52 to 14.59)**
Subjects with time >10 mmol/L <25% (%)	16.0	23.8	**7.9; p<0.0001 (7.85 to 7.91)**	9.3	20.2	**10.9; p<0.0001 (10.84 to 10.90)**	49.6	49.8	**0.3; p<0.0001 (0.23 to 0.30)**
Subjects with time >13.9 mmol/L <5% (%)	20.6	31.7	**11.0; p<0.0001 (11.01 to 11.07)**	17.2	29.9	**12.7; p<0.0001 (12.68 to 12.74)**	46.6	54.1	**7.5; p<0.0001 (7.47 to 7.55)**
Daily scans (number/day)	14.2	12.5	**-1.6; p<0.0001 (-2.05 to -1.22)**	14.4	12.7	**-1.7; p<0.0001 (-2.12 to -1.25)**	15.0	13.5	**-1.5; p<0.0001 (-1.92 to -1.05)**

Data are presented as means, except for time < 3.0 and 3.9 mmol/L, these are medians. For all data the mean difference with 95% CI are provided. Significant outcome presented in bold (p<0.05). Abbreviations: CV, coefficient of variation; eHbA1c, estimated HbA1c;TIR, time in range; SD, standard deviation.

Supplemental Table S3. Countries represented in the study

Country	Total number of subjects, (%)
Germany	8341 (60.7%)
The Netherlands	1114 (8.1%)
Portugal	676 (4.9%)
United Kingdom	528 (3.8%)
Spain	530 (3.9%)
Belgium	549 (4.0%)
Italy	443 (3.2%)
Swiss Republic	424 (3.1%)
Finland	203 (1.5%)
Greece	175 (1.3%)
Poland	200 (1.5%)
Sweden	166 (1.2%)
Ustria	173 (1.3%)
France	85 (0.62%)
Denmark	27 (0.20%)
Ireland	31 (0.22%)
Luxembourg	59 (0.43%)
Czechia	8 (0.058%)
Croatia	2 (0.015%)



Chapter 7

The impact of socioeconomic factors, social determinants and ethnicity on the utilization of glucose sensor technology among persons with diabetes mellitus: a narrative review

R.A. Been [1], A. Lameijer [1], R.O.B. Gans [2], A.P. van Beek [1], A.P. Kingsnorth [3], P. Choudhary [4], P.R. van Dijk [1]

1. University of Groningen, University Medical Center Groningen, Department of Endocrinology, 9713 GZ, Groningen, The Netherlands.
2. University of Groningen, University Medical Center Groningen, Department of Internal Medicine, 9713 GZ, Groningen, The Netherlands.
3. School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, LE11 3TU United Kingdom
4. University of Leicester, Leicester General Hospital, Leicester, Leicester Diabetes Centre - Bloom, LE5 4PW, United Kingdom.

Abstract

Continuous glucose monitoring (CGM) usage has been shown to improve disease outcomes in people living with diabetes by facilitating better glycaemic management. However, previous research has suggested that access to these devices can be influenced by non-medical factors such as socio-economic status and ethnicity. It is critical that equitable access to CGM devices is ensured as people from those groups experience poorer diabetes-related health-outcomes. In this narrative review we provide an overview of the various healthcare systems worldwide and how socio-economic status, social context, and ethnicity shape device usage and the associated health outcomes. In general, we found that having a lower socio-economic status and belonging to an ethnic minority group negatively impacts on CGM usage. While financial means proved to be an important mediator in this process, it was not the sole driver as disparities persisting even after adjustment for factors such as income and insurance status. Recommendations to increase CGM usage for people of a lower socio-economic status and ethnic minorities include increasing the availability of financial, administrative, and educational support, for both patients and health care providers. However, recommendations will vary due to local country specific circumstances, such as reimbursement criteria and healthcare ecosystems.

Novelty statement:

- The use of continuous glucose monitor (CGM) technology is known to be influenced by socio-economic status; however, an overview of available evidence was lacking.
- This overview found that the relationship between socio-economic status and CGM use might be mediated by limited financial means and reimbursement options, a lower educational level, and a minority status.
- Possible solutions to address and overcome current barriers are suggested.

Introduction

Over the past decades, technological innovations have dramatically altered the available treatment options for diabetes (1,2). Continuous subcutaneous insulin infusion (CSII) has emerged as a viable alternative to multiple daily injections (MDI) (3), and the development of continuous glucose monitoring (CGM) has done the same for capillary measurements (4). Those technologies, in combination with glucose stabilizing algorithms, have led to the development of hybrid closed-loop systems (HCLS), which utilize the continuous stream of data of the monitoring devices to titrate the continuous administration of insulin (5). These CGM devices have been proven to be beneficial to both people with type 1 (6,7) and type 2 diabetes (8). Additionally, it has been found that those with higher baseline HbA1c gain greater benefit once initiated on CGM technology (9).

However, with the increase in options, comes the question of who has access to them. It is known that access to diabetes care (10) and technology in general (11) is affected by factors such as socioeconomic status (SES) and ethnicity. SES is the social standing or class of an individual or group; it is defined as a measure of one's combined economic and social standing (12). It is part of the social determinants of health (SDOH), which, also encompass factors such as social context and physical environment (13). In research, there are multiple methods to quantify SES (14), which typically include measures of income, education, and occupational social class. Lower SES has been associated with reduced access to healthcare (15) and greater mortality in general (16), and this also holds true for diabetes (10). The prevalence of type 2 diabetes is higher among persons with lower SES (10). Additionally, these people with diabetes and with lower SES suffer from lower attainment of treatment goals (17–19) and higher morbidity (20,21) and mortality (22–24).

Ethnicity, then, is a factor that further influences access to care (25) and health outcomes (20). SES and ethnicity have always been closely intertwined and adjusting for the confounding effect of ethnicity can be a complicated matter (26). However, even if such adjustment have taken place, disparities in access to diabetes treatment and outcomes persist (17). This shows it to be an independent factor, meriting specific attention.

Summarizing, it can be stated that CGM technology can improve the treatment outcomes of people with diabetes (6,8,27), especially in those with worse baseline glycaemic regulation (9). Furthermore, people with lower SES and/or belonging to an ethnic minority, are affected disproportionally more by diabetes (10,17–23,28). Additionally, access to CGM technology is lower in people with lower SES and/or belonging to an ethnic minority (10,11).

It stands to reason that the population that can gain the most from CGM technology, would also use it the most. Yet this is not case. As such, efforts must be made to address this discrepancy. The first step to approaching this issue is identifying the underlying mechanism(s). To that end, we will review the available literature on the subject and how these inequities might be addressed.

Methods

A literature search of the PubMed and Embase databases was performed using the search strategy described in Appendix A. The resulting articles were then reviewed for eligibility based on the following criteria:

- The article should mainly concern the access to, the use of and/or the efficacy of CGM devices as affected by SES and/or ethnicity. Consequently, articles mainly concerning the effects of insulin pumps, smart pens and/or telehealth are excluded.
- Articles should be published after 2000, after the emergence of CGM technology.
- Articles should be written in English.

Where applicable, references of articles were similarly investigated and included as per the criteria above. Furthermore, Google Scholar was employed using the search-terms described in Appendix A to source further articles.

The employed search strategy automatically excluded articles according to criterium 2. Duplicates were similarly excluded. The remaining results were screened first by title, then by abstract and finally per full text. Of the 1.750 PubMed results and 89 Embase results, 199 (193 PubMed, 6 Embase) were selected based on their title for review of the abstract. Of those, 64 were selected for full-text review, of which 44 were selected for inclusion. Review of references revealed an additional 8 studies suitable for inclusion. Data were extracted from these articles and grouped per domain of SES (financial/occupational and education), social factors and/or ethnicity. For the full results of this data extraction, please see Appendix B.

Current situation

Currently, the healthcare systems of most western nations have adopted CGMs into their diabetes care. However, the regulations and protocols surrounding the prescription of these devices differs among them. These differences affect which parts of the population gain and maintain access to these devices upon introduction.

USA

The USA utilizes a mixed healthcare insurance system, with publicly financed insurance in the form of Medicare (generally targeted at those >65) and Medicaid (targeted at those with limited incomes), and private insurance providers, which is often provided through employers (29). Medicare reimburses CGM technology for patients with type 1 or type 2 diabetes with a need for frequent measurements of blood glucose levels and routine in-clinic visits (30). Medicaid coverage is state-dependent, with some offering no reimbursements or restricting them to specific patient populations (31). If reimbursements are granted by either, deductibles and co-pay do still apply, with costs estimated at 50 dollars per month (32). Coverage by private insurers varies per package but is estimated to cost between 10 to 75 dollars per month, in addition to normal insurance costs (33). This interplay of requirements and costs has shaped the distribution of CGMs to patients, with those having lower SES being less likely to receive CGM treatment (odds ratio (OR) 0.48 between low vs high incomes (34)). Additionally, minorities, such as non-Hispanic Black (NHB) and Hispanic patients, are less likely to receive CGMs (OR 0.40, OR 0.73 vs non-Hispanic White (NHW) patients, respectively) (34).

Europe

CGM usage statistics have been documented in a variety of European countries. For instance, in Germany, the DPV registry was used to track CGM and insulin pump usage in a nationwide cohort (35). Disparities in CGM usage were noted in 2016 (OR 1.85 [1.63-2.10], Q1 vs Q5 of deprivation, according to the German Index of Multiple Deprivation 2016). However, this disparity gradually decreased over the years, and was no longer significant in 2019 (OR 0.97 [0.88-1.08]). This was mainly due to a sharper increase of CGM usage in the lower SES quintiles than in the higher one, theorized to be due to the inclusion of various CGM devices in statutory health insurance plans. These plans fully reimburse the devices for those needing intensive treatment with insulin (36). The contents of these plans are decided upon by the German government and cover 90% of the population (37). The remainder are covered via private insurances that had reimbursed intermittent scanning continuous glucose monitor (is-CGM) devices ahead of national reimbursements (38).

In England, the National Institute for Health and Care Excellence (NICE) evaluates the economics of reimbursing healthcare practices (38). These evaluations are then formulated into guidelines, which are then implemented by the Integrated Care Systems (ICS) (39). Prior to reimbursement of is-CGMs, usage thereof was primarily restricted to the affluent, with 60.2% of users belonging to the least-deprived quintile, compared to 4.1% of the most-deprived (40). These disparities have lessened over the years but remain present

(41,42). Currently, real-time continuous glucose monitors (rt-CGMs) are reimbursed for type 1 patients and those with type 2 requiring intensive monitoring (43,44).

In France, 99% of the population is covered via statutory health insurance, with is-CGMs being reimbursed as of 2017 for all insulin-dependent patients. A study running from 2017 to 2018 found no association of deprivation with CGM utilization, theorized to be due to the pervasiveness of the health insurance system (45).

Australia

Australia introduced coverage of CGM devices into their universal Medicare insurance in 2017. This publicly funded governmental insurance scheme forms the basis of the healthcare system in Australia, which can be further augmented via private insurance (46). A study comparing the situation prior to its introduction to 2 years thereafter, found that CGM uptake had increased from 5% to 79%, which coincided with improved odds of attaining optimal glycaemic regulation (HbA1c <7.0% / 53 mmol/mol, OR 2.5, p<0.001) (47). Factors regarding SES and ethnicity were not included in the study but assumed to be of no relevance due to the universal nature of the reimbursements.

Canada

A study from Toronto found that rt-CGM utilization in the area differed significantly per deprivation quintile (48). Those least-deprived used rt-CGM significantly more than those most-deprived (20.8% vs 12.9%). This difference was not found among is-CGM users, which was theorized to be due to the is-CGM being included in the regional public insurance scheme, whereas the rt-CGM was not. Rt-CGM had to then be acquired via either private insurance or self-funding, allowing for disparities in wealth to affect access.

The influences of SES, social context, and ethnicity

The effects of SES and ethnicity on healthcare access, and access to CGMs in particular, has become a topic of global interest. Several studies, mostly employing large, registry-based databases, clearly show the impact of SES on CGM utilization (49,50). A transatlantic comparison study comparing the USA and the German registries for type 1 diabetes showed a clear gradient of CGM utilization across the SES quintiles, with the less affluent using less devices (51). The gradient was more pronounced in the USA (slope 0.460, p<0.001) than in Germany (slope 0.068, p<0.001), most likely due to differences in healthcare systems and culture. Of note, the disparities in HbA1c, once corrected for technology usage, were

less severe. This indicates that diabetes technology, such as CGMs, is a driver behind the disparities in treatment outcomes. This has been corroborated by other studies (34,52–55). Another study calculated that 16.4% of the disparities in HbA1c between NHB and NHW patients were due to differences in diabetes technology use (which includes CSII in addition to CGM) and 37.6% was due to SES factors (19). Similarly, in Canada it was reported that differences in rt-CGM utilization between SES quintiles accounted for 12% of the differences in HbA1c, after correction for age, gender, and disease duration (48). Notably, the efficacy of CGM technology does not seem to be affected by SES (42), indicating that low SES is not a valid reason to withhold CGM technology.

In the above-mentioned studies, SES is often evaluated as a composite structure. This, by nature, obfuscates the impact of each subdomain of SES, i.e. income, occupational and educational domains, as well as the social context. Moreover, ethnicity is a factor of considerable importance, which is deeply intertwined with SES and SDOH (56). As such, it will be discussed separately.

Income/Occupational

A relationship between income, which is closely related to occupational status, and CGM use has often been reported, from the introduction of CGM devices (54), to the present day (57), in which those in high income groups (>$100.000 annually) are twice as likely to use a CGM than those in low-income groups (<$25000 annually). Similar patterns have been found across all ages (58) and cost is the most often cited barrier to the use of CGMs, by both patients (59) and providers (60), in the USA and abroad (61). An important factor regarding cost is the insurance status, with private insurance being a significant predictor of consistent CGM usage (62). This was found to be in part mediated by prescription biases, as found by one study in a paediatric provider cohort (63) and another in both the paediatric and adult provider cohorts (64). Both studies employed vignettes which differed in either public or private insurance status, and both found their cohort to be biased against public insurance (in 84.6% and 61% of the cohort, respectively). Both studies also found that longer practice duration resulted in a higher likelihood of bias. This was theorized to be due to an increasing number of past encounters with the cumbersome nature of acquiring coverage for individuals with public insurance, and as such, the practice-shaping effects of such restrictions. In Germany, France and Australia, inclusion of CGMs in universal healthcare plans correlated with large increases in usage, predominantly among those of lower SES (35,45,47). In California generous is-CGM reimbursements practices for their Medicaid recipients impacted disparities to such a degree that no significant differences in CGM utilization were found among the various ethnicities (65).

Education

Higher levels of educational attainment have been shown to be positively correlated with the odds of acquiring CGM technology, independent of income and ethnicity (34,54,66,67). This is theorized to be due to more awareness of the various options regarding glucose management, more knowledge about their disease, and more ways of successfully navigating the bureaucratic landscape of insurance requirements. As part of elucidating the effects of educational attainment on CGM use, a focus group study revealed that biases on the part of endocrinologists (as reported by the recipients) were a significant mediator in this process (68). These biases most often involved statements regarding the suitability of the participants for the use of CGM, stating that the technology would be too difficult for them to use, or that their glycaemic regulation was too poor. This reflected in another study, which found a marked discrepancy in barriers reported by endocrinologists and patients (69). Whereas 40-46% of endocrinologists endorsed the notion that the information provided by CGMs would be too difficult to understand, only 4.5% of patients agreed. If a provider perceives more barriers, they are naturally less inclined to prescribe CGMs (70).

Social context

While the effects of social context have been widely studied as a determinant of diabetes prevalence and outcomes (13), it has been less studied regarding CGM adoption. Most CGM-focussed studies have been based upon SES. One part of the social context is elucidated in a study which found that among Hispanic patients, English-speakers were less likely to use CGM and had higher HbA1c than their Spanish-speaking counterparts (33% vs 62%, p=0.002, 9.69%±2.22% (82.4±24.3 mmol/mol) vs 8.49%±1.94% (69.3±21.2 mmol/mol), p=0.003, respectively) (71). These differences were theorized to be because Spanish-speaking patients were often served by Spanish-speaking providers, eliminating the language barrier. Moreover, Spanish-speaking Hispanic people are more likely to have a stronger family support network and oversight. This highlights both the importance of a strong social structure, as well as the role of the language barrier.

Negative perceptions also play a role in the adoption of CGM technology. It was found that NHB parents experienced that their children were treated different for wearing CGM devices, being bullied for it (72). Additionally, NHB parents reported higher levels of shame regarding the diagnosis of diabetes, being judged for having a child with the disease. It would be said that the disease, T1D in this case, was the consequence of a faulty lifestyle, even if this belief is untrue. This combination of factors makes NHB parents more likely to want to cover up the fact that their child has diabetes, thus avoiding any outward signs thereof, such as CGMs.

Ethnicity

In the USA, after correction for SES and diabetes care factors, CGM utilization differed according to ethnicity, with NHB persons utilizing less CGMs than NHW and Hispanic persons (31% vs 53% vs 58%) (19). Similar results were found by other studies, in the USA (55,57,66,73–75), and abroad (41). In Germany, after inclusion of CGM devices in the statutory healthcare plans, the effect of a migration background (a proxy for ethnicity) on CGM utilization decreased, but did not disappear (OR 1.79 prior, OR 1.30 after) (35). This indicates that cultural and language barriers do remain and should be addressed separately. These ethnic disparities might be mediated by prescriber biases. One study found that NHB persons were less likely to have documented discussions about CGM initiation (OR 0.41, 0.29-0.90) and CGM prescriptions (OR 0.61, 0.41-0.93), even after adjustment for SES and clinic attendance (76). A similar pattern was found in another study (77). In addition, they also found higher rates of discontinuation among NHB children. After correction for insurance type, age at diagnosis and sex, NHW children were 3.9 (2.2-6.9) times as likely to continue CGM use 1 year after diagnosis. As such, not only are ethnic minorities less likely to be initiated on CGMs, but they are also less likely to continue it once attained. The lower prescription rate could be indicative of the use of subjective criteria and the presence of implicit biases in offering CGMs to ethnic minorities, which was also found by Howe et al. (72). They found that the argument of needing to have stable blood glucose levels prior to initiation was often used in communication with NHB parents, whereas it was not with NHW parents. Additionally, Agarwal et al. (78) found that providers often played the role of gatekeeper, with some participants (either NHB or Hispanic) only learning about the existence of these technologies once participating in the study. Other participants stated the same experiences as those found by Howe et al. (72). The lower continuation rate could be due to issues with the support systems surrounding CGM use or due to changes in reimbursement eligibility. The presence of implicit bias was further investigated in a vignette study, in which the patients had different names, which demonstrated the presence of ethnic bias in 34% of the provider cohort (64). This needs to be addressed to ensure equitable access to optimal care.

Recommendations

All these studies demonstrate that the effects of SES, social context, and ethnicity on the utilization of CGMs are multi-faceted. As such, any attempt at remedying these disparities must be equally multi-faceted. In this paragraph, we will discuss the known facets, such as income and behavioural barriers, and how they might be addressed.

Throughout the studies, income, either measured directly, or via proxy (such as insurance status), emerges as a main driver behind the disparities in CGM utilization (53,55,57,66). These disparities differed in degree between countries, dependent on the construction of their healthcare system. It was present even in those countries with socialized healthcare, with the impact being lessened in those with more generous reimbursement practices. Expanding reimbursement coverage has then been argued to decrease disparities in CGM access (79). In practice, addressing this aspect has been found to significantly increase CGM utilization in the lower SES quintiles. In Germany (35) and Australia (47), this has been achieved via inclusion of the CGMs into the pre-existing universal healthcare structures. In California, USA, a similar structure was introduced, which provided is-CGM devices with $0 co-pay for all Medicaid recipients (65). This was found to have equalized CGM uptake among ethnicities, however, large 95%-CI intervals remained. This could indicate that, while generous reimbursement practices could go a long way in addressing disparities, it is possible that it may not wholly negate disparities. Other studies have also found a reduction in disparities, but not total negation, after expanding reimbursement practices (35). Supporting this, other studies have found evidence of prescription biases that extend beyond that of insurance eligibility. One such study found that NHB children were less likely to use CGMs compared to NHW children in both the publicly and commercially insured populations (80). Additionally, not all cost-related barriers are necessarily related to the reimbursement of the devices to the patients. They also manifest as opportunity costs, for instance as a lack of training resources and staff and the allotted time for reviewing CGM data being inadequate, as reported by both Kompala et al. (60) and Rosenfeld et al. (81). Additionally, improvements in 'CGM-infrastructure' are also needed, as the time between the prescription of CGMs and receiving them is long, namely 152 days on average when prescribed through a commercial provider (82). This is reported to be mostly due to administrational burden and the need to resubmit documentation for the eligibility of the CGMs (83).

Behavioural barriers also need to be addressed. For instance, the provider could suffer from implicit biases against ethnic minorities or those of lower SES (63,64). This could be addressed via bias-prevention training, but it might be more effective to further enforce the use of objective criteria, circumventing subjective bias entirely. Such criteria could also be embedded within the previously mentioned streamlining of the prescription process.

The higher rate of discontinuations can be addressed by offering specialized programs, which can be fine-tuned to the needs of the population (77). One instance of this was the CGM Time-In-Range program in California, which, prior to the reimbursement changes, provided additional aid for navigating the insurance system and CGM usage (84). In all six reported cases, this resulted in improved glycaemic regulation and sustained, effective use of CGMs. This is further a study which reported that offering CGM education prior

to prescription impressively increases the odds of CGM initiation (OR 12.29, 95%-CI 5.57-27.10) (82). Another successful showcase is reported on by Schmitt et al. (85). They used stakeholder interviews to identify problem areas, and then implemented measures to address these issues. These were summarized and addressed as follows:

1 Increasing provider awareness of CGM coverage, benefits, and disparities in access.
   a Solution 1: Providing summary documents of CGM devices and insurance criteria, supported via education during meetings as needed.
   b Solution 2: Providing providers with weekly analysis of their scheduled T1D patient contacts, assessing them for T1D high-risk status (HbA1c >9%/74.9 mmol/mol) and CGM access (at least 1 document instance of CGM use, past or present). Subsequent updates also provided statistics concerning their patients CGM access relative to the clinic average.
   c Solution 3: Providing patients questionnaires aimed at identifying strong and weak points regarding their diabetes regulation, as well as possible solutions.

2 Provide CGM sampling opportunities.
   a Solution: Having single-use professional and personal CGMs available at the clinic for distribution. These could immediately be provided to the patient as needed.

3 Advocate for CGM coverage criteria simplification of the publicly insured.
   a Solution: Contacted the Alabama Medicaid commissioner with the aim of removing the requirement of two documented episodes of hypoglycaemia in a 4 week-period. This was successful.

While the combined implementation of these measures prevents us from assessing which measure is the most effective, its combined effects cannot be understated. Overall CGM access increased from 50% to 82% over the 13-month period, with high-risk patients specifically increasing from 34% to 85%, NHB from 27% to 81% (for comparison, NHW patients achieved 86%), and the publicly insured from 25% to 78%. It can be argued that this is simply the result of natural progression, as some increase in access was already present before introduction of these measures. However, strong and persistent stepwise increases in access were seen after each subsequent introduction of a measure, making it more likely that it was the measures that improved access. This program matches the barriers identified via group interviews (86). In addition, the same study also found a need for enhanced low-literacy and peer-to-peer support. A comparable program, implemented by Mathias et al. (87). This program included the formation of specialty clinics, the inclusion of social needs-trained practice nurses in that clinic, additional CGM training for the staff, including bias training, and streamlining CMG prescription workflow. After implementation,

CGM prescription rates increased from 15% to 69% over the 3-year period, which was more than national prescription rates, with all ethnicities enjoying equal increases.

In summary, a successful CGM access program would need to contain multiple forms of support:

1 Financial support: Ensuring that all those who need CGMs can financially afford them. This can be achieved by eliminating factors such as co-pay.

2 Objective criteria: The utilization and enforcement of objective criteria, rather than subjective criteria, could further reduce SES and ethnic disparities. Ideally, those criteria should be based on measurements already collected as part of routine care, as not to place any additional burdens on healthcare providers and to streamline auditing of those criteria. Galindo et al. (88) provide guidance on which criteria would be suitable, which are in-line with statements from the American Diabetes Association (89) and the American Association of Clinical Endocrinology (90), namely one of the following:
   a Diagnosed type 1 diabetes.
   b Diagnosed type 2 diabetes treated with any kind of insulin.
   c Diagnosed type 2 diabetes and problematic hypoglycaemia, documented via either BGM, professional CGM or self-reported incidence and severity, defined as either:
      - At least 7 level 2 (moderate) hypoglycaemic event (glucose ≤ 3.0 mmol/L or 54 mg/dL) over the prior 30-day period.
      - At least one level 3 (severe) hypoglycaemic event (hypoglycaemia requiring third-party intervention due to physical or mental dysfunction of the patient) over the prior 30-day period.

   In all cases, the initiation of CGM devices should both be preceded and followed up upon with regular consultations from the prescribing provider (for instance, every 6 months), either in-person or via telemedicine, in order to assure proper utilization of the device.

3 Bureaucratic support: The paperwork surrounding attaining CGMs is often reported as onerous, often based on the need to document a proven need for the devices, and efforts to streamline this process have proven effective. One method of doing this would be providing simple checklists based on the aforementioned criteria as sufficient proof. This could be further strengthened by providing support staffing and documentation.
4 Educational support (for providers): Improving familiarity with CGMs and associated practices will better enable providers to use them efficiently, thus increasing the

likelihood of prescription and decreasing workload. Additionally, the inclusion of anti-bias training could further reduce disparities. Examples of such programs are provided by Mathias et al. (87) and Schmitt et al. (85)

5 Educational support (for patients): Providing tailored education opportunities, incorporating cultural and language differences, can further enhance CGM attainment and retainment. Including features such as CGM sampling opportunities, peer-to-peer support networks, trained social-needs specialists and tools for handling diabetes stigma will be necessary for forming a robust training program.

A combination of the above could form the basis for successfully eliminating SDOH-related and ethnic disparities. Which combination of these suggestions are most suited for implementation is dependent upon the local circumstances and needs of the population of that country or region. For instance, in countries where the income of the patient is more impactful for the quality of care, such as those where people are predominantly privately insured, financial support would be of great importance. In countries with more socialized systems of healthcare, educational support could be more impactful.

It should be noted that the majority of the collected evidence in this review stems from research originating from the USA. This may restrict the relevance of the findings and recommendations provided in this review to countries beyond the USA. Nevertheless, the results of studies conducted in Europe and Oceania, which are also incorporated into this review, underscore that the issues described are not exclusive to the USA. Furthermore, the comparison of various health systems in this article, and the fact that disparities persist across this system, shows that there is no ‘silver bullet’ for remedying disparities, but rather, that there is a need for a multi-faceted approach. Therefore, we argue that by tailoring CGM access programs to the specific requirements of each local population, there is a real opportunity to enhance the adoption of CGM technology and consequently enhance diabetes care in these diverse regions.

References

1. Galindo RJ, Aleppo G. Continuous Glucose Monitoring: the achievement of 100 years of innovation in diabetes technology. Diabetes Res Clin Pract [Internet]. 2020 Dec 1 [cited 2023 Feb 20];170:108502. Available from: /pmc/articles/PMC7736459/
2. Bailey TS, Walsh J, Stone JY. Emerging Technologies for Diabetes Care. https://home.liebertpub.com/dia [Internet]. 2018 Jun 1 [cited 2023 Feb 20];20:S278–84. Available from: https://www.liebertpub.com/doi/10.1089/dia.2018.0115
3. Pańkowska E, Błazik M, Dziechciarz P, Szypowska A, Szajewska H. Continuous subcutaneous insulin infusion vs. multiple daily injections in children with type 1 diabetes: a systematic review and meta-analysis of randomized control trials. Pediatric Diabetes. 2009;10(1):52–8.
4. Gilbert TR, Noar A, Blalock O, Polonsky WH. Change in Hemoglobin A1c and Quality of Life with Real-Time Continuous Glucose Monitoring Use by People with Insulin-Treated Diabetes in the Landmark Study. Diabetes Technol Ther [Internet]. 2021 Mar 1 [cited 2023 Feb 20];23(Suppl 1):S-35. Available from: /pmc/articles/PMC7957368/
5. Templer S. Closed-Loop Insulin Delivery Systems: Past, Present, and Future Directions. Front Endocrinol (Lausanne). 2022 Jun 6;0:1120.
6. Dicembrini I, Cosentino C, Monami M, Mannucci E, Pala L. Effects of real-time continuous glucose monitoring in type 1 diabetes: a meta-analysis of randomized controlled trials. Acta Diabetol [Internet]. 2021 Apr 1 [cited 2022 Aug 8];58(4):401–10. Available from: https://pubmed.ncbi.nlm.nih.gov/32789691/
7. Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. The Lancet [Internet]. 2018 Apr 7 [cited 2022 May 27];391(10128):1367–77. Available from: http://www.thelancet.com/article/S0140673618302976/fulltext
8. Ida S, Kaneko R, Murata K. Utility of real-time and retrospective continuous glucose monitoring in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials. J Diabetes Res. 2019;2019.
9. Oser TK, Litchman ML, Allen NA, Kwan BM, Fisher L, Jortberg BT, et al. Personal Continuous Glucose Monitoring Use Among Adults with Type 2 Diabetes: Clinical Efficacy and Economic Impacts. Curr Diab Rep [Internet]. 2021 Nov 1 [cited 2022 Jun 27];21(11):3. Available from: /pmc/articles/PMC8655087/
10. Hill-Briggs F, Adler NE, Berkowitz SA, Chin MH, Gary-Webb TL, Navas-Acien A, et al. Social Determinants of Health and Diabetes: A Scientific Review. Diabetes Care [Internet]. 2021 Jan 1 [cited 2022 Aug 2];44(1):258–79. Available from: https://diabetesjournals.org/care/article/44/1/258/33180/Social-Determinants-of-Health-and-Diabetes-A
11. Stern MJ. Inequality in the Internet Age: A Twenty-First Century Dilemma*. Sociol Inq [Internet]. 2010 Feb 1 [cited 2022 Oct 13];80(1):28–33. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1475-682X.2009.00314.x
12. Baker EH. Socioeconomic Status, Definition. The Wiley Blackwell Encyclopedia of Health, Illness, Behavior, and Society [Internet]. 2014 Feb 21 [cited 2022 Jul 12];2210–4. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/9781118410868.wbehibs395
13. Hill-Briggs F, Adler NE, Berkowitz SA, Chin MH, Gary-Webb TL, Navas-Acien A, et al. Social Determinants of Health and Diabetes: A Scientific Review. Diabetes Care [Internet]. 2021 Jan 1 [cited 2023 Sep 4];44(1):258. Available from: /pmc/articles/PMC7783927/

14. Conway DI, McMahon AD, Brown D, Leyland AH. Measuring socioeconomic status and inequalities. Reducing social inequalities in cancer: evidence and priorities for research [Internet]. 2019 [cited 2023 Feb 20]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK566205/

15. Caballo B, Dey S, Prabhu P, Seal B, Chu P. The Effects of Socioeconomic Status on the Quality and Accessibility of Healthcare Services.

16. Stringhini S, Carmeli C, Jokela M, Avendaño M, Muennig P, Guida F, et al. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1·7 million men and women. The Lancet [Internet]. 2017 Mar 25 [cited 2022 Jul 6];389(10075):1229–37. Available from: http://www.thelancet.com/article/S0140673616323807/fulltext

17. Willi SM, Miller KM, DiMeglio LA, Klingensmith GJ, Simmons JH, Tamborlane W V., et al. Racial-Ethnic Disparities in Management and Outcomes Among Children With Type 1 Diabetes. Pediatrics [Internet]. 2015 Mar 1 [cited 2022 May 30];135(3):424–34. Available from: /pediatrics/article/135/3/424/75545/Racial-Ethnic-Disparities-in-Management-and

18. Rechenberg K, Whittemore R, Grey M, Jaser S. Contribution of income to self-management and health outcomes in pediatric type 1 diabetes. Pediatr Diabetes [Internet]. 2016 Mar 1 [cited 2022 Jun 23];17(2):120–6. Available from: https://pubmed.ncbi.nlm.nih.gov/25545117/

19. Agarwal S, Kanapka LG, Raymond JK, Walker A, Gerard-Gonzalez A, Kruger D, et al. Racial-Ethnic Inequity in Young Adults With Type 1 Diabetes. J Clin Endocrinol Metab [Internet]. 2020 Aug 1 [cited 2022 Jun 24];105(8):E2960–9. Available from: https://pubmed.ncbi.nlm.nih.gov/32382736/

20. Saydah S, Imperatore G, Cheng Y, Geiss LS, Albright A. Disparities in Diabetes Deaths Among Children and Adolescents — United States, 2000–2014. Morbidity and Mortality Weekly Report [Internet]. 2017 May 5 [cited 2022 May 31];66(19):502. Available from: /pmc/articles/PMC5657647/

21. Saydah SH, Imperatore G, Beckles GL. Socioeconomic status and mortality: contribution of health care access and psychological distress among U.S. adults with diagnosed diabetes. Diabetes Care [Internet]. 2013 Jan [cited 2022 Aug 16];36(1):49–55. Available from: https://pubmed.ncbi.nlm.nih.gov/22933434/

22. Zhang GQ, Canner JK, Kayssi A, Abularrage CJ, Hicks CW. Geographical socioeconomic disadvantage is associated with adverse outcomes following major amputation in diabetic patients. J Vasc Surg [Internet]. 2021 Oct 1 [cited 2022 Jun 22];74(4):1317-1326.e1. Available from: https://pubmed.ncbi.nlm.nih.gov/33865949/

23. Talbo MK, Katz A, Dostie M, Legault L, Brazeau AS. Associations Between Socioeconomic Status and Patient Experience With Type 1 Diabetes Management and Complications: Cross-sectional Analysis of a Cohort From Québec, Canada. Can J Diabetes [Internet]. 2022 Mar [cited 2022 Aug 17]; Available from: https://pubmed.ncbi.nlm.nih.gov/35864032/

24. Vandenheede H, Deboosere P, Stirbu I, Agyemang CO, Harding S, Juel K, et al. Migrant mortality from diabetes mellitus across Europe: The importance of socio-economic change. Eur J Epidemiol [Internet]. 2012 Feb 14 [cited 2022 May 25];27(2):109–17. Available from: https://link.springer.com/article/10.1007/s10654-011-9638-6

25. Turpin RE, Akré ERL, Williams ND, Boekeloo BO, Fish JN. Differences in Health Care Access and Satisfaction Across Intersections of Race/Ethnicity and Sexual Identity. Acad Med [Internet]. 2021 [cited 2023 Mar 1];96(11):1592–7. Available from: https://pubmed.ncbi.nlm.nih.gov/34261863/

26. Williams DR, Priest N, Anderson NB. Understanding Associations between Race, Socioeconomic Status and Health: Patterns and Prospects. Health Psychol [Internet]. 2016 Apr 1 [cited 2024 Jan 5];35(4):407. Available from: /pmc/articles/PMC4817358/

27. Anderson NB, Bulatao RA, Cohen B, National Research Council (US) Panel on Race E and H in LL. Race/Ethnicity, Socioeconomic Status, and Health. 2004 [cited 2024 Jan 12]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK25526/

28. LaVeist TA. Disentangling race and socioeconomic status: A key to understanding health inequalities. J Urban Health [Internet]. 2005 Jun [cited 2023 Mar 1];82(Suppl 3):iii26. Available from: /pmc/articles/PMC3455905/

29. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. JAMA [Internet]. 2017 Jan 24 [cited 2022 May 27];317(4):371–8. Available from: https://pubmed.ncbi.nlm.nih.gov/28118453/

30. Qi Y, Koster A, Boxtel M Van, Köhler S, Schram M, Schaper N, et al. Adulthood Socioeconomic Position and Type 2 Diabetes Mellitus-A Comparison of Education, Occupation, Income, and Material Deprivation: The Maastricht Study. Int J Environ Res Public Health [Internet]. 2019 Apr 2 [cited 2022 May 25];16(8). Available from: https://pubmed.ncbi.nlm.nih.gov/31018480/

31. ISPOR - US Healthcare System Overview-Background [Internet]. [cited 2023 May 4]. Available from: https://www.ispor.org/heor-resources/more-heor-resources/us-healthcare-system-overview/us-healthcare-system-overview-background-page-1

32. Continuous Glucose Monitoring | AAFP [Internet]. [cited 2023 May 4]. Available from: https://www.aafp.org/family-physician/patient-care/care-resources/continuous-glucose-monitoring.html

33. CGM and Medicaid: Who's Covered? | diaTribe Change [Internet]. [cited 2023 May 4]. Available from: https://diatribechange.org/news/cgm-and-medicaid-whos-covered

34. Medicare Coverage of Diabetes Supplies, Services, & Prevention Programs.

35. Medicare Now Covers Abbott's FreeStyle Libre CGM [Internet]. [cited 2023 May 4]. Available from: https://diatribe.org/medicare-now-covers-abbott%E2%80%99s-freestyle-libre-cgm

36. Venkatesh KK, Powe CE, Buschur E, Wu J, Landon MB, Gabbe S, et al. Disparities in Continuous Glucose Monitoring Use Among Women of Reproductive Age with Type 1 Diabetes in the T1D Exchange. Diabetes Technol Ther [Internet]. 2023 Mar 1 [cited 2023 Mar 28];25(3):201–5. Available from: https://www.liebertpub.com/doi/10.1089/dia.2022.0412

37. Auzanneau M, Rosenbauer J, Maier W, von Sengbusch S, Hamann J, Kapellen T, et al. Heterogeneity of Access to Diabetes Technology Depending on Area Deprivation and Demographics Between 2016 and 2019 in Germany. J Diabetes Sci Technol. 2021;15(5):1059–68.

38. Continuous glucose monitoring (CGM) | informedhealth.org [Internet]. [cited 2023 May 8]. Available from: https://www.informedhealth.org/continuous-glucose-monitoring-cgm.html

39. Germany | International Health Care System Profiles | Commonwealth Fund [Internet]. [cited 2023 May 8]. Available from: https://www.commonwealthfund.org/international-health-policy-center/countries/germany

40. Seidel D, Boggio Mesnil F, Caruso A. Reimbursement Pathways for New Diabetes Technologies in Europe: Top-Down Versus Bottom-Up. J Diabetes Sci Technol [Internet]. 2019 Jan 1 [cited 2023 May 8];13(1):118–22. Available from: https://pubmed.ncbi.nlm.nih.gov/30033750/

41. Gongora-Salazar P, Glogowska M, Fitzpatrick R, Perera R, Tsiachristas A. Commissioning [Integrated] Care in England: An Analysis of the Current Decision Context. Int J Integr Care [Internet]. 2022 [cited 2023 May 8];22(4). Available from: /pmc/articles/PMC9541117/

42. McKnight JA, Gibb FW. Flash Glucose Monitoring is associated with improved glycaemic control but use is largely limited to more affluent people in a UK diabetes centre. Diabet Med [Internet]. 2017 May 1 [cited 2022 Aug 16];34(5):732. Available from: https://pubmed.ncbi.nlm.nih.gov/28103416/

43. Ng SM, Evans ML. Widening health inequalities related to type 1 diabetes care in children and young people in the UK: A time to act now. Diabetic Medicine [Internet]. 2021 Nov 1 [cited 2023 Mar 31];38(11):e14620. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/dme.14620

44. Fallon C, Jones E, Oliver N, Reddy M, Avari P. The impact of socio-economic deprivation on access to diabetes technology in adults with type 1 diabetes. Diabet Med [Internet]. 2022 Jun 30 [cited 2022 Aug 17]; Available from: https://pubmed.ncbi.nlm.nih.gov/35751860/

45. Flash Glucose Monitoring: National Arrangements for Funding of Relevant Diabetes Patients. [cited 2023 May 8]; Available from: https://www.nice.org.uk/advice/mib110/chapter/The-technology

46. Type 2 diabetes prescribable CGM pathway from primary care [Internet]. 2023 [cited 2023 May 8]. Available from: https://nhsdorset.nhs.uk/Downloads/aboutus/medicines-management/Other%20Guidelines/T2DM%20prescribable%20CGM%20pathway%2029.03.23.pdf

47. Delagrange M, Dalla-Vale F, Salet R, Asensio-Weiss V, Moulin P, Cabaret B, et al. Impact of deprivation on glycaemic control in youth with type 1 diabetes in the southwestern region of France. Pediatr Diabetes [Internet]. 2021 Aug 1 [cited 2022 Aug 16];22(5):796–806. Available from: https://pubmed.ncbi.nlm.nih.gov/33205845/

48. The Australian health system | Australian Government Department of Health and Aged Care [Internet]. [cited 2023 May 8]. Available from: https://www.health.gov.au/about-us/the-australian-health-system

49. Johnson SR, Holmes-Walker DJ, Chee M, Earnest A, Jones TW, ADDN Study Group:, et al. Universal Subsidized Continuous Glucose Monitoring Funding for Young People With Type 1 Diabetes: Uptake and Outcomes Over 2 Years, a Population-Based Study. Diabetes Care. 2022 Feb 1;45(2):391–7.

50. Coverage Map | JDRF Canada [Internet]. [cited 2024 Jan 12]. Available from: https://www.jdrf.ca/advocacy/access-for-all/coverage-map/

51. Stanley JR, Clarke ABM, Shulman R, Mahmud FH. Mediating Effects of Technology-Based Therapy on the Relationship Between Socioeconomic Status and Glycemic Management in Pediatric Type 1 Diabetes. Diabetes Technol Ther [Internet]. 2022 Dec 5 [cited 2022 Dec 16]; Available from: https://pubmed.ncbi.nlm.nih.gov/36409503/

52. Auzanneau M, Lanzinger S, Bohn B, Kroschwald P, Kuhnle-Krahl U, Holterhus PM, et al. Area Deprivation and Regional Disparities in Treatment and Outcome Quality of 29,284 Pediatric Patients With Type 1 Diabetes in Germany: A Cross-sectional Multicenter DPV Analysis. Diabetes Care [Internet]. 2018 Dec 1 [cited 2022 Aug 17];41(12):2517–25. Available from: https://pubmed.ncbi.nlm.nih.gov/30327359/

53. Dover AR, Strachan MWJ, McKnight JA, Stimson RH, Mackenzie SD, Lyall MJ, et al. Socioeconomic deprivation, technology use, C-peptide, smoking and other predictors of glycaemic control in adults with type 1 diabetes. Diabet Med [Internet]. 2021 Mar 1 [cited 2023 Apr 3];38(3). Available from: https://pubmed.ncbi.nlm.nih.gov/33128811/

54. Addala A, Auzanneau M, Miller K, Maier W, Foster N, Kapellen T, et al. A Decade of Disparities in Diabetes Technology Use and HbA 1c in Pediatric Type 1 Diabetes: A Transatlantic Comparison. Diabetes Care [Internet]. 2021 Jan 1 [cited 2022 May 25];44(1):133–40. Available from: https://pubmed.ncbi.nlm.nih.gov/32938745/

55. Everett EM, Wisk LE. Relationships Between Socioeconomic Status, Insurance Coverage for Diabetes Technology and Adverse Health in Patients With Type 1 Diabetes. J Diabetes Sci Technol [Internet]. 2021 [cited 2022 May 25]; Available from: https://pubmed.ncbi.nlm.nih.gov/34632819/

56. Burnside MJ, Williman JA, Davies HM, Jefferies CA, Paul RG, Wheeler BJ, et al. Inequity in access to continuous glucose monitoring and health outcomes in paediatric diabetes, a case for national continuous glucose monitoring funding: A cross-sectional population study of children with type 1 diabetes in New Zealand. Lancet Reg Health West Pac [Internet]. 2023 Feb 1 [cited 2023 Mar 29];31:100644. Available from: /pmc/articles/PMC9676142/

57. Wong JC, Foster NC, Maahs DM, Raghinaru D, Bergenstal RM, Ahmann AJ, et al. Real-Time Continuous Glucose Monitoring Among Participants in the T1D Exchange Clinic Registry. Diabetes Care [Internet]. 2014 Oct 1 [cited 2022 May 30];37(10):2702–9. Available from: https://diabetesjournals.org/care/article/37/10/2702/30862/Real-Time-Continuous-Glucose-Monitoring-Among

58. DeSalvo DJ, Noor N, Xie C, Corathers SD, Majidi S, McDonough RJ, et al. Patient Demographics and Clinical Outcomes Among Type 1 Diabetes Patients Using Continuous Glucose Monitors: Data From T1D Exchange Real-World Observational Study. J Diabetes Sci Technol [Internet]. 2021 [cited 2022 Aug 17]; Available from: https://pubmed.ncbi.nlm.nih.gov/34632823/

59. Williams DR, Priest N, Anderson NB. Understanding Associations between Race, Socioeconomic Status and Health: Patterns and Prospects. Health Psychol [Internet]. 2016 Apr 1 [cited 2023 May 9];35(4):407. Available from: /pmc/articles/PMC4817358/

60. Bailey R, Donthi S, Markt S, Drummond C, Cullen J. Evaluating Factors Associated With Continuous Glucose Monitoring Utilization With the Type 1 Diabetes Exchange Registry. J Diabetes Sci Technol [Internet]. 2022 [cited 2022 Aug 17]; Available from: https://pubmed.ncbi.nlm.nih.gov/35506181/

61. Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, Dimeglio LA, et al. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther [Internet]. 2019 Feb 1 [cited 2022 Jun 27];21(2):66–72. Available from: https://pubmed.ncbi.nlm.nih.gov/30657336/

62. Messer LH, Tanenbaum ML, Cook PF, Wong JJ, Hanes SJ, Driscoll KA, et al. Cost, Hassle, and On-Body Experience: Barriers to Diabetes Device Use in Adolescents and Potential Intervention Targets. Diabetes Technol Ther [Internet]. 2020 Oct 1 [cited 2022 Sep 27];22(10):760–7. Available from: https://pubmed.ncbi.nlm.nih.gov/32163719/

63. Kompala T, Wong J, Neinstein A. Diabetes Specialists Value CGM Despite Challenges in Prescribing and Data Review Process. J Diabetes Sci Technol [Internet]. 2022 Apr 11 [cited 2023 Mar 27]; Available from: https://journals.sagepub.com/doi/full/10.1177/19322968221088267?rfr_dat=cr_pub++0pubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org

64. Karakuş KE, Sakarya S, Yeşiltepe Mutlu G, Berkkan M, Muradoğlu S, Can E, et al. Benefits and Drawbacks of Continuous Glucose Monitoring (CGM) Use in Young Children With Type 1 Diabetes: A Qualitative Study From a Country Where the CGM Is Not Reimbursed. J Patient Exp [Internet]. 2021 Dec 1 [cited 2023 Mar 27];8. Available from: /pmc/articles/PMC8646182/

65. Sinisterra M, Wang CH, Marks BE, Barber J, Tully C, Monaghan M, et al. Patterns of Continuous Glucose Monitor Use in Young Children Throughout the First 18 Months Following Type 1 Diabetes Diagnosis. Diabetes Technol Ther [Internet]. 2021 Nov 1 [cited 2023 Mar 31];23(11):777–81. Available from: https://pubmed.ncbi.nlm.nih.gov/34252292/

66. Addala A, Hanes S, Naranjo D, Maahs DM, Hood KK. Provider Implicit Bias Impacts Pediatric Type 1 Diabetes Technology Recommendations in the United States: Findings from The Gatekeeper Study. J Diabetes Sci Technol [Internet]. 2021 [cited 2023 Apr 3];15(5):1027–33. Available from: https://pubmed.ncbi.nlm.nih.gov/33858206/

67. Odugbesan O, Addala A, Nelson G, Hopkins R, Cossen K, Schmitt J, et al. Implicit Racial-Ethnic and Insurance-Mediated Bias to Recommending Diabetes Technology: Insights from T1D Exchange Multicenter Pediatric and Adult Diabetes Provider Cohort. Diabetes Technol Ther [Internet]. 2022 Sep 1 [cited 2023 Mar 2];24(9):619–27. Available from: https://pubmed.ncbi.nlm.nih.gov/35604789/

68. Ni K, Tampe CA, Sol K, Richardson DB, Pereira RI. Effect of CGM Access Expansion on Uptake Among Patients on Medicaid With Diabetes. Diabetes Care [Internet]. 2023 Feb 1 [cited 2023 Mar 29];46(2):391–8. Available from: https://pubmed.ncbi.nlm.nih.gov/36480729/

69. Kommareddi M, Wherry K, Vigersky RA. Racial/Ethnic Inequities in Use of Diabetes Technologies Among Medicare Advantage Beneficiaries with Type 1 Diabetes. J Clin Endocrinol Metab [Internet]. 2023 Jan 30 [cited 2023 Mar 28]; Available from: https://pubmed.ncbi.nlm.nih.gov/36715293/

70. Chen CW, Tinsley LJ, Volkening LK, Anderson BJ, Laffel LM. Observed Characteristics Associated with Diabetes Device Use Among Teens with Type 1 Diabetes. J Diabetes Sci Technol [Internet]. 2023 Jan 1 [cited 2023 Mar 29];17(1):186–94. Available from: https://pubmed.ncbi.nlm.nih.gov/34652236/

71. Walker AF, Hood KK, Gurka MJ, Filipp SL, Anez-Zabala C, Cuttriss N, et al. Barriers to Technology Use and Endocrinology Care for Underserved Communities With Type 1 Diabetes. Diabetes Care [Internet]. 2021 [cited 2022 Aug 15];44(7):1480–90. Available from: https://pubmed.ncbi.nlm.nih.gov/34001535/

72. Tanenbaum ML, Adams RN, Hanes SJ, Barley RC, Miller KM, Mulvaney SA, et al. Optimal Use of Diabetes Devices: Clinician Perspectives on Barriers and Adherence to Device Use. J Diabetes Sci Technol [Internet]. 2017 May 1 [cited 2022 May 30];11(3):484–92. Available from: https://journals.sagepub.com/doi/10.1177/1932296816688010

73. Lanning MS, Tanenbaum ML, Wong JJ, Hood KK. Barriers to Continuous Glucose Monitoring in People With Type 1 Diabetes: Clinician Perspectives. Diabetes Spectr [Internet]. 2020 Nov 1 [cited 2022 Sep 27];33(4):324. Available from: /pmc/articles/PMC7666603/

74. Tsai D, Flores Garcia J, Fogel JL, Wee CP, Reid MW, Raymond JK. Diabetes Technology Experiences Among Latinx and Non-Latinx Youth with Type 1 Diabetes. J Diabetes Sci Technol [Internet]. 2022 Jul 1 [cited 2022 Aug 16];16(4). Available from: https://pubmed.ncbi.nlm.nih.gov/34225480/

75. Howe CJ, Morone J, Hawkes CP, Lipman TH. Racial Disparities in Technology Use in Children With Type 1 Diabetes: A Qualitative Content Analysis of Parents' Perspectives. The science of diabetes self-management and care [Internet]. 2023 Feb 1 [cited 2023 Mar 29];49(1):55–64. Available from: https://pubmed.ncbi.nlm.nih.gov/36609201/

76. Majidi S, Ebekozien O, Noor N, Lyons SK, McDonough R, Gandhi K, et al. Inequities in health outcomes in children and adults with type 1 diabetes: Data from the T1D exchange quality improvement collaborative. Clinical Diabetes. 2021 Jul 1;39(3):278–83.

77. Ebekozien O, Agarwal S, Noor N, Albanese-O'Neill A, Wong JC, Seeherunvong T, et al. Inequities in Diabetic Ketoacidosis Among Patients With Type 1 Diabetes and COVID-19: Data From 52 US Clinical Centers. J Clin Endocrinol Metab [Internet]. 2021 Apr 1 [cited 2023 Mar 2];106(4):E1755–62. Available from: https://pubmed.ncbi.nlm.nih.gov/33410917/

78. Wirunsawanya K, Rizo I, Fantasia K. OR30-03 Racial Differences in Technology Use Among Type 1 Diabetes in a Safety-Net Hospital. J Endocr Soc [Internet]. 2020 May 8 [cited 2022 Jun 27];4(Supplement_1). Available from: https://academic.oup.com/jes/article/4/Supplement_1/OR30-03/5833169

79. Kanbour S, Jones M, Abusamaan MS, Nass C, Everett E, Wolf RM, et al. Racial Disparities in Access and Use of Diabetes Technology Among Adult Patients With Type 1 Diabetes in a U.S. Academic Medical Center. Diabetes Care [Internet]. 2023 Jan 1 [cited 2023 Mar 29];46(1):56. Available from: /pmc/articles/PMC9797654/

80. Lai CW, Lipman TH, Willi SM, Hawkes CP. Racial and Ethnic Disparities in Rates of Continuous Glucose Monitor Initiation and Continued Use in Children With Type 1 Diabetes. Diabetes Care [Internet]. 2021 Jan 1 [cited 2022 May 31];44(1):255–7. Available from: https://diabetesjournals.org/care/article/44/1/255/33277/Racial-and-Ethnic-Disparities-in-Rates-of

81. Agarwal S, Crespo-Ramos G, Long JA, Miller VA. "I Didn't Really Have a Choice": Qualitative Analysis of Racial-Ethnic Disparities in Diabetes Technology Use Among Young Adults with Type 1 Diabetes. Diabetes Technol Ther [Internet]. 2021 Sep 1 [cited 2022 Aug 16];23(9):616–22. Available from: https://pubmed.ncbi.nlm.nih.gov/33761284/

82. Isaacs D, Bellini NJ, Biba U, Cai A, Close KL. Health care disparities in use of continuous glucose monitoring. Diabetes Technol Ther [Internet]. 2021 Sep 1 [cited 2022 Aug 15];23(S3):S81–7. Available from: https://www.liebertpub.com/doi/10.1089/dia.2021.0268

83. Lipman TH, Smith JA, Patil O, Willi SM, Hawkes CP. Racial disparities in treatment and outcomes of children with type 1 diabetes. Pediatr Diabetes [Internet]. 2021 Mar 1 [cited 2022 Aug 15];22(2):241–8. Available from: https://pubmed.ncbi.nlm.nih.gov/33871154/

84. Rosenfeld C, Blevins T, Aleppo G, Forlenza G, Isaacs D, Morales J, et al. Expert Roundtable on Continuous Glucose Monitoring. Endocrine Practice. 2022 Jun 1;28(6):622–7.

85. Modzelewski KL, Murati J, Charoenngam N, Rehm C, Steenkamp DW. Delays in Continuous Glucose Monitoring Device Initiation: A Single Center Experience and a Call to Change. Diabetes Technol Ther [Internet]. 2022 Jun 1 [cited 2023 Mar 27];24(6):390–5. Available from: https://pubmed.ncbi.nlm.nih.gov/35099277/

86. Huynh P, Toulouse A, Hirsch IB. ONE-YEAR TIME ANALYSIS IN AN ACADEMIC DIABETES CLINIC: QUANTIFYING OUR BURDEN. Endocrine Practice. 2018 May 1;24(5):489–91.

87. Lee MY, Tanenbaum ML, Maahs DM, Prahalad P. Overcoming Barriers to Diabetes Technology in Youth with Type 1 Diabetes and Public Insurance: Cases and Call to Action. Case Rep Endocrinol [Internet]. 2022 [cited 2022 May 25];2022. Available from: https://pubmed.ncbi.nlm.nih.gov/35273814/

88. Schmitt J, Fogle K, Scott ML, Iyer P. Improving Equitable Access to Continuous Glucose Monitors for Alabama's Children with Type 1 Diabetes: A Quality Improvement Project. Diabetes Technol Ther [Internet]. 2022 Jul 1 [cited 2023 Mar 27];24(7):481–91. Available from: https://pubmed.ncbi.nlm.nih.gov/35156834/

89. Agarwal S, Crespo-Ramos G, Leung SL, Finnan M, Park T, McCurdy K, et al. Solutions to Address Inequity in Diabetes Technology Use in Type 1 Diabetes: Results from Multidisciplinary Stakeholder Co-creation Workshops. Diabetes Technol Ther [Internet]. 2022 Jun 1 [cited 2022 Aug 16];24(6):381–9. Available from: https://pubmed.ncbi.nlm.nih.gov/35138944/

90. Mathias P, Mahali LP, Agarwal S. Targeting Technology in Underserved Adults With Type 1 Diabetes: Effect of Diabetes Practice Transformations on Improving Equity in CGM Prescribing Behaviors. Diabetes Care [Internet]. 2022 Oct 1 [cited 2023 Mar 29];45(10):2231. Available from: /pmc/articles/PMC9649356/

91. Galindo RJ, Aleppo G, Parkin CG, Baidal DA, Carlson AL, Cengiz E, et al. Increase Access, Reduce Disparities: Recommendations for Modifying Medicaid CGM Coverage Eligibility Criteria. J Diabetes Sci Technol [Internet]. 2022 Dec 16 [cited 2023 Sep 5]; Available from: https://journals.sagepub.com/doi/10.1177/19322968221144052?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed

92. Diabetes Technology: Standards of Medical Care in Diabetes-2022. Diabetes Care [Internet]. 2022 Jan 1 [cited 2023 Sep 22];45(Suppl 1):S97–112. Available from: https://pubmed.ncbi.nlm.nih.gov/34964871/

93. Grunberger G, Sherr J, Allende M, Blevins T, Bode B, Handelsman Y, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons With Diabetes Mellitus. Endocr Pract [Internet]. 2021 Jun 1 [cited 2023 Sep 22];27(6):505–37. Available from: https://pubmed.ncbi.nlm.nih.gov/34116789/

Supplemental material

Appendix A: Search Query

PubMed:
("Diabetes Mellitus"[Mesh] OR diabet*[ti])

AND

("Technology"[Mesh:NoExp] OR "Blood Glucose Self-Monitoring"[Mesh] OR ((blood-glucose[tiab] OR blood-sugar[tiab]) AND (self-monitor*[tiab] OR (home[tiab] AND monitor*[tiab]) OR continuous-monitoring[tiab])) OR continuous-glucose-monitoring[tiab] OR (home[tiab] AND glucometer*[tiab]) OR technolog*[tiab] OR access*[ti])

AND

("Socioeconomic Factors"[Mesh] OR "Health Status Disparities"[Mesh] OR "Social Determinants of Health"[Mesh] OR "Health Status Disparities"[Mesh] OR "Vulnerable Populations"[Mesh] OR socioeconomic[tiab] OR sociodemograph*[tiab] OR subsid[tiab] OR low-income[tiab] OR high-income[tiab] OR barrier*[tiab] OR raci[tiab] OR ethnic[tiab] OR social-economic[tiab] OR socio-economic[tiab] OR ses[tiab] OR social-class*[tiab] OR disparit*[ti] OR inequalit*[ti] OR ((vulnerable[tiab] OR underserved[tiab]) AND (communit*[tiab] OR population*[tiab])))

Embase:
('socioeconomics' OR 'ethnic group' OR 'minority group' OR 'social determinants of health' OR 'health disparity' OR 'vulnerable population' OR 'lowest income group' OR 'highest income group' OR 'sociodemographics' OR 'social class' OR 'inequality') AND 'diabetes mellitus'/dm AND (2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022:py) AND ('blood glucose meter'/dv OR 'blood glucose test strip'/dv OR 'continuous glucose monitoring system'/dv OR 'glucose regulation system'/dv OR 'glucose sensor'/dv OR 'glucose test kit'/dv OR 'information processing device'/dv OR 'monitor'/dv OR 'pump'/dv OR 'sensor'/dv OR 'wearable sensor'/dv)

Appendix B: Data extraction

Authors, date, and country	Domain(s)	Study methods	Subjects
Addala et al., 2021, USA/ Germany (54)	Income/ Occupational, Education, Social, Ethnicity.	**Design:** Cross-sectional analysis of the Type 1 Diabetes Exchange (T1DX, USA, n=16.457) and Diabetes Prospective Follow-up (DPV, Germany, n=39.836) registries **Period:** 2010-2012 and 2016-2018. **Area:** National registries USA and Germany **SES indicators:** Insurance type, education level and annual income (USA), and the German Index of Multiple Deprivation (GIMD), a validated tool for regional SES in Germany, for the DPV. **Ethnicity indicators:** Registered ethnicity (USA), personal or parental history of being born outside of Germany (Germany)	**% DM1:** 100% (USA, Germany) **% male:** 51.6% (USA), 52.4% (Germany) **Mean age (Years+sd):** 13.0±3.5 (USA), 13.1±3.7 (Germany) **Ethnicity:** 22.3% (USA), 23.9% (Germany) minority status **Mean HbA1c (+sd):** 8.9%±1.7% (73.8±18.6 mmol/mol) (USA), 7.9%±1.4% (62.8 ±15.3 mmol/mol) (Germany)
Agarwal et al., 2021, USA (94)	Income/ Occupational, Education, Social, Ethnicity.	**Design:** Cross-sectional analysis of survey and dossier data (n=300). **Period:** Not stated **Area:** Six different urban geographic regions across the USA **SES indicators:** Insurance status, personal income, education level, Hollingshead Four-Factor Index (measure of social class), neighbourhood poverty level, health literacy **Ethnicity indicators:** self-reported as either non-Hispanic White (NHW), non-Hispanic Black (NHB) or Hispanic.	**% DM1:** 100% **% male:** 45% **Mean age (Years, IQR):** 20 (19-22) **Ethnicity:** 32.33% NHB, 34.33% Hispanic **Mean HbA1c (95% CI):** 9.5% (80.3 mmol/mol) (7.7%-11.3%, 60.7-100mmol/mol)
Auzanneau et al., 2021, Germany (37)	Income/ Occupational, Education, Social, Ethnicity.	**Design:** Cross-sectional analysis of the Diabetes Prospective Follow-up registry (n=37.798) **Period:** 2016-2019 **Area:** Germany **SES indicators:** German Index of Multiple Deprivation, a validated tool for regional SES in Germany. **Ethnicity indicators:** Migration background (personal or parental history of being born outside of Germany)	**% DM1:** 100% **% male:** 52.8% **Mean age (Years, IQR):** 13.7 (10.3-16.5) **Ethnicity:** 24.3% migration background **Mean HbA1c (+IQR):** 7.52% (58.7 mmol/mol) (6.83-8.31%, 51.1-67.3 mmol/mol)

Results	Authors' conclusions
CGM use was correlated with the SES quintile, adjusted for sex, age, diabetes duration and minority status. In the T1DX registry data from 2016-2018, 15.0% employed a CGM in SES quintile Q1, vs 52.3% in Q5 (slope 0.460, P<0.001). For the DPV registry from 2016-2018, 48.5% of Q1 employed a CGM, vs 57.1% of Q5 (slope 0.068, p<0.001). HbA1c was higher in those more deprived, in the DPV registry (Q1 vs Q5 7.8% (61.7 mmol/mol) vs 7.5% (58.5 mmol/mol), slope -0.078%, p<0.001) and the T1DX (9.3% (78.1 mmol/mol) vs 8.0% (63.9 mmol/mol), slope -0.354%, p<0.001). After correction for technology use, the effect was lessened (DPV slope: 0.074%, p<0.001, T1DX slope -0.276%, p<0.001).	The larger impact of SES on CGM use and HbA1c in the USA might be due to differences in culture and healthcare between the USA and Germany. For example, insulin and out-of-pocket costs are higher in the USA. Furthermore, the T1DX SES measures were on the individual level, whereas the DPV employed area-based measures. As such, they are not directly comparable. The authors raise a concern that youths with T1DM from lower SES quintiles might be systematically disadvantaged regarding diabetes treatment.
After adjustment for SES, demographics, health care factors and diabetes self-management, the non-Hispanic White and Hispanic populations used more CGM than the non-Hispanic Black population (in percentages and 95-CI's, 53% (48-58), vs. 58% (52-64) vs 31% (25-37)).	The authors argue that, while SES does affect CGM use, it is not the sole driver of disparities based on ethnicity. The effects of health care factors and diabetes self-management were found to be small, although this was theorized to be due to the self-reported nature of the data. It was concluded that the issue of ethnicity should be addressed separately from SES, for instance by counteracting implicit bias and culturally tailored treatment approaches.
CGM use was found to increase from 17.9% to 70.3% in the population over the period from 2016 to 2019. In 2016, odds of CGM use were higher for those in the least deprived quintile vs the most deprived (OR 1.85, 1.63-2.10, p<0.001). This effect was no longer significant in 2019, which was due to a larger increase in CGM use in the lower quintiles. CGM use was higher in those without migration background than those with it in 2016 (OR 1.79, 1.64-1.95), which significantly decreased over the years to 1.30 (OR 1.22-1.39) in 2019. All values are adjusted for area deprivation, migration background, gender, age, diabetes, and duration as is necessary.	The increased adoption of CGMs, especially among those in the lower SES quintiles, is due to the inclusion of CGM devices in the statutory health insurances. Regarding the effects of migration status, authors argue that this could be due to language and cultural barriers. However, more complex discriminatory reasons cannot be excluded.

Authors, date, and country	Domain(s)	Study methods	Subjects
Everett et al., 2021, USA (55)	Income/ Occupational, Education, Social, Ethnicity	**Design:** Cross-sectional analysis of the T1D Exchange Registry (n=4.895) **Period:** 2015-2016. **Area:** USA **SES indicators:** Parental education, employment status, household income, insurance type and reported generosity in coverage. **Ethnicity indicators:** Self-reported, defined as NHW, NHB, Asian/Pacific islander, Hispanic or other.	**% DM1:** 100% **% male:** 41.2% **Mean age (Years):** 31.36 (24.6% <18, 21.4% 16-<26) **Ethnicity:** 88.7% NHW **Mean HbA1c (+sd):** Not reported
Venkatesh et al. 2023, USA (36)	Income/ Occupational, Education, Ethnicity	**Design:** Cross-sectional analysis of the T1D Exchange Registry, selecting only women of reproductive age (n=6.643) **Period:** 2015-2018. **Area:** USA **SES indicators:** Education, household income, insurance **Ethnicity indicators:** Self-reported, defined as NHW, NHB, Asian/Pacific islander, Hispanic or other.	**% DM1:** 100% **% male:** 0% **Median age (Years, IQR):** 20.0 (17.0-28.0) **Ethnicity:** 5.9% NHB, 9.3% Hispanic **Mean HbA1c (IQR):** 8.3%, (67.2 mmol/mol) (7.4%-9.6%, 57.4-81.4 mmol/mol)
Kommareddi et al., 2023, USA (69)	Income/ Occupational, Education, Social, Ethnicity	**Design:** Cross-sectional analysis of Optum's deidentified Clinformatics Data Mart, an administrative health claims database containing Medicaid beneficiaries (n=34.649) **Period:** 2017-2020. **Area:** USA **SES indicators:** Education, income, probable homeownership, insurance eligibility **Ethnicity indicators:** Derived from multiple sources, including name and geographic location. Defined as NHW, NHB, Hispanic, Asian, or Unknown (Unknown and missing were excluded from analysis)	**% DM1:** 100% **% male:** Not reported **Median age (Years, IQR):** Not reported. **Ethnicity:** >70% NHW, >12% NHB, >8% Hispanic, >2% Asian (exact percentages differed per annual cohort) **Mean HbA1c:** Not reported

Results	Authors' conclusions
More charitable insurance coverage and higher SES were directly associated increased CGM use (β=1.21, SE=0.14, P<.0001 and β=1.52, SE=0.12, P<.0001, respectively) and decreased adverse outcomes (β=-0.40, SE=0.09, P<.0001 and β=-0.33, SE=0.09, P=.0002, respectively). The effect on adverse outcomes was partly mediated through CGM use (β=-0.23, SE=0.06, P=.0002).	That by addressing disparities in access to diabetes technology, inequalities in treatment outcomes can be equalized.
CGM use increased over time, from 20.6% to 30.0% between 2015 and 2018. In multiple regression analysis, NHB and Hispanic people had lower odds of CGM use than NHW people (OR 0.40, 95%CI 0.28-0.65 and OR 0.73, 95%CI 0.57-0.92, respectively). Lower income and lower educational attainment were similarly associated (OR 0.48, 95%CI 0.39-0.59 and OR 0.45, 95%CI 0.34-0.60, between respective lowest and highest categories). Medicaid had lower odds of CGM use than private insurance (OR 0.30, 95%CI 0.24-0.36). CGM use was associated with improved glycaemic control, lower odds of DKA (OR 0.57, 95%CI 0.41-0.78), but not severe symptomatic hypoglycaemia.	Findings in this population were in line with findings in the general population. This could contribute to adverse pregnancy outcomes. Possible causes of this disparity in CMG use were systemic racism, diminished health care access, provider bias and inadequate patient-provider communication, and strict eligibility criteria.
CGM use increased from 3.8% in 2017 to 35.2% in 2020. CGM users were generally younger, more likely to have attended at least college, to have incomes >$60.000 annually and to be likely homeowners (p<0.001 for all associations). These associations remained significant after multivariate analysis (including age, gender, SES factors, insurance eligibility and endocrinology visit history). In the multivariate analysis, Hispanic and NHB beneficiaries were less likely to receive a CGM than NHW beneficiaries (OR 0.47, 95%CI 0.42-0.54 and OR 0.67, 0.95%CI 0.61-0.74, respectively). From 2017 to 2020, absolute differences in CGM use increased between NHW and NHB beneficiaries (2.6% to 11.1%), Hispanic beneficiaries (3.0% to 15.5%) and Asian beneficiaries (1.5% to 8.0%).	The increase in CGM disparities, despite increase attention to these issues, is worrisome. Offered causes include language barriers, inequal access and/or implicit bias. This indicates a need for policy changes, as well as interventions on the level of patients, providers, and the system as a whole.

Authors, date, and country	Domain(s)	Study methods	Subjects
Ni et al., 2023, USA (68)	Income/ Occupational, Ethnicity	**Design:** Retrospective analysis of charts of Medicaid recipients at urban safety-net hospital (n=3.036) **Period:** 2020-2022. **Area:** Colorado, USA **SES indicators:** Main language **Ethnicity indicators:** As noted in dossier, defined as either NHW, NHB, Hispanic, Asian, American Indian/Alaskan Native or Other	**% DM1:** 8% **% male:** 43% **Median age (Years, IQR):** 54 (43-60) **Ethnicity:** 19% NHW, 20% NHB, 53% Hispanic, 3.4% Asian, 1.3% American Indian/Alaskan Native, 2.5% Other **Median HbA1c (IQR):** 7.6% (59.6 mmol/mol) (6.40%-10.10%, 46.4-86.9 mmol/mol)
Johnson et al., 2022, Australia (49)	Income/ Occupational	**Design:** Longitudinal analysis of the Australasian Diabetes Database Network registry and the National Diabetes Service Scheme registry (n=3.060) **Period:** 2016-2019 (12 months pre-subsidy until 24 months post-subsidy) **Area:** Australia **SES indicators:** Not included. **Ethnicity indicators:** Not included	**% DM1:** 100% **% male:** 51.8% **Mean age (Years+sd):** 11.8±4.1. **Ethnicity:** Not reported **Mean HbA1c (+sd):** 8.4%±1.6% (68.3±17.5 mmol/mol)
Burnside et al. 2023, New Zealand (56)	Income/ Occupational, Education, Social, Ethnicity	**Design:** Cross-sectional analysis of chart data from all regional diabetes centres in New Zealand (n=1.205) **Period:** 2021 **Area:** New Zealand **SES indicators:** New Zealand Index of Deprivation, an area level score of SES **Ethnicity indicators:** Self-reported, as noted in the chart, as either European/ Other, Asian, Pacific or Māori	**% DM1:** 100% **% male:** 49.9% **Age (Years):** 6.0% <5, 30.7% 5-<10, 63.3% 10-<15 **Ethnicity:** 70.2% European/ Other, 4.6% Asian, 7.1% Pacific, 18.1% Māori **Median HbA1c (IQR):** 8.0% (64 mmol/mol) (7.3%-9.0%, 56-75 mmol/mol)

Results	Authors' conclusions
Of the CMGs prescribed, 94.1% resulted in a CGM dispensed. Non-NHW persons formed a smaller proportion of the group prescribed CGMs than they did in the group not prescribed CGMs, with NHW persons forming a larger proportion (p<0.001). The odds of a CGM dispensed after prescription did not differ between ethnicities. English and Spanish speaking persons also had the same odds, however, 'other'-language speakers had lower odds for both prescription and dispensation (0.48, 0.25-0.91, and 0.51, 0.26-0.96, respectively). CGM adherence was not affected by ethnicity and/or language spoken, nor did it affect HbA1c improvement after CGM initiation, with all group improving (1.2% (13.1 mmol/mol) for type 2, type 1 did not significantly improve).	California's regional Medicaid plan offers the FSL-2 with no restrictions and 0$ co-pay. In the population dependent on Medicaid, a traditionally underserved population, this negated previously find disparities between ethnicities, or, at the least, made them no longer significant. Regarding Spanish-speakers, the language barrier was also negated. This could be due to that the reimbursed devices supported Spanish natively, as the barrier was still present for 'other' languages. The authors note that full reimbursement of CGM devices could be a major part of addressing disparities in diabetes care.
CGM uptake increased from 5% to 79% after the subsidy was introduced. 12 months after introduction, the odds ratio (OR) of achieving the HbA1c target of <7% (53 mmol/mol) was 2.5, p<0.001, which was sustained at 24 months (2.3, p<0.001). The OR for suboptimal HbA1c (>9.0%, 74.9 mmol/mol) was 0.34, p<0.001, at 24 months. 65% of CGM users used the CGM >75% of the time, which correlated with a lower HbA1c than those who used it <25% of the time (7.8%±1.3% (61.7±14.2 mmol/mol) vs 8.6±1.8% (70.5±19.7 mmol/mol), p<0.001). In the >75% user group, the incidence of ketoacidosis was also lowered (incidence rate ratio, 0.34, 0.33-0.74, p<0.001)	The introduction of universal funding correlated with a sharp increase in CGM use. However, this might also in part be explained by increased usability and popularity of the devices, unrelated to the reimbursement options. The increased CGM use also correlated with increased odds of achieving sufficient glycaemic control, which was sustained for the duration of the study. The universal nature of the subsidy was stated to allow for analysis without additional correction disparities in healthcare access. However, this would only apply to the disparities of an economic nature, not those relating to educational, social, or ethnic backgrounds.
Adjusting for age, gender, deprivation, diabetes duration, healthcare centre and insulin modality, European/Other children were more likely than Māori children to use CGM (1.20, 1.04-1.38), and Pacific children were less likely than Māori to use CGM (OR 0.62, 0.40-0.96). Increased deprivation was similarly associated with less CGM use (OR 0.69, 0.57-0.84, most deprived vs least deprived quintiles). Mean HbA1c was lowest for those using rt-CGM, followed, in order, by is-CGM and SMBG. Differences in mean HbA1c by ethnicity were most pronounced in SMBG users, lessened in is-CGM users, and insignificant in rt-CGM users.	Of note, CGMs in New Zealand are completely self-funded. Disparities in CGM usage were present between the various ethnicities, in favour of European/Other ethnicities, and SES quintiles, favouring the least-deprived. Moreover, the usage of these technologies was found to impact HbA1c disparities in those groups, rendering them insignificant in those using rt-CGM. The authors state that this is an important argument for full funding of CGM technology, as well as addressing other barriers, such as implicit prescription biases.

Authors, date, and country	Domain(s)	Study methods	Subjects
Lee et al., 2022, USA (87)	Income/ Occupational, Education.	**Design:** Case Series concerning the efficacy of a specialized support program for CGM use, including financial and educational support (n=6). **Period:** Not reported **Area:** California, USA **SES indicators:** Public insurance status with inconsistent eligibility for CGM coverage **Ethnicity indicators:** Not reported	**% DM1:** 100% **% male:** 50% **Mean age (Years+sd):** 16.33±2.21. **Ethnicity:** **Mean HbA1c (+sd):** Not reported
Wong et al, 2014, USA (57)	Income/ Occupational, Education, Ethnicity	**Design:** Cross-sectional analysis of the T1D Exchange Registry (n=17.317) **Period:** 2011 **Area:** USA **SES indicators:** Household income, health insurance status, education level **Ethnicity indicators:** Self-reported ethnicity	**% DM1:** 100% **% male:** 49.4% **Age (years):** 29% <13, 28% 13-<18, 16% 18-<26, 27% ≥26 **Ethnicity:** 83% NHW, 4% NHB, 8% Hispanic, 4% Other **Mean HbA1c (+sd):** 8.2%±1.5% (66±7 mmol/mol)
Agarwal et al., 2020, USA (19)	Ethnicity	**Design:** Cross-sectional analysis of patient and chart data of 6 T1D Exchange centres (n=300) **Period:** 2018 **Area:** Urban areas in the USA **SES indicators:** Insurance type, education level, household income, neighbourhood poverty level, Hollingshead Index, food insecurity **Ethnicity indicators:** Self-reported as NHW, NHB or Hispanic	**% DM1:** 100% **% male:** Not reported **Median age (Q1, Q3):** 20 (19-22) **Ethnicity:** 33% NHW, 32 NHB, 34% Hispanic **Mean HbA1c:** 9.0% (75mmol/mol)
Bailey et al., 2022, USA (60)	Income/ Occupational, Ethnicity	**Design:** Cross-sectional analysis of T1D Exchange Registry (n=22.418) **Period:** 2016-2018 **Area:** USA **SES indicators:** Annual income, Education level, Insurance type **Ethnicity indicators:** self-reported as NHW, NHB, Hispanic, Asian, Hawaiian/ Pacific Islander, American Indian/Alaskan Native or multiple	**% DM1:** 100% **% male:** 48% **Age (Years):** 46% <18, 49% 18-64, 4.8% ≥65 **Ethnicity:** 89% NHW, 5.6% NHB, 5.6% Hispanic, 1.1% Asian, <0.1% Hawaiian/ Pacific Islander, 0.2% American Indian/Alaskan Native, 2.2% multiple **Median HbA1c (IQR):** 7.80% (61.7 mmol/mol (7.25%-8.43%, 55.7-68.6 mmol/mol)

Results	Authors' conclusions
Across all 6 cases, initiation of CGM technology (separate of CSII initiation) and increased support from healthcare professionals, improved HbA1c and reduced complications.	Specialized programs could be used to address barriers to CGM adoption, and subsequently improve treatment outcomes. However, removing 'outdated' reimbursement requirements is essential to the scalability of the program.
CGM use was found to more likely in those with higher education levels, higher household incomes and private health insurance ($p<0.01$ for all correlations, excepting household income in the age group 18-25). Among children aged below 13, non-Hispanic White children used more CGMs ($p<0.001$). This effect was not found in those aged >13.	The study was not designed to show the substrate of the found disparities, only their existence. No further conclusions regarding the effects of SES or its mechanisms could be made.
CGM use was lower among non-Hispanic Black (28%) and Hispanic (37%) participants than non-Hispanic White participants (71%, $p<0.001$). HbA1c levels, after adjusting for age, sex, and diabetes duration, were 2.26% (24.7 mmol/mol) higher in non-Hispanic Black than non-Hispanic White participants ($p<0.001$). The difference between Hispanic and non-Hispanic White participants were not significant. Further analysis found that 16.4% of disparity between non-Hispanic White and non-Hispanic Black participants was related to technology use, which included CSII in addition to CGM. 37.6% was related to SES.	A significant discrepancy in HbA1c between various ethnicities was found, and this discrepancy is in part mediated by differences in technology access.
Compared to the NHW population, NHB and American Indian/ Alaskan Native ethnicities were significantly less likely to use a CGM (OR 0.45, 0.36-0.57, $p<0.001$ and 0.33, 0.14-0.70, $p=0.008$, respectively). Individuals with higher incomes had greater odds of using a CGM, with those earning over $100.000 annually having 2.06 times the odds compared to those earning <$25.000 ($p<0.001$). Comparing those on government insurance to those commercially insured, the odds ratio was 0.59 ($p<0.001$). Odds were not adjusted.	CGM utilization in the USA is significantly correlated with insurance status and ethnicity.

Authors, date, and country	Domain(s)	Study methods	Subjects
Kanbour et al., 2023, USA (79)	Ethnicity	**Design:** Retrospective chart review (n=1.258) **Period:** 2013-2020 **Area:** Baltimore, Maryland, USA **SES indicators:** Primary language, marital status, employment status, insurance type, area deprivation index **Ethnicity indicators:** Based on chart data, for analysis defined as either NHB or non-NHB.	**% DM1:** 100% **% male:** 48.3% **Median Age (Years, IQR):** 36 (26-52) **Ethnicity:** 74.2% NHW, 19.2% NHB, 4.1% Hispanic 6.2% Other, 0.5% Unknown **Median HbA1c (IQR):** 7.8% (61.7 mmol/mol) (7.0%-8.9%, 53.0-73.8 mmol/mol)
DeSalvo et al., 2021, USA (58)	Income/ Occupational, Ethnicity	**Design:** Cross-sectional analysis T1D Exchange Quality Improvement (T1DX-QI) Collaborative Cohort (n=11.469) **Period:** 2017-2019 **Area:** USA **SES indicators:** Insurance type **Ethnicity indicators:** NHW, NHB, Hispanic, Other, or Unknown	**% DM1:** 100% **% male:** Not reported **Age (Years):** 19% 2-12, 47% 13-16, 19% 27-55, 6% >55 **Ethnicity:** 72% NHW, 6% NHB, 10% Hispanic, 2% Other, 10% Unknown **Mean HbA1c:** Not reported
Lai et al., 2021, USA (80)	Income/ Occupational, Ethnicity	**Design:** Retrospective chart review (n=1.509) **Period:** 2015-2018 **Area:** Philadelphia, USA **SES indicators:** Insurance type **Ethnicity indicators:** NHW, NHB, Hispanic	**% DM1:** 100% **% male:** 56% **Age:** Not reported, inclusion <17 **Ethnicity:** 73% NHW, 18% NHB, 8% Hispanic **Mean HbA1c:** Not reported
Majidi et al. 2021, USA (76)	Ethnicity	**Design:** Cross-sectional analysis T1D Exchange Quality Improvement (T1DX-QI) Collaborative Cohort (n=19.226). **Period:** 2018-2020 **Area:** USA **SES indicators:** Insurance status **Ethnicity indicators:** NHW, NHB, Hispanic or Other	**% DM1:** 100% **% male:** 51% **Age:** Not reported **Ethnicity:** 73.5% NHW, 7.5% NHB, 8.7% Hispanic, 10.3% Other **Mean HbA1c:** 8.5% (69.4 mmol/mol)

Results	Authors' conclusions
NHB persons were less likely to use a CGM at inclusion (7.9% vs 30.3%, p<0.001) and throughout the study (43.6% vs 72.1%, p<0.001). Likewise, NHB persons were less likely to have documented discussion about CGMs (aOR 0.41, 0.29-0.90) and prescription (aOR 0.61, 0.41-0.93), adjusted for pump use, marital status, deprivation, and number of clinic visits.	NHB persons use less CGMs, largely mediated through lessened discussion and subsequent prescription, as compared to non-NHB persons. This could be related to differences in insurance types, subjective criteria's regarding CGM eligibility, implicit biases and other factors influencing shared decision making.
NHW participants used more CGM than NHB or Hispanic participants (49.5% vs 17.7% vs 38.4%, p<0.001). Those on private insurance used more CGM than those on public insurance (33.3%). This effect persisted even after stratification for ethnicity and insurance type. NHW participants, those using CGM and those privately insured experienced better healthcare outcomes, as evidenced by lower HbA1c and lower incidence of ketoacidosis and severe hypoglycaemia.	The uptake of CGMs was negatively correlated with ethnic minority status and government insurance, despite the found positive effects of these devices. In the privately insured population, ethnic minority status was still negatively correlated with CGM use, alluding to the presence of other social and provider barriers.
Of the 1.509 eligible children, 48% was initiated on CGM. A higher percentage of non-Hispanic White children was initiated than Hispanic and non-Hispanic Black children (54% vs 33% vs 31%) Correcting for insurance, age of diagnosis and sex, non-Hispanic White children were 2.2 (1.6-3) times more likely to start CGM therapy than non-Hispanic Black children, and 2.0 (1.3-3) times more likely than Hispanic children. Of those who were started on CGM, 86% of non-Hispanic White children still used it after 1 year, versus 61% of non-Hispanic Black children and 85% of Hispanic children. Correcting for insurance, age of diagnosis and sex, non-Hispanic White children were 3.9 (2.2-6.9) times as likely to continue CGM use at 1 year after initiation.	Non-Hispanic Black children are less likely to be initiated on CGM therapy and continue it. Hispanic children were also less likely to start on CGM therapy, but when started, had the same odds of continuing it. No other SES factors, such as education and income, had been included in the analysis, so it is unknown if these could confound or mediate the found effects.
Regarding CGM use, these were more likely to be used by Non-Hispanic White patients (40%) and Other (55%) than non-Hispanic Black (17%), Hispanic (37%) (p<0.001). No correction was performed for confounding factors. This was mirrored by an increased incidence of ketoacidosis and severe hypoglycaemia	There is a clear difference in CGM utilization based on ethnicity, and that further investigation regarding underlying aetiologies is necessary.

Authors, date, and country	Domain(s)	Study methods	Subjects
Foster et al., 2019, USA (61)	Income/ Occupational, Ethnicity	**Design:** Cross-sectional analysis of the T1D Exchange Registry **Period:** 2010-2012, (n=24.833), 2016-2018, (n=22.697) **Area:** USA **SES indicators:** Insurance status **Ethnicity indicators:** NHW, NHB, Hispanic or Other	**% DM1:** 100% **% male:** 50% **Mean age (Years+sd):** 22±17 (2010-2012), 26±18 (2016-2018) **Ethnicity:** 82% NHW, 6% NHB, 8% Hispanic, 4% Other **Mean HbA1c:** 7.8% (62 mmol/mol) (2010–2012), 8.4% (68 mmol/mol) (2016–2018)
Isaacs et al., 2021, USA. (82)	Income/ Occupational, Education, Social, Ethnicity	**Design:** Narrative review No search strategy was given, however, cited research predominantly originated from the USA.	N/A
Auzanneau et al., 2018, Germany (52)	Income/ Occupational, Education, Social, Ethnicity	**Design:** Cross sectional analysis of the Diabetes Prospective Follow-up registry (n=29.284) **Period:** 2015-2016 **Area:** Germany **SES indicators:** German Index of Multiple Deprivation, an area measurement of SES **Ethnicity indicators:** Migration background (personal or parental history of being born outside of Germany)	**% DM1:** 100% **% male:** **Median age (Years, Q1, Q2):** 13.4 (9.8-16.2) **Ethnicity:** 21.6% migration background **Mean HbA1c:** Not reported
Delagrange et al., 2020, France (47)	Income/ Occupational, Education, Social	**Design:** Cross-sectional study (n=1.154) **Period:** 2017-2018 **Area:** France **SES indicators:** EPICES, a construct based on financial status, social connections/ status, and education level. Area deprivation was based on the French European Deprivation Index **Ethnicity indicators:** Not included	**% DM1:** 100% **% male:** 49.1% **Mean age (+SD):** 12.4±3.8. **Ethnicity:** Not included **Mean HbA1c (+sd):** 7.9%±1.0%, (62.8±10.9 mmol/mol)

Results	Authors' conclusions
In the period 2016-2018, ethnic disparities were found in CGM use across all age groups. For example, in the age group <13, household income <50.000 annually, 25% of NHW participants used CGM, vs 8% of NHB. A gradient according to income could be seen as well. In the Hispanic population, aged<13, 15% of those with annual household incomes <50.000 used a CGM, vs 55% of those with incomes >75.000. No p-values were given, no data regarding 2010-2012 was given.	In the article, the disparities are noted, not discussed.
The authors state that diabetes disproportionately affects those of lower SES and those NHB and Hispanic ethnicities. Similarly, CGM use is stated to be lower in those self-same populations.	The found differences were theorized to be due to SES, lesser access to healthcare and lower quality of healthcare, restrictive and excessive insurance criteria, physician shortages and implicit bias among healthcare providers. The authors then argue to address these issues by advocating expanded CGM coverage, the utilization of community health workers and telehealth services to address physician shortages and individualization of care.
CGM technology was used less by those in the most deprived quintile than those in the least deprived quintile (3.4% vs 6.3%. p<0.002, adjusting for federal state)	Effects of SES on CGM use were found. However, this study was performed before the introduction of CGMs in statutory insurance reimbursements.
HbA1c was negatively affected by socioeconomic deprivation, with 45.8% of those with HbA1c >8.5%, 69.4 mmol/mol had EPICES score >30 (the cut-off for deprivation), vs 29.6% of those with HbA1c <8.5%, 69.4 mmol/mol. On the area level, 32.7% of the most deprives quintile had HbA1c levels >8.5%, 69.4 mmol/mol, vs 13.6% in the least deprived quintile. CGM utilization did not differ between EPICES and EDI quintiles	Both individual and area deprivation were correlated with worse glycaemic control. However, CGM use was unaffected by deprivation. This was theorized by the authors to be due to the effectiveness of the French healthcare system in granting equal access to technology. It also suggests that CGM access will not function as a universal equalizer of the effects of SES on glycaemic control.

Authors, date, and country	Domain(s)	Study methods	Subjects
Chen et al., 2023, USA (70)	Income/ Occupational, Education, Social, Ethnicity	**Design:** Cross-sectional study from earlier RCT (n=301) **Period:** 2013-2016 **Area:** Texas, USA **SES indicators:** Household income, parental education, insurance type **Ethnicity indicators:** self-reported	**% DM1:** 100% **% male:** 50% **Mean age (+SD):** 15.0±1.3. **Ethnicity:** 75.3% NHW **Mean HbA1c (+sd):** 8.5%±1.1% (69.4±12.0 mmol/mol)
Dover et al., UK, 2020 (53)	Income/ Occupational, Education, Social	**Design:** Cross-sectional study of patients attending the Edinburgh Centres for Endocrinology & Diabetes (n=4.954) **Period:** 2018-2020 **Area:** Edinburgh, Scotland, UK **SES indicators:** The Scottish Index of Multiple Deprivation, an area score of SES **Ethnicity indicators:** not included	**% DM1:** 100% **% male:** 55% **Median age (IQR):** 46 (32-58) **Ethnicity:** N/A **HbA1c:** 9.3% HbA1c ≤6.5% (<48 mmol/mol), 30% HbA1c <7.5% (<58 mmol/mol), 26% HbA1c >9.0% (>75 mmol/mol)
Odugbesan et al., 2022, USA (67)	Income/ Occupational, Ethnicity	**Design:** Vignette and ranking exercise-based study, concerning care for adults with diabetes, targeting healthcare providers associated with clinics part of the T1D Exchange Network (n=109) **Period:** 2021 **Area:** USA **SES indicators:** Varying insurance status per vignette **Ethnicity indicators:** Varying 'ethnic' name per vignette	**% DM1:** N/A **% male:** 31% **Mean age (Years+sd):** N/A **Ethnicity:** 69% NHW **Mean HbA1c (+sd):** N/A
Addala et al., 2021, USA (66)	Income/ Occupational	**Design:** Vignette and ranking exercise-based study, concerning care for children with diabetes, targeting healthcare (n=39). **Period:** 2021 **Area:** USA **SES indicators:** Varying insurance status per vignette **Ethnicity indicators:** not included	**% DM1:** N/A **% male:** 27% **Mean age (Years+sd):** 44.1±10.0. **Ethnicity:** 79% NHW, 2.6% Hispanic, 15.4% Asian/ Pacific Islander, 2.6% Other **Mean HbA1c (+sd):** N/A

Results	Authors' conclusions
CGM users (compared to non-users) were more likely to be NHW (88% vs 70%, p=0.009), have an annual household income ≥$150.000 (44% vs 23%, p=0.0001), a parent with a college education or higher (81% vs 64%, p=0.004), and private health insurance (95% vs 82%, p=0.005)	Study outcomes were in line with other studies.
Use of is-CGM decreased when deprivation increased, with 27.6% of the most deprived using is-CGM, vs 52.6% of the least deprived. Use of is-CGM was associated with meeting HbA1c treatment goals of <7.5% (<58 mmol/mol), aOR 1.56 (1.35-1.80), but not with ≤6.5% (≤48 mmol/mol), aOR 1.16 (0.92-1.45), including adjustment for SES. A similar relationship was found for SES itself (aOR 1.56, 1.35-180, aOR 1.32, 1.06-1.65 for the <7.5%/<58 mmol/mol and ≤6.5%/≤48 mmol/mol treatment goals, respectively)	SES deprivation is associated with poorer outcomes, with is-CGM as a possible mediator in this process. Ethnic minorities were underrepresented in the sample, and as such, this factor could not be analysed. Findings may not be generalizable to other populations.
Ethnic bias was present in 34% of the cohort. This was significantly associated with the self-reported ability to identify their own biases (OR 4.66, 1.60-17.09, p=0.009). It did not differ by age, provider role and/or type, setting or years of experience. Insurance-mediated bias was present in 61%. In univariate analysis, age and years in practice were correlated, however, this effect was not found after adjusting for confounders. Patient preference was ranked as most important factor, followed by the patients self-monitoring habits, HbA1c, age, income and lastly, ethnicity. Paediatric providers ranked HbA1c higher than insurance, but followed largely the same order.	Implicit ethnic bias was present in the study population, and that this was not protected against by the self-reported ability to identify bias. As most antiracism training focusses on enhancing awareness of implicit bias, and this study demonstrates that this is insufficient. Furthermore, respondents were aware of the nature of the study, which might have influenced their answers.
Family preference was ranked as most important overall for recommending CGM therapy (mean rank 1.69±1.05), followed by insurance coverage (2.83±1.56). Ethnicity was considered least important (6.91±0.37). In agreement with this, implicit bias against public insurance was common, being present in 84.6% of the sample, with the likelihood of this bias increasing per practice-year (aOR per year 1.47, 95%CI 1,92-2.13, p=0.007).	Implicit bias against public insurance is common within the U.S. cohort. This can affect recommendations of CGM therapy for underserved populations, who are more likely to have public insurance.

Authors, date, and country	Domain(s)	Study methods	Subjects
Lipman et al., 2020, USA (83)	Income/ Occupational, Ethnicity	**Design:** Retrospective chart review (n=1.331) **Period:** 2018-2019 **Area:** Philadelphia, USA **SES indicators:** Insurance status **Ethnicity indicators:** Self identified as NHW, NHB or Hispanic	**% DM1:** 100% **% male:** 53% **Median Ages (Years, IQR):** NHW 14.3 (11.5, 16.4), NHB 13.9 (11.2, 1603), Hispanic 14.0 (11.6-15.6) **Ethnicity:** 77% NHW, 15% NHB, 8% Hispanic **Median HbA1c (IQR):** NHW 7.8% (7.1%-8.7%) (61.7 mmol/mol, 54.1-71.6 mmol/mol), NHB 9.4% (8.2%-11.0%) (79.2 mmol/mol, 66.1-96.7 mmol/mol), Hispanic 8.6% (7.7%-9.9%) (79.5 mmol/mol, 60.7-84.7 mmol/mol)
Walker et al., 2021, USA (71)	Income/ Occupational, Education, Social	**Design:** Focus group interviews, including pre-focus group survey (n=86), of underserved populations **Period:** 2018-2019 **Area:** Florida/California, USA **SES indicators:** Targeted inclusion of subject with recent DKA, HbA1c >9% and recent 'no-shows', or received care from a Federally Qualified Health Center **Ethnicity indicators:** self-reported as NHW, NHB, Hispanic, Asian, American Indian/Alaskan Native, or 'multiple'	**% DM1:** 100% **% male:** Not reported **Mean age (Years+sd):** 42.0±16.2. **Ethnicity:** NHW 64%, NHB 12.8%, Hispanic 12.8%, Asian 2.3%, American Indian/Alaskan Native 1.2%, Multiple 7.0% **Mean HbA1c:** N/A
Tanenbaum et al., 2017, USA (72)	Income/ Occupational, Education	**Design:** Survey of clinicians regarding barriers to the use of diabetes technology (n=209) **Period:** 2016 **Area:** USA **SES indicators:** N/A **Ethnicity indicators:** Self reported as NHW, NHB, Hispanic Asian/Pacific Islander or Native American	**% DM1:** N/A **% male:** 7.7% **Ages:** 16.8% <35, 23.9% 35-45, 23.4% 46-55, 35.4% ≥56 **Ethnicity:** NHW 91.4%, NHB 2.4%, Hispanic 3.8%, Asian/ Pacific Islander 7.7%, Native American 1.9% **Mean HbA1c:** N/A

Results	Authors' conclusions
Government insurance (proxy of low SES) was present in 60% of non-Hispanic Black, 53% of Hispanic and 18% of non-Hispanic White children (p<0.001). In total 63% of the cohort used a CGM. After stratification for insurance status, NHW children wore more likely than NHB children to use CGM in both the governmentally insured population (47% vs 35%, p<0.001) and the commercially insured (46% vs 71%, p<0.001). This was not significant when comparing Hispanic with NHW children. Among the populations, total appointment attendance was not found to be significantly different.	Since government insurance provides universal coverage for CGMs, the found discrepancies may be ethnically motivated or due to SES factors not accounted for in the study. Appointment attendance was similar between populations, so the quantity of patient-provider interactions seems unlikely to be related.
Survey data revealed significant differences in CGM use by ethnicity and education status in California (p=0.05, p=0.02, respectively). These findings were not significant in Florida. Focus groups identified 2 main barriers: judgemental endocrinologists and unclear criteria for receiving a CGM. The former was most often noted as having too poor a glycaemic control to use a CGM, or that the technology would be too difficult. The latter was most often cited as a difficulty in gaining financial coverage for the device.	The stigma of poor diabetes control plays a large role in underserved individuals being offered or receiving support in acquiring a CGM. This was theorized to be in part due to the providers own perceptions about coverage criteria. However, the other underlying biases cannot be excluded. The study was not powered to analyse the influences of ethnicity.
Providers in urban settings prescribed more CGMs than those in suburban and rural settings (29.3% vs 21.5%). The most reported barrier to CGM use was that of cost and insurance coverage (66%). The most reported top modifiable barrier was a perceived patient dislike of having a device on their body (63%) and that there were too many alarms (61%). Insufficient knowledge or education on how to use the CGM was most often ranked as second top barrier (12%). This data was compared to barriers reported by adult patients with T1D. The largest difference was found in the barrier of understanding the information provided by the CGM. This barrier was endorsed by 40-46% of clinicians vs 4.5% patients. Regarding 'a dislike of having a device on their body' this was 64-73% vs 35%	Clinicians in general perceive more barriers to the use of CGMs than patients themselves do. Whether or not these barriers were warranted was not studied. However, clinicians who perceive more barriers may be reluctant to encourage CGM uptake in their practice. Identifying which barriers might or might not be present per patient could be used to guide individualized treatment approaches.

Authors, date, and country	Domain(s)	Study methods	Subjects
Messer et al., 2020, USA (62)	Income/ Occupational, Education	**Design:** Interview study regarding barriers to technology use (n=411) **Period:** 2018 **Area:** USA **SES indicators:** Not included. **Ethnicity indicators:** self-reported as either NHW, Hispanic or Other.	**% DM1:** 100% **% male:** 47.2% **Mean age (Years+sd):** 16.30±2.25. **Ethnicity:** 83% NHW, 11.4% Hispanic, 5.6% Other **Mean HbA1c (+sd):** N/A
Howe et al., 2023, USA (75)	Income/ Occupational, Education, Social, Ethnicity	**Design:** Interview study regarding barriers to technology use by children in parents (n=21) **Period:** 2020-2022 **Area:** Philadelphia, USA **SES indicators:** Education level, income, marital status **Ethnicity indicators:** Inclusion if either NHW or NHB	**% DM1:** N/A **% male:** 24% **Mean age (Years+sd):** 44.8±7.1. **Ethnicity:** 38% NHW, 62% NHB **Mean HbA1c:** N/A
Lanning et al., 2020, USA (73)	Income/ Occupational, Education	**Design:** Survey study regarding provider-perceived barriers to CGM use (n=127) **Period:** 2016 **Area:** USA **SES indicators:** N/A **Ethnicity indicators:** Not reported.	**% DM1:** N/A **% male:** N/A **Mean age (Years+sd):** Not Reported **Ethnicity:** Not Reported **Mean HbA1c (+sd):** N/A
Kompala et al., 2022, USA (63)	Income/ Occupational, Education	**Design:** Survey study regarding provider-perceived barriers to CGM use (n=182) **Period:** 2020 **Area:** USA **SES indicators:** N/A **Ethnicity indicators:** Self-reported as either NHW, NHB, Hispanic, Asian, or Other/Multiple	**% DM1:** N/A **% male:** 27% **Age:** Not Reported **Ethnicity:** 68% NHW, 1.2% NHB, 5.9% Hispanic, 22% Asian, 3.0% Other/Multiple **Mean HbA1c:** N/A
Rosenfeld et al., 2022, USA (84)	Income/ Occupational, Education	**Design:** Expert round table (n=23) **Period:** 2021 **Area:** USA **SES indicators:** N/A **Ethnicity indicators:** N/A	**% DM1:** N/A **% male:** Not reported **Age:** Not reported **Ethnicity:** Not reported **Mean HbA1c:** N/A

Results	Authors' conclusions
54.7% of participants used a CGM, of which 99% used a rt-CGM. Cost and wear-related barriers were cited most often (60.8% and 58.6%) respectively. CGM discontinuers reported more barriers than current users (4.31±2.85 vs 3.29±2.52, p=0.044)	The most common barriers are in line with earlier research. The authors state that further improvements in technology could address wear-related barriers, whereas cost-related barriers could be addressed by implementing measure to increase device longevity (i.e., proper site selection and skin preparation) and advocating for device reimbursement.
There were differences in barriers reported between NHW and NHB parents. For instance, device stigma, such as bullying because of the visible device, was reported by NHB parents, where it wasn't by NHW parents. NHB parents also reported negative communications with HCP's, where NHW parents did not. NHB parents more often reported being told to wait with starting a CGM, often until blood glucose levels were steady, whereas NHW parents reported that CGMs were repeatedly offered, even after prior refusal, and that blood glucose levels were not used as a criterium.	NHB parents reported more barriers than NHW parents, often related to stigma and negative provider interactions. Especially the provider interactions are worrisome, as they indicate that systemic treatment differences between ethnicities. This is in line with previous studies on the subject, and is something that needs to be addressed. In the sample, highly educated (71% college education or higher) and affluent (43% >$106.000 annual income), which can skew the found effects. No data regarding the distribution of these factors within the NHW and NHB parent groups were reported.
Providers were divided into 'Ready' and 'Cautious' personas as indicated by their attitudes towards CGM use. In daily practice, the highest rated barrier was insurance coverage (91%). Excluding cost-related barriers, it was 'not wanting a device on the body'(72%). Those identified as Cautious reported more barriers than those Ready (9.9 vs 4.8, p<0.001) and lower confidence (4.4 vs 6.0 on a 1-10 scale, p=0.003). Cautious providers did not report more prerequisites for CGM use or lesser access to clinic resources for CGM training than Ready providers.	The higher prevalence of barriers among Cautious providers without higher requirements for CGM use could be indicative of the limitations of the study, namely an incomplete survey of barriers. Cautious providers could benefit from targeted training on how to address barriers to CGM use.
Most respondents prescribed CGMs to >51% of their patients with T1DM. Prescription to patients with T2DM were lower, with half reporting prescription percentages less than 10% of the population, the other half reporting between 10 and 50% of the population. Nearly all respondents agreed that CGMs are an important technology for treating DM, and that most of their patients were interested. They, however, experienced barriers in the form of prohibitive costs (73% of respondents) and inadequate time (55%) and training resources (60%). This was also reflected in the open-ended portion of the survey.	Addressing these barriers could increase device uptake. This requires changes at multiple levels, such as policy changes, increased training/ education of healthcare providers and an improved infrastructure for prescribing and utilizing CGM technology.
Regarding initiating CGMs in general, 87% reported a lack of knowledge as greatest barrier. Initiating CGMs for people with T2DM specifically, cost was reported as greatest barrier (53%). Moreover, clinician reimbursement for CGMs were not in line with the true cost. Regarding interpreting CGM data, lack of staff, resources and/or time as greatest barrier (56%).	The expert group developed a toolkit to aid in initiating and interpreting CGMs.

Authors, date, and country	Domain(s)	Study methods	Subjects
Ng et al., 2021, UK (43)	Ethnicity	**Design:** Report on national paediatric audit data (n=29.242) **Period:** 2019-2020 **Area:** UK **SES indicators:** English (IMD, 2019) and Welsh (WIMD, 2019) Indices of Multiple Deprivation, regional area level scores of SES **Ethnicity indicators:** Reported as NHW, NHB, Asian, Mixed or Other	**% DM1:** N/A **% male:** 52.7% **Age:** Not reported **Ethnicity:** 79.3% NHW, 4.0% NHB, 6.7% Asian, 3.2% Mixed, 2.4% Other **Mean HbA1c:** 8.0% (64 mmol/mol)
Fallon et al., 2022, UK (44)	Income/ Occupational, Education, Social, Ethnicity	**Design:** Retrospective chart review (n=1.631) **Period:** Not reported **Area:** Northwest London, UK **SES indicators:** English Indices of Deprivation, an area level score of SES **Ethnicity indicators:** Self reported as either NHW, NHB, Asian, Mixed, Other or Unknown.	**% DM1:** 100% **% male:** 54% **Mean age (Years+sd):** 44±15. **Ethnicity:** 51% NHW, 8.0% NHB, 5.6% Asian, 2.3% Mixed, Other 9.1%, 24% Unknown **Mean HbA1c:** Not stated.
Modzelewski et al., 2022, USA (85)	Income/ Occupational, Education, Social, Ethnicity	**Design:** Retrospective cohort study (n=271) **Period:** 2017-2020 **Area:** Boston, Massachusetts, USA **SES indicators:** Primary language, insurance status **Ethnicity indicators:** NHW, NHB or Other	**% DM1:** 41.3% **% male:** 52% **Mean age (Years+sd):** 50.8±15.2. **Ethnicity:** 39.1% NHW, 40.2% NHB, Other 20.7%, **Mean HbA1c:** 9.04%±1.83% (75.3±20 mmol/mol)
Stanley et al., 2023, Canada (51)	Income/ Occupational, Education, Social	**Design:** Cross-sectional analysis (n=813) **Period:** 2018-2020 **Area:** Toronto, Canada **SES indicators:** The Ontario Marginalization Index, an area level score for SES **Ethnicity indicators:** Not included	**% DM1:** 100% **% male:** 53% **Mean age (Years+sd):** 12.2±4.0. **Ethnicity:** N/A **Mean HbA1c (+sd):** 8.70%±1.73% (71.6±18.9 mmol/mol)

Results	Authors' conclusions
HbA1c was found to be higher in NHB persons, as compared to NHW persons (8.7%, 71.9 mmol/mol vs 8.1%, 64.6 mmol/mol). Similarly, there differences in rt-CGM use between ethnicities and quintiles of deprivation, with NHB persons being the most negatively affected.	Treatment outcomes and access to technology is negatively affected by deprivation and belonging to an ethnical minority. These disparities need to be addressed, and to that end, barriers must be investigated.
Those in the most deprived quintiles used significantly less rt-CGM (20.5% vs 45%, p=0.032) and is-CGM (25.5 vs 54%, p=0.001). HbA1c reduction was seen in the whole population, (-6.7±11.5 mmol/mol, -6.4±12.8 mmol/mol, respectively. Although it did not reach significance, the reduction seemed larger in the most-deprived quintile than the least-deprived (-10 mmol/mmol vs -4 mmol/mol) for rt-CGMs. Those with NHB ethnicity used less rt-CGM than those of NHW and 'mixed' ethnicity (p=0.013). This relationship was not significant for is-CGM (p=0.059). Participation in structured education was lower in those most deprived (23% vs 43%, p<0.001)	Is-CGM and rt-CGM technology was shown to be effective, regardless of SES. However, uptake was shown to be lower among those of lower SES and minority ethnicities. This was theorized to be due to financial barriers separate from insurance coverage and lack of knowledge regarding the benefits of diabetes technology.
CGMs prescribed through pharmacy benefits was acquired significantly faster than through a durable medical equipment company, or DME (78±138 days vs 152±142, p<0.0001). Among patients unable to initiate CGM (n=63), lack of insurance was the main barrier (93.6%). 6.4% did not like or want to wear the device. Of those who stopped using a CGM (n=8), again cost was the main barrier (61.5%). In intermittent users (n=3), cost was again the main barrier (67%). Multivariate analysis identified lower odds of initiating CGM for NHB and Hispanic patients (OR 0.32, 0.14-0.78, OR 0.31, 0.10-0.96, respectively). Private insurance was a facilitator of CGM initiation, as was CGM education prior to CGM prescription (OR 2.80, 1.37-5.73, OR 12.29, 5.57-27.10, respectively)	The long wait times between prescribing and acquiring a CGM were deemed unacceptable due to the clear benefits of CGM technology. The longer wait times for DME-prescribed CGMs was mainly due to a larger need for administration and evidence of CGM necessity. This is doubly disadvantageous to the those with low literacy and/or speaking English as their main language, as it would increase their rate of acquisition failure. Cost-related reasons were the main barrier to acquisition itself, indicating a need for improved insurance coverage. Lastly, CGM education was highly correlated to CGM acquisition, indicating the potency of this intervention.
rt-CGM use was lower in the most deprived quintile than the least deprived quintile (12.9% vs 20.8%, p<0.0001), and rt-CGM users had lower HbA1c (7.93%±1.17%, 63.2 mmol/mol± 12.8 mmol/mol vs 8.86%±1.87%, 73.3 mmol/mol± 20.4 mmol/mol, p<0.001. No significant differences were found in is-CGM use. Rt-CGM use was found to explain 12.0% of the found difference in HbA1c between the most and least-deprived quintiles, after correction for age, gender, and diabetes duration (p<0.0001).	Rt-CGM was found to differ significantly between deprivation quintiles and to be a possible mediator of HbA1c disparities. This was not the case for is-CGM. However, this could be due to regional public coverage of is-CGM as opposed to rt-CGM, which relies on private insurance or self-funding.

Authors, date, and country	Domain(s)	Study methods	Subjects
Lai et al., 2021, USA (95)	Ethnicity	**Design:** Retrospective Chart review (n=345) **Period:** 2016-2018 **Area:** Pennsylvania, USA **SES indicators:** Insurance type **Ethnicity indicators:** Self-identified as either NHW, NHB, or Hispanic	**% DM1:** 100% **% male:** 57% **Age:** Not reported (exclusion if age >18) **Ethnicity:** 76% NHW, 16% NHB, 8% Hispanic **Mean HbA1c:** Not reported
Ebekozien et al., 2021, USA (77)	Ethnicity	**Design:** Cross sectional analysis of hospitalized COVID19 patients with T1D. CGM use was included as a potential confounding factor for ketoacidosis (n=180). **Period:** 2020 **Area:** USA **SES indicators:** Insurance status **Ethnicity indicators:** As registered by HCP, either NHW, NHB or Hispanic	**% DM1:** 100% **% male:** 47% **Age:** 42% ≤19, 58% >19 **Ethnicity:** 44% NHW, 31%% NHB, 26% Hispanic **Median HbA1c (IQR):** 8.3% (67.2 mmol/mol) (2.4%, 26.2 mmol/mol) NHW, 11.7% (104.4 mmol/mol) (4.7%, 51.4 mmol/mol) NHB, 9.7% (82.5 mmol/mol) (3.1%, 33.9 mmol/mol) Hispanic
Wirunsawanya et al., 2020, USA (78)	Ethnicity	**Design:** Retrospective chart review (n=277) **Period:** 2017 **Area:** Safety net hospital, USA **SES indicators:** Insurance type, language **Ethnicity indicators:** Registered as either NHW, NHB, Hispanic, Asian, or Other	**% DM1:** 100% **% male:** 59% **Mean age (Years+sd):** Not reported (inclusion if ≥18) **Ethnicity:** 43% NHW, 25% NHB, 15% Hispanic, 2% Asian, 15% Other **Mean HbA1c:** Not reported
Sinisterra et al. 2021, USA (65)	Income/ Occupational, Ethnicity	**Design:** observational study (n=157, parent-child pairings) **Period:** 2016-2019 **Area:** Texas, USA **SES indicators:** Primary caregiver marital status, yearly household income, insurance type **Ethnicity indicators:** Self reported as either NHW, NHB, Hispanic, Asian (American), American Indian/Alaskan Native or Multiracial	**% DM1:** 100% **% male:** 9% **Mean age child (Years+sd):** 4.5±1.7. **Ethnicity:** 62.2% NHW, 14.7% NHB, 12.2% Hispanic, 7.7% Asian (American), <1% American Indian/Alaskan Native, 2.5% Multiracial **Mean HbA1c (+sd):** 8.4% (68.3 mmol/mol) (1.4%, 15.3 mmol/mol)

Results	Authors' conclusions
NHW children were more often started on CGM within 1 year after diagnosis than NHB children (50.8% vs 27.8%, p=0.006). This effect was only apparent in the commercially insured population, not in those governmentally insured. A greater proportion of those commercially insured started on CGM than those governmentally insured (54% vs 27%, p<0.001). A lower proportion of NHB than NHW children continued CGM use 1 year after initiation (73% vs 96%, p=0.003).	NHB children experience both lower rates of initiation and continuation than NHW children.
Non-Hispanic Black and Hispanic patients used significantly less CGM than non-Hispanic White patients (13% vs 37% vs 62%, p=0.001 and 0.004, respectively).	CGM use was not a primary outcome of the study, rather a potential confounder. As such, CGM use was not adjusted for other factors.
Non-Hispanic Black and Hispanic participants used CGM technology less than non-Hispanic White participants (14% vs 22% vs 47%, respectively). Multivariate analysis, adjusted for insurance and language, found lower odds of technology use, which included CSII in addition to CGM, for non-Hispanic Black and Other ethnicities compared non-Hispanic White participants (0.25, 0.11-0.53 and 0.33, 0.12-0.89, respectively).	Non-Hispanic White participants used significantly more diabetes technology, including CGM, than non-Hispanic Black and Other ethnicities, in the population attending a safety-net hospital.
Rates of CGM use increased over time, from 24.2% at baseline, to 65.8% 18 months after diagnosis. The population was categorized according to their CGM usage as 'always' for those who started CGM at baseline and continued using it, 'later, stable', for those who started later, 'inconsistent', for those who used it intermittently, and 'never', for those who used it never. Participants with private insurance were more likely than those on public insurance to belong to the 'always' (OR 19.94), 'later, stable' (OR 4.78) and 'inconsistent' (OR 3.75) (p<0.05 for all). Ethnicity and marital status were found to have no significant effects. Those in the 'always' and 'later, stable' groups were found to have lower HbA1c's than those in the 'never' group (7.1% (54.1 mmol/mol) vs 7.6% (59.6 mmol/mol) vs 8.4%, (68.3 mmol/mol), p<0.003), but no differences between the 'inconsistent' and 'never' groups (8.0% (63.9 mmol/mol) vs 8.4% (68.3 mmol/mol), p=0.11)	Insurance type was a primary predictor of CGM usage within the first 18 months post-diagnosis of T1D in children, and that this affects treatment outcomes. Ethnicity was not significantly correlated, which is contradictory to other studies. Authors hypothesize that this could be due to the small subgroup sizes.

Authors, date, and country	Domain(s)	Study methods	Subjects
Agarwal et al. 2021, USA (81)	Ethnicity	**Design:** Interview study (n=40) **Period:** 2019 **Area:** Bronx, New York, USA **SES indicators:** Not reported. **Ethnicity indicators:** Self reported.	**% DM1:** 100% **% male:** 38% **Mean age (Years+sd):** 21.5±2.2. **Ethnicity:** 28% NHB, 72% Hispanic **Mean HbA1c (+sd):** 10.3% (89.1 mmol/mol) (2.3%, 25.2 mmol/mol)
Karakuş et al. Turkey, 2021 (64)	Income/ Occupational	**Design:** Caretaker interview study (n-Child=10, n-caretaker=15) **Period:** 2020 **Area:** Turkey **SES indicators:** Not reported. **Ethnicity indicators:** N/A	**% DM1:** 100% **% male Child:** 30% **Mean age child (Years):** 5.67 **Ethnicity:** N/A **Mean HbA1c (+sd):** 6.81% (50.9 mmol/mol) (0.67%, 7.3mmol/mol)
McKnight et al., UK, 2017 (42)	Income/ Occupational, Education, Social	**Design:** Retrospective Chart Review **Period:** 2015-2017 **Area:** Edinburgh, Scotland, UK **SES indicators:** The Scottish Index of Multiple Deprivation, an area score of SES **Ethnicity indicators:** Not included	**% DM1:** 100% **% male:** Not reported **Median age (Years, IQR):** 40 (29-51) for is-CGM users, 40 (30-50) for non-is-CGM users **Ethnicity:** Not reported **Mean HbA1c:** Not reported
Schmitt et al., 2022, USA (88)	Income/ Occupational, Education, Ethnicity	**Design:** Stakeholder-based healthcare improvement plan **Period:** 2020- **Area:** Alabama, USA **SES indicators:** Insurance status **Ethnicity indicators:** NHW, NHB	**% DM1:** 100% **% male: Not reported** **Age:** Age ≥2 years for inclusion. **Ethnicity:** 29.7% NHB **Mean HbA1c:** Not reported.

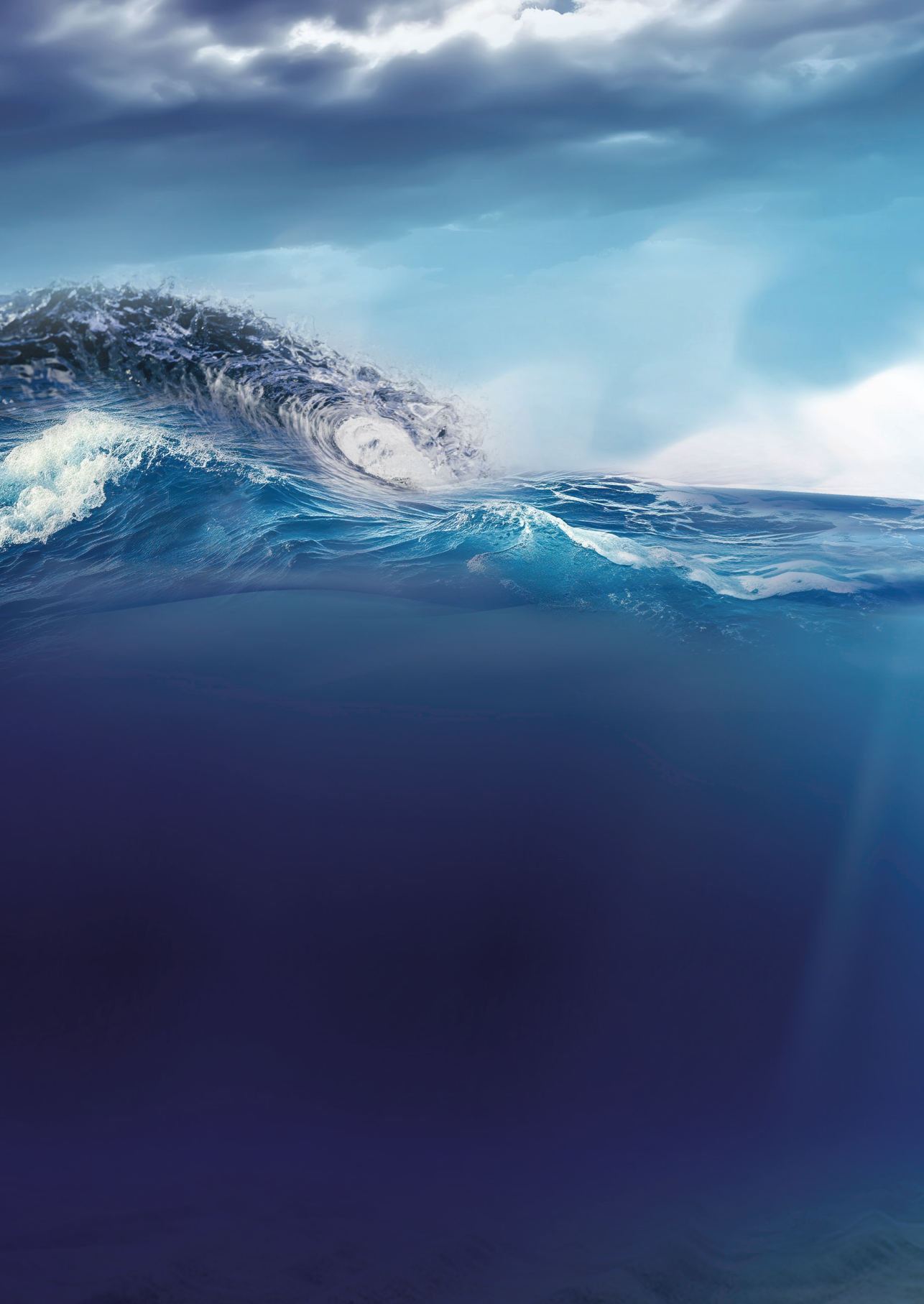
Results	Authors' conclusions
Most participants stated that they had received information about diabetes technology, but were not offered it. Many said they were restricted from using diabetes technology because of their poor glycaemic control, or if it was offered, it was prescribed without considering patient input. Other barriers reported were those regarding distrust of the accuracy of de device, the number of alarms, interference with daily activities and wearing a device on the body and the associated stigma. Alleviating factors were those of healthcare provider optimism, tailored information, patient knowledge and Medicaid coverage. No numbers were given as to the frequency of each barrier and alleviating factor.	Provider related factors were found to be major factor in access to diabetes technology, with technology being offered in the first place and a lack of shared decision-making being especially noteworthy. Regarding the other barriers found, the authors note that shared decision making could also be a tool in addressing these factors. Furthermore, issues such as stigma and daily issues could be addressed by including patient representatives in the educational process, which could be further modified to account for cultural differences.
Caretakers reported significant benefits from CGMs in terms of metabolic control. Three barriers were reported, namely cost (major barrier), concerns with accuracy and reliability (acceptable barrier), and insertion, adhesion, and removal difficulties (manageable barrier). CGMs are not reimbursed in Turkey, and thus paid out-of-pocket.	Overall, caretakers agreed CGMs were a necessity, not a luxury, and worth the additional costs. In use, cost is the main barrier. The study was performed at a private hospital, and thus the included population was well-of financially. Likely, this barrier is larger for the general population. Additionally, the quality of HCP-patient interactions is assumed to be higher in private hospitals, which might attribute to the positive attitudes regarding CGMs
Of those with current or previous use of a is-CGM, 60.2% was part of the least-deprived quintile, vs 4.1% of the most deprives. is-CGM use, at this time, was self-funded. In is-CGM users, the median change in HbA1c was a 2.5 mmol/mol decrease, compared with 1 mmol/mol rise in non-users.	Relying on patients funding technology use themselves can widen deprivation-related inequalities. The efficacy of the is-CGM cannot be ascertained in this study, as it might be confounded by other factors.
Based on stakeholder input, 3 areas of focus were identified: Increasing HCP awareness of CGM coverage, benefits, and disparities in access Provide the opportunity to sample CGMs during routine visits Advocate for public insurance coverage criteria simplification Area 1 was addressed via summary documents regarding CGM devices and insurance criterions, as well as summaries of their patients regarding their CMG use and access and at-risk status. Area 2 was addressed by providing single-use professional and personal CGMs to interested patients. Area 3 was addressed by successfully advocating the removal of 2 documented hypoglycaemic episodes in 4 weeks for CGM reimbursement as a requirement. After addressing this issues, CGM access increased from 50% to 82%. Specifically, for NHB patients, access increased from 27% to 81%. Disparities between NHB and NHW patients fell from 18% to 6%. For publicly insured patients, access rose from 25% to 78%	Part of the found increases in access had already occurred before implementation of the measures. However, the changes in access were much larger after implementation of the measures than before, likely indicating a cause-and-effect. Due to the combined implementation of measures, it is difficult to say which measures were most effective.

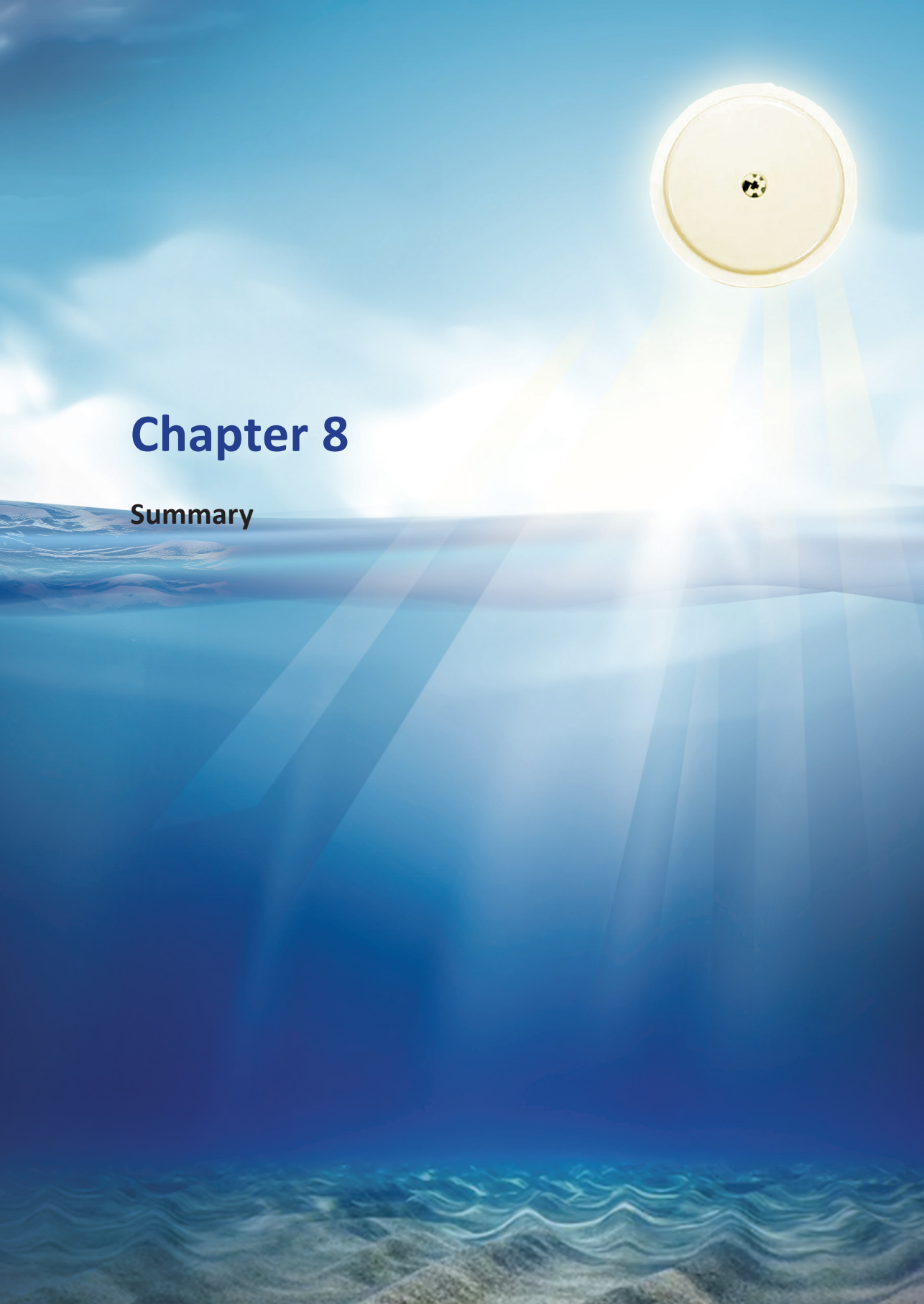
Authors, date, and country	Domain(s)	Study methods	Subjects
Agarwal et al, 2022, USA (96)	Ethnicity	**Design:** Narrative Review The literature search was limited to English papers focused on CGM, insulin pumps and telehealth published in the preceding 5 years.	N/A
Chalew et al., 2021, USA (97)	Education, Ethnicity	**Design:** Narrative review No search strategy was given.	N/A
Tanenbaum et al., 2022, USA (98)	Income/ Occupational, Education, Social, Ethnicity	**Design:** Narrative review No search strategy was given.	N/A
Datye et al., 2021, USA (99)	Income/ Occupational, Ethnicity	**Design:** Narrative review No search strategy was given.	N/A
McAdam-Marx, 2022, USA (100)	Income/ Occupational, Education, Social, Ethnicity	**Design:** Narrative review No search strategy was given.	N/A

Results	Authors' conclusions
The authors state that adoption of CGM technology is modified by ethnicity, even after accounting for SES, insurance, education level, health literacy, diabetes distress and self-management practices. This is then stated to be the product of insufficient affordability, provider bias and lack of individualized support programs.	Diabetes technology can greatly improve the level of care, but enhancing it's utilization by underserved populations requires a multi-pronged approach. This will need to address the barriers of affordability, bias, and support systems.
The author state that NHB patients meet treatment goals less often than NHW patients. In part because of biological factors, but also because of lower treatment quality and SES.	Advanced hybrid closed loop devices combined with intensified contact utilizing telehealth services would be an ideal solution to addressing disparities.
Barriers on the following levels were found: - System level: cost of devices, lack of insurance coverage, burdensome eligibility criteria for coverage, racial/ethnic biases - Provider level: implicit biases, negative attitudes towards diabetes technology, inexperienced with diabetes technology - Individual level barriers: lower parental education level, greater device-dislike and/or distrust - Device level: skin irritation, alarm fatigue, device-burden, device training requirements Facilitators on the following levels were found: - System level: increased insurance coverage - Provider level: education guidelines and training for providers, structured training programs, personalized patient support - Community level: (online) peer community - Individual level: Positive attitudes toward technology, higher perceived usefulness, and ease of use - Device specific: patient-tailored functionality and features	An increased focus on reducing barriers and increasing facilitators may improve device adoption and therefore increase the quality of diabetes management and care
In addition to the cost-barrier, young adults and adolescents report issues with self-image as a barrier to CGM use more often than adults. Ethnicity was also found to affect the rate of CGM usage, partly mediated by provider-bias. Additionally, despite evidence that CGMs are cost-effective, reimbursement practices remain lacking	Further research regarding the cost-effectiveness of CGMs for various indications is needed. Issues regarding body-image need to be assessed and addressed by the provider. Disparities between ethnic groups need to be addressed
It is stated that inequities in the use of CGMs exist between various ethnicities in the USA, which is responsible for disparities in health outcomes. The disparities in access are theorized to be mediated, in part, via implicit bias and insurance disparities.	Recent changes in reimbursement requirements might lessen disparities in CGM use, however, significant barriers remain. Access can also be improved through offering CGMs through pharmacies, as opposed to medical companies. Implementing CMG-based quality metrics and rewards might increase stakeholder support and reduce the financial risk associated with equitable coverage of CGMs

Authors, date, and country	Domain(s)	Study methods	Subjects
Tsai et al., 2022, USA (74)	Ethnicity	**Design:** Survey study (n=172) **Period:** 2018-2020 **Area:** Los Angeles, California, USA **SES indicators:** Insurance type **Ethnicity indicators:** Self-reported as either NHW, NHB, Hispanic, Asian-American/Pacific Islander or Other/ Declined	**% DM1:** 100% **% male:** 57% **Mean age (Years):** 16.69 **Ethnicity:** 27% NHW, 2.9% NHB, 2.9% Asian American, 51% Other/Declined **Mean HbA1c:** 9.03% (75.2 mmol/mol)
Agarwal et al., 2022, USA (89)	Ethnicity	**Design:** Group interview study including HCPs (n=22) and minority patients (n=11) **Period:** 2020 **Area:** Bronx, New York, USA **SES indicators:** N/A **Ethnicity indicators:** Self-reported	**% DM1:** 100% **% male:** 36% HCPs, 10% patients **Mean age (Years+sd):** 46.4±12.3 HCPs, 22.2±5.6. **Ethnicity:** 50% NHB, 50% Hispanic among the patients **Mean HbA1c:** 8.0% (63.9 mmol/mol)
Mathias et al., 2022, USA (90)	Education, Social, Ethnicity	**Design:** Retrospective chart review, comparing pre- and postpractice transformation situations (n=1.357). **Period:** 2019-2021 **Area:** Bronx, New York, USA **SES indicators:** Insurance type **Ethnicity indicators:** Self-reported	**% DM1:** 100% **% male:** 48% **Mean age (Years+sd):** 38.0±18.1. **Ethnicity:** 12.0% NHW, 29.9% NHB, 45.0% Hispanic, 12.8% Other **Mean HbA1c:** Not stated

Results	Authors' conclusions
Both English and Spanish speaking Hispanic patients were more likely to be publicly insured than their non-Hispanic counterparts. Spanish-speaking Hispanic participants were younger, and English-speaking Hispanic participants reported higher HbA1c levels, even after adjusting for age. Hispanic English-speakers were less likely to have ever used a CGM than Hispanic Spanish-speakers and non-Hispanic English-speakers (33% vs 62% vs 61%, p=0.002). Higher HbA1c and Hispanic English-speaking was negatively correlated with negative attitudes towards diabetes technology. Hispanic Spanish-speaker attitudes towards technology did not differ significantly form non-Hispanic English-speakers. Those with public insurance were less likely to have ever used a CGM (OR 0.31, 0,13-0.72, p=0.007). Attitudes towards technology were not significantly related to CGM use. No significant differences in the frequency of barriers encountered were found between the groups. Dislike of wearing a (noticeable) device on the body was the most often cited barrier, with distrust of the device following second.	The higher CGM exposition in Hispanic Spanish-speakers than Hispanic English-speakers may be due to the stronger family support and oversight and improved glycaemic control found in that population. Another factor is that at the centre in question, Spanish-speaking patients are most often served by Spanish-speaking providers, whereas a language barrier might be present for the Hispanic English-speakers, should their English proficiency be more limited.
Barriers noted consisted of a fear of new devices as well as inadequate support in acquiring and using the devices. Interventions mainly concerned increased hands-on education, with low-literacy options, peer-to-peer support and increasing access to the devices.	The adoption of CGM technology in underserved populations would best served by a multipronged approach.
The following practice transformations were implemented: • Specialty clinic formation to centralize expertise. • Inclusion of social needs-trained licensed practice nurses in diabetes practices • Staff (including nurses and medial assistants) CGM training and device trials. • Streamlined CGM prescription workflow. • Provider CGM education and bias training After implementation of these measures, CGM prescriptions rates increased from 15% to 69% over the 3-year period (p<0.001), with equal improvements for all ethnicities (p=0.053).	The study demonstrates a model for improving equity of access to CGM technology. According to the authors, CGM prescription rates in this model increased more than would be expected based on national trends.





Chapter 8

Summary

FGM is increasingly used as an alternative to self-monitoring of glucose using fingerpricks and the insight in additional glycemic parameters such as time in range (TIR), time below range (TBR), time above range (TAR) and glucose variability has changed diabetes management. Reimbursement of FGM by health insurance companies for all persons with diabetes with an intensive (basal-bolus) insulin treatment made this system the most widely used technology to monitor glucose in the Netherlands and Europe to date.

This thesis explored the use of FGM to improve longer-term glycemic control and well-being in persons with DM, with a focus on the additional benefits of FGM versus fingerprick measurements. Furthermore, changes in glycemic parameters were evaluated in persons with either T1DM or T2DM with different levels of glycemic (dys)regulation, different treatment modalities and differences in glucose monitoring frequency. Lastly (the access to) use of CGM was evaluated in persons with differences in socio-economic background.

In **chapter 1** we provided a general introduction and outlined the aims of this thesis. In **chapter 2** we evaluated which clinical factors predict change in HbA1c in persons with DM who started FGM. Based on data derived from the Dutch nation-wide FLARE-NL registry, we found that baseline HbA1c levels significantly predict HbA1c decline over a 12-month period. No other factors (such as age, gender, type of diabetes, presence of micro- or macrovascular complications, SF-12 physical and mental component scores) were identified as predictors of change in HbA1c.

Data on longer-term outcomes of FGM use was limited. Therefore, **in chapter 3** we investigated the effect of FGM use on glycemic control over a two-year period, compared to the period before FGM. Furthermore, changes in health-related quality of life and disease burden were investigated and comparisons were made between persons who continued FGM for at least two years versus persons who stopped FGM before the two-year follow-up was completed. We observed sustained improvement of HbA1c and quality of life, including levels of anxiety and depression, among persons who continued to use FGM for two years. HbA1c remained unchanged compared to baseline among persons who stopped FSL-FGM and stopping FSL-FGM was associated with a deterioration in the percentage of persons who reported work absenteeism and diabetes-related hospital admissions, compared to persons who continued FSL-FGM. This study emphasized the valuable impact of FGM use in clinical practice over a longer period of time and endorses the continued reimbursement of FGM.

Depressive disorders are more common among persons with diabetes, as compared to persons without diabetes. In chapter 3 we had observed improvement in self-reported

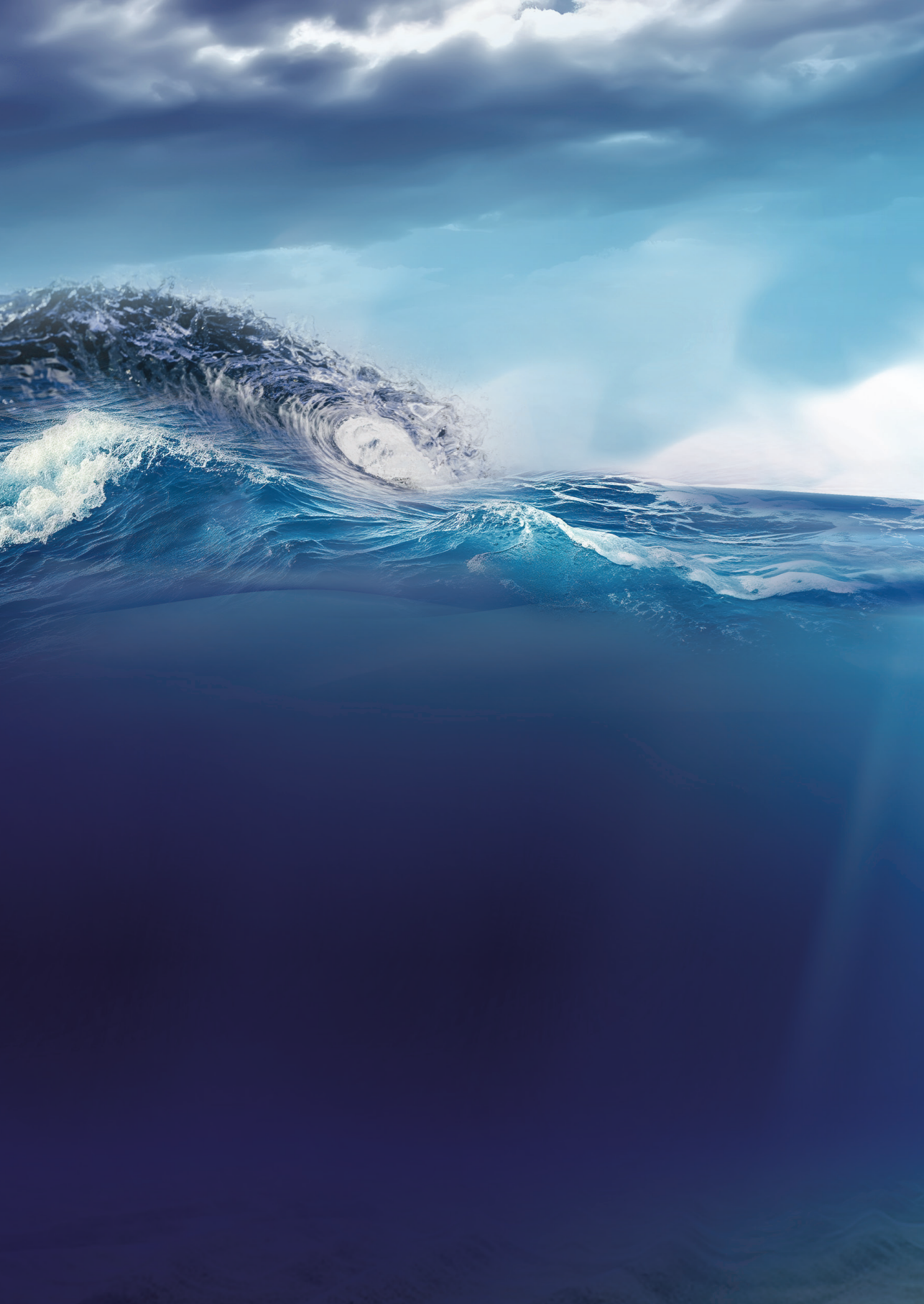
levels of anxiety and depression in persons with DM who used FGM for two years. Since data on the effects of FGM use on mental health and the rate depressive disorders in persons with DM was scarce, we wanted to provide more insight into the effects of commencement and long-term use of FGM on rates of depressive disorders in diabetes. In **chapter 4** we demonstrate that the rate of depressive disorders decreases in persons who start using FGM and continue its use for 6 and 12 months. Furthermore, during follow-up there is also an improved mental well-being among FSL-FGM users.

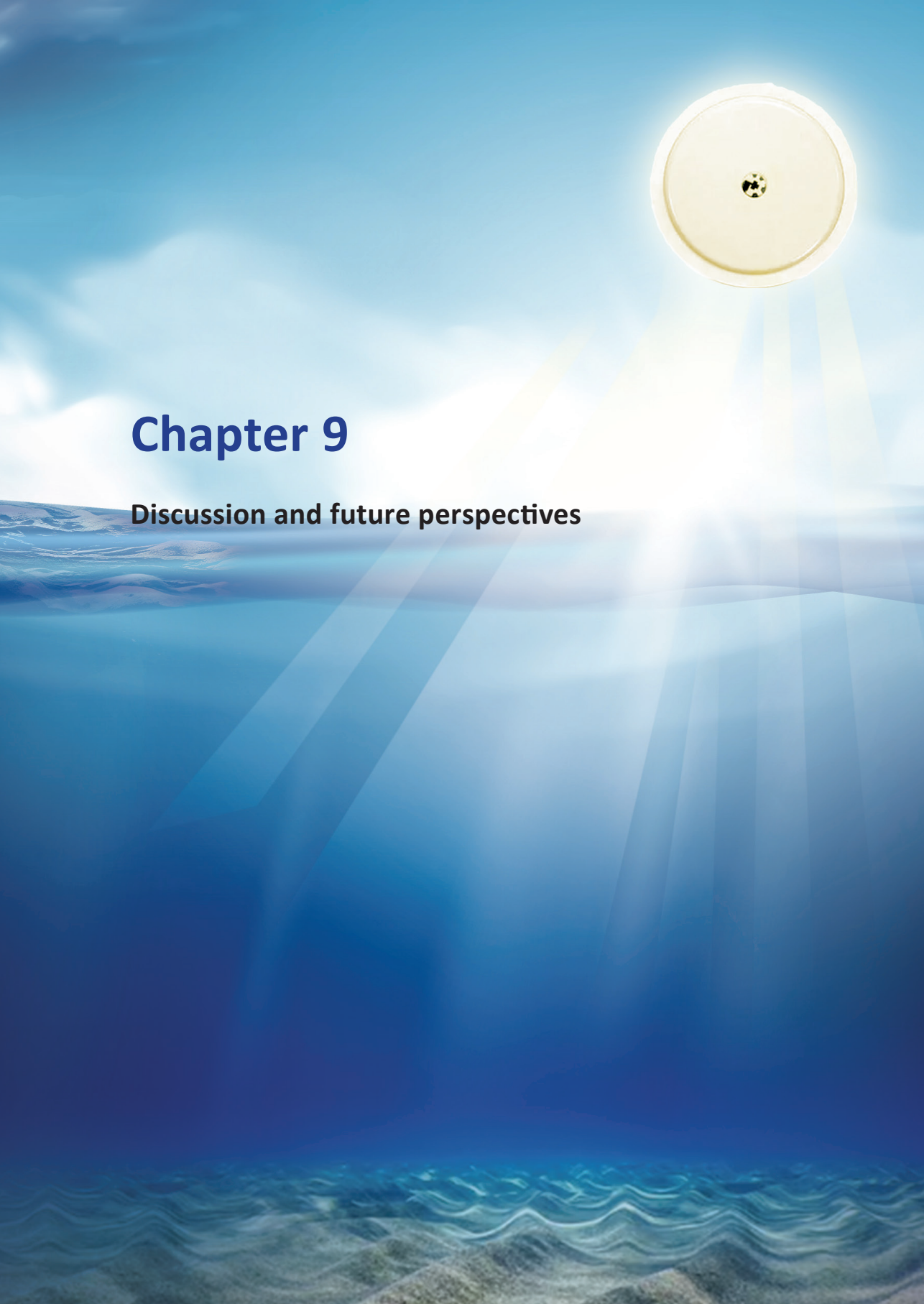
Beyond previously analyzed effects of FGM use on HbA1c, evaluation of changes in FGM-derived glycemic parameters (TIR, time in hyper- and hypoglycemia, glycemic variability and estimated HbA1c (eHbA1c)) in lager groups was needed for a thorough understanding of the effects of FGM. In **chapter 5** we investigated the association between FGM scan frequency and changes in glycemic parameters, using real-life data from FGM users with DM in the Netherlands. In this cross-sectional design, we observed improvement of glycemic parameters with increasing scan rate, including time in range, time in hyperglycemia, glycemic variability and eHbA1c. On average, FGM users scanned about 13 times daily. In general, a scanning frequency of 15 times per day was associated with an eHbA1c level close to the target of 53 mmol/mol (7.0%). Additionally, we observed that persons with higher eHbA1c levels, who scan with a low frequency, tend to concentrate scanning in the hypoglycemic range and tend to disregard scanning in the hyperglycemic range. Users with a low scan rate potentially do not reap the benefits of FGM compared to users who scan more frequently and advising users who scan with a low frequency to scan more often seems beneficial.

In **chapter 6** real-life effects of FGM on changes in glycemic parameters was further explored among European FGM users. To extend existing literature, effects of FGM were analyzed in persons with either type 1 or type 2 diabetes with different treatment modalities and in subgroups with different types of glycemic dysregulation. Over-all FGM use for 24 weeks was associated with improvement of glycemic parameters in most of the users, irrespective of pre-use regulation or treatment modality. In persons with T1DM or T2DM treated with basal-bolus insulin and with an initial TIR <70%, a concurrent improvement of TIR, time in hyperglycemia, time in hypoglycemia, and CV was observed, indicating more stable glucose levels after 24 weeks of FGM. In the T1DM subgroup with >4% TBR, a significant reduction of time in hypoglycemia was observed, along with less time in level 2 hyperglycemia and only a small decrease in TIR. In persons with T2DM on basal insulin with an initial TIR <70% improvements in eHbA1c, TIR, and time in hyperglycemia were observed. Lastly in the small group of persons with T2DM without insulin treatment and suboptimal glycemic regulation (TIR <70% or TAR >25%) improvement of eHbA1c, TIR and TAR was observed. Although more data is needed on persons with T2DM without

insulin use to allow firmer conclusions for this specific group, we suggest that FLASH use may be also of benefit for persons with T2DM without insulin treatment, for those with suboptimal glucose regulation.

Lastly, in **chapter 7** the impact of socio-economic status (SES), social determinants and ethnicity on the use of continuous glucose monitoring systems was evaluated via a narrative review of available literature. Persons with a lower SES and ethnic minorities experience worse diabetes-related health-outcomes. We found that having a lower SES negatively influences CGM usage, as does belonging to an ethnic minority group. Ethnic minorities use CGM less often and are more likely to discontinue CGM use. Income appears to be the main driver behind disparities in CGM use and extension of reimbursement coverage has been shown to increase CGM utilization in the lower SES quintiles. However, disparities in CGM use persist even after adjustment for this factor. Other important factors of influence are educational level, social context, implicit biases by healthcare providers against ethnic minorities or persons with a lower SES, limited training resources and lack of objective criteria for CGM prescription. Recommendations to improve CGM use among persons with a lower SES and ethnic minorities include availability of financial, administrative, and educational support, for both healthcare providers and persons with diabetes. It depends on the local circumstances and CGM reimbursement criteria within a specific country which of these recommendations is most relevant.





Chapter 9

Discussion and future perspectives

Discussion of main findings

Adequate glucose level assessment is of utmost importance for persons with DM when aiming for optimal glycemic control to prevent or delay micro- and macrovascular complications [1–3]. When FGM was introduced as an alternative to conventional fingerprick measurements, its efficacy, safety and (longer term) benefits for persons with diabetes needed to be examined. In the first part of this thesis (chapters 2, 3 and 4) we aimed to assess longer-term effects of FGM on glycemic control, quality of life, disease burden, mental wellbeing, and other relevant PROMS, because data on longer term effects of FGM on these domains were lacking. Furthermore, it was unknown how intensive the FGM sensor needed to be scanned to improve glycemic outcomes and who would benefit the most from FGM use. Therefore, in the second part of this thesis, we investigated the effects of the FGM monitoring frequency on glycemic parameters (chapter 5) and the effects of FGM initiation on glycemic outcomes in persons with different levels of glycemic (dys)regulation and different treatment modalities (chapter 6). Lastly, we evaluated the use of CGM in persons with differences in socio-economic status and ethnicity and assessed barriers for CGM uptake (chapter 7).

PART I

Effects of continuous glucose monitoring on glycemic control, quality of life and mental well-being

Important steps have been taken in recent years before FGM became widely available for persons with diabetes with an intensive insulin treatment in the Netherlands. When the FreeStyle Libre (version 1) FGM sensor was first introduced in the Netherlands in 2014, this sensor was not reimbursed by healthcare authorities and insurance companies because its effectivity, both for persons with diabetes and the healthcare system, needed to be established. To gain more data on the effectiveness of FGM, the FlAsh monitor REgister in The NetherLands (FLARE-NL) registry was set up in the Netherlands in 2016 in collaboration with the Dutch diabetes patient organization (Diabetes Vereniging Nederland). The FLARE-NL4 study [4] reported on one-year data from this registry and demonstrated improvement of glycemic control, quality of life and patient reported outcomes (PROMS) after one year of FGM. These findings, amongst others, contributed to the decision to provide reimbursement of FGM in the Netherlands for persons with diabetes who fulfilled the reimbursement criteria as of December 2019.

In **chapter 2**, we evaluated if there are factors that can predict change in HbA1c in persons with DM who started FGM. We showed that that baseline HbA1c levels predict

HbA1c decline over a 12-month period: i.e. a higher baseline HbA1c resulted in a greater decline in HbA1c. This has been confirmed in a recent meta-analysis, demonstrating a larger reduction in HbA1c in FGM users with a higher baseline HbA1c in both T1DM and T2DM [5]. Obviously, in persons with poor glycemic control as indicated by a high HbA1c, there is more room for improvement of HbA1c. A probable explanation for the achieved improvement of HbA1c among these persons is that improved insight in glycemic excursions and immediate feedback provided by FGM (I) increases awareness of high glucose values, (II) motivates to make insulin dosage, behavioural and dietary changes and (III) facilitates feeling more comfortable with lower glucose values [6].

It is also important to note that HbA1c improvement is not the main goal for all persons with diabetes. In the subgroup of persons with hypoglycemia unawareness or frequent unexpected hypoglycemia, the treatment goal will prioritize hypoglycemia reduction over tight glucose control. FGM can serve as a system to address hypoglycemia at an early stage in these persons, because more frequent glucose measurements are possible as compared to fingerprick measurements and FGM data-informed insulin dose adjustments can be made to prevent hypoglycemia, based on the 24-hour glucose (and hypoglycemia) patterns. Nevertheless, both in the subgroup of persons with hypoglycemia unawareness or frequent unexpected hypoglycemia (n= 566) and the subgroup of persons with a mean HbA1c >70 mmol/mol (>8.5%) (n=294) as indication for FGM initiation, baseline HbA1c was a predictor of HbA1c improvement over time in our study. Higher HbA1c levels are common in persons with hypoglycemia unawareness due to behaviorial strategies that intends to maintain higher blood glucose and thus avoid hypoglycemia [7]. Taken together, although the main reason for starting FGM was different, persons with high baseline HbA1c values in both indication groups showed benefit from FGM initiation with regards to significant HbA1c reduction (of ≥5 mmol/mol (≥0.5%)).

No significant impact of age, gender, type of diabetes, presence of complications, physical and mental component score or number of hypoglycemic events was observed as explanatory factor for change in HbA1c in our analysis. A recent subgroup analysis of a RCT comparing FGM with fingerprick measurements in persons with T1DM analysed several additional factors and found no impact of treatment modality, prior participation in a structured education course, education level, impaired awareness of hypoglycemia, socio-economic status, ethnicity or depressive symptoms on HbA1c reduction [8]. These findings suggest that FGM is effective across a range of baseline characteristics.

In the RCT, younger age was associated with a larger reduction in HbA1c, in contrast to our findings. When investigated as a linear effect, the size of the reduction in effect with age was 2.7 mmol/mol (0.25%) HbA1c for every additional 15 years of age. Mean age

was slightly lower and mean HbA1c was higher in their study (44 versus 47 years and 71 mmol/mol (8.6%) versus 65 mmol/mol (8.1%)), as compared to our study. Younger patients might have a higher HbA1c reduction in their study due to infrequent testing of glucose with fingerprick measurements and more frequent testing with FGM (as this is more convenient), whereas the change in frequency of glucose measurements differed less in older persons (as the authors suggest). Another study found no impact of age on HbA1c improvement, although there were smaller changes in the older age group (>64 years) and the greatest HbA1c reduction was observed in the 19–24 year subgroup (with higher baseline HbA1c), consistent with this hypothesis [9].

After the one-year FLARE-NL4 study 24% of participants stopped FGM, with financial constraints as the most reported reason (55%). This provided us the opportunity to investigate the course of glycemic control and well-being in persons who continued FGM versus persons who stopped using FGM, as compared to evaluation of longer-term (two year) effects of FGM use.

In **chapter 3**, we evaluated the two-year results of the FLARE-NL study and observed sustained improvement of HbA1c, quality of life and disease burden after two years of FGM among persons who continued FGM for 2 years. Previous studies had a limited follow-up period and were mainly focused on change in HbA1c as outcome parameter. In our study HbA1c decreased from 60.7 (95% CI 59.1, 62.3) mmol/mol (7.7% (95% CI 7.6%, 7.9%) before the use of FSL-FGM to 57.3 (95% CI 55.8, 58.8) mmol/mol (7.4% (95% CI 7.3%, 7.5%) after one year and 57.8 (95%CI 56.0, 59.5) mmol/mol (7.4% (95% CI 7.3%, 7.6%) after two years of FGM. In persons who stopped FGM after one year of use, HbA1c had returned to baseline after two years. A recent meta-analysis of 75 observational studies also demonstrated a sustained improvement of HbA1c for up to 24 months in T1DM and for at least 12 months in T2DM after starting FGM [5]. The reduction in HbA1c was most prominent 3 months after the introduction of FGM (-5.8 mmol/mol (-0.53%) in T1DM and -4.9 mmol/mol (-0.45%) in T2DM) and these gains persisted throughout the follow-up period, indicating a long durability of change in HbA1c among FGM users in accordance with our study findings. This longer-term improvement of glycemia was further emphasized by a recent RCT among persons with T1DM and suboptimal HbA1c levels (69 ± 8.7 mmol/mol (8.5 ± 0.8%) – 72 ± 9.8 mmol/mol (8.7 ± 0.9%)) who were randomly assigned to use the second generation FGM (FreeStyle Libre version 2 (FSL 2)), with optional alarms for high and low blood glucose levels, or continuation of fingerprick testing [10]. The adjusted mean between-group difference in HbA1c was -5.5 mmol/mol (−0.5%) and the change in HbA1c from baseline to 24 weeks -8.7 mmol/mol (−0.8%) Although our study lacked a control group and persons used the FSL 1 without alarm function, the findings of this RCT confirm and extend the observed long-term improvement of HbA1c among FGM users.

With regards to evaluation of quality of life in persons with diabetes who initiate FGM, long-term follow-up studies are scarce as well [11]. We observed sustained improvement in read-outs of quality of life (SF-12 MCS, EQ-5D Dutch tariff score and levels of anxiety and depression) in persons who continued FGM for two years, compared to persons who stopped. A recent real-life study with one year of follow-up demonstrated improvement of quality of life in T1DM after FGM initiation, measured by the Quality of Life associated with T1DM Questionnaire (QoLT1DMQ) as primary endpoint, although the sample size was small (n=36) [12]. Glycemic control (HbA1c, TIR, TAR, TBR and CV) also improved, which was most pronounced in persons with a baseline HbA1c >58 mmol/mol (>7.5%). This is in accordance with the findings in chapter 2 were we found a relation between a high baseline HbA1c and the degree of decline in Hba1c. Interestingly, improvement of TIR was found to be a predicative factor for the decrease in disease burden in their study. This is probably a reflection of increased patient satisfaction and perceived enhancement of (glycemic) control among FGM users. Increased diabetes treatment satisfaction was also demonstrated in persons with T1DM who continued FGM (FSL 2) for 24 months [10], in persons with well controlled T1DM who used FGM (FSL 1) for 6 months [13] and in persons with T2DM on intensive insulin therapy who used FGM (FSL 1) for 6 months [14]. Treatment satisfaction was not measured via the same questionnaire (Diabetes Treatment Satisfaction Questionnaire) in our study. However, via a PROMS questionnaire we did observe that persons who continued FGM for 2 years reported a better understanding of glucose fluctuations and they felt more secure since they used FGM, as compared to persons who stopped FGM. These findings indicate improved treatment satisfaction.

Furthermore, the percentage of persons who reported work absenteeism and hospital admission after two years was lower for persons who continued FGM for two years as compared to persons who stopped FGM (5.0% vs 14.6%, $p<0.01$ and 5.4% vs. 12.2%, $p<0.05$, respectively). Among persons who stopped FGM use after 1 year, the percentage of persons who reported diabetes-related hospital admissions and work absenteeism was back at baseline level after 2 years. Previous studies among persons with T1DM and T2DM have also shown a reduced number of diabetes-related hospital admissions [15–17] and diabetes-related work absenteeism after FGM initiation [17]. Our study adds value to the existing literature because no other study evaluated the effect of stopping FGM use on the percentage of hospital admissions and work absenteeism. Our results emphasize the benefits of continuation of FGM, for persons with diabetes as well as for societal benefits.

A limitation of the studies presented in chapter 2 and 3 was the lack of data on glycemic parameters such as TIR, TAR, TBR and CV, which targets have been formulated in 2019 [18]. At the time when the FLARE-NL register was established, in 2016, HbA1c was still regarded as the gold standard for glycemic control and data on time in target ranges could

not be obtained unfortunately. In chapters 5 and 6 we did analyse these CGM-derived glycemic metrics, as they were complementary to HbA1c with regards to assessment of glycemic regulation [19,20] and provide important information for therapy adjustment in clinical practice.

In **chapter 4**, we explored the effects of FGM initiation on mental health and the rate of depressive disorders among persons with diabetes, because depressive disorders are common among persons with diabetes (12% in persons with type 1 DM [21] and 28% in persons with type 2 DM [22]) and have a severe impact on well-being. Studies on this subject are scarce and focused on diabetes-related distress (often as a secondary study outcome) instead of depression [16,23]. In our study we analyzed the mental component scores (MCS, a subscale derived from the 12-Item Short Form Health Survey version 2 (SF-12^{v2}) questionnaire) of participants of the FLARE-NL study, were a SF-12 MCS score ≤ 45 is indicative of a depressive disorder [24]. The findings of our study suggest that the rate of depressive disorders decreases in persons who start using FGM and continue its use for 6 and 12 months. Previous research showed a correlation between improvement of HbA1c after FGM initiation and improvement of diabetes distress (indicated by the score on the items "feeling overwhelmed with demands of living with diabetes" and "feeling that I am failing with my diabetes routine") with the highest level of diabetes distress among persons with a baseline HbA1c >69 mmol/mol (>8.5%) and the lowest in those with baseline HbA1c <48 mmol/mol (6.5%) [25]. In our study, we observed improvement of the MCS in all HbA1c subgroups (≤53, >53 and >64 mmol/mol (≤7%, >7% and >8%)). Although diabetes distress will influence mental health, MCS is a much broader domain compared to diabetes distress, entailing the following components: vitality, social functioning, role limitations due to emotional problems and general mental health. According to our findings, improvement of mental health after FGM initiation appears to be related to other factors than the level of HbA1c decrease, as we observed no correlation between the degree of improvement of HbA1c and improvement of mental health.

Other important factors that influence mental wellbeing of persons with diabetes after FGM initiation are for example a better understanding of glucose fluctuations, feeling more secure, less severe hypoglycemic episodes and reduced worry among family members about their glucose regulation, as shown in chapter 3 (the PROMS in supplementary table 5). Furthermore, we showed an association between (a lower) MCS at baseline and improvement of MCS after 12 months of FSL-FGM use, indicating that persons with the lowest MCS might benefit the most from FGM initiation with regards to improvement of mental health.

Future studies are needed to further evaluate the effects of FGM on depression rates in persons with diabetes, preferably including analysis of the correlation between changes in all FGM derived glycemic parameters (i.e. TIR, TAR, TBR, CV and time in sever hypo- and hyperglycemia) and depression rates. This provides a more complete picture of the effects of changes in these parameters on depression rates and offers the possibility to assess if a change in one of these glycemic parameters is of most important influence on improvement of depression rates.

The SF-12 MCS we used is not a regular screening tool for depression and depressive disorders in persons with diabetes, but a valid generic instrument for measuring quality of life in persons with diabetes [26]. Use of other scales, such as the Center of Epidemiological Studies-Depression Scale (CES-D) seems to be the preferred questionnaire to measure depressive symptoms in future studies, with regards to internally consistency and validity [27].

PART 2

Changes in parameters of glycemic control among users with different backgrounds

In the second part of this thesis, we evaluated changes in glycemic parameters in FGM users in more detail, including outcomes in persons with different levels of glycemic control prior to FGM commencement, and in persons with either T1DM or T2DM with different treatment modalities. Furthermore, we evaluated the use of CGM in persons with differences in socio-economic status and ethnicity.

In **chapter 5** we evaluated the impact of FGM scanning frequency on glycemic regulation and observed improvement of glycemic parameters (TIR, TAR, CV and estimated HbA1c (eHbA1c)) with increasing scan rate. The eHbA1c calculation was based on the average glucose values measured with FGM. Dutch FGM users scanned approximately 13 times daily. A scanning frequency of 15 times per day was associated with an eHbA1c level close to the target of 53 mmol/mol (7%) when data was subdivided in 20 equally sized eHbA1c bins (n = 817 each). An eHbA1c of 53 mmol/mol (7%) translated in approximately 65% time in target range, 30% time in hyperglycemia and 5% time in hypoglycemia (<3.9 mmol/L). This is less than current guidelines advice as ideal TIR, TAR and TBR for most people with type 1 and type 2 diabetes [18], probably a reflection of the difference between the more stable eHbA1c and the more dynamic TIR as outcome parameter which provides important information about day-to-day glycemic variability and glycemic excursions. If data were stratified by mean daily scan rate, the group of persons who scanned 15 times achieved an eHbA1c of 58 mmol/mol (7.5%) and only persons who scanned 40 times

per day reached an eHbA1c of <53 mmol/mol (<7%). In Poland persons with a scanning frequency of between 15-20 scans per day achieved the target eHbA1c of <53 mmol/mol (<7%), but in general in Europe 20-25 scans per day were needed to reach this goal [28,29]. This difference is probably related to a higher educational level of the Polish persons who had the opportunity to use FGM. Information about the consequences of more frequent scanning, in terms of adjustment of insulin dose, meal composition or change in activity level for example is lacking in these studies and ours, which is an important limitation and makes it difficult to make a definitive statement about the most optimal scan frequency. Furthermore, the currently available second generation FGM sensor (the FSL 2) has the option to set alarms for high and low glucose values, which makes it likely that glycemic targets can be reached with a lower scanning frequency nowadays.

We also analyzed scanning patterns while in hypo-, normo- and hyperglycemia in persons with different levels of glycemic control. We observed that persons with the lowest HbA1c values monitored their glucose most often during hyperglycemia. In contrast, persons with higher eHbA1c levels tend to concentrate scanning when having glucose levels in the hypoglycemic range and tend to disregard scanning in the hyperglycemic range, most likely because they feel uncomfortable during (impending) hypoglycemia and due to fear of hypoglycemia which is one of the main barriers to achieving tight glycemic control [30]. In summary, based on our observations, advising users who scan with a low frequency to scan more often, both during hyper- and hypoglycemia, may result in better glycemic control. The current ADA standard also states that a higher frequency of scanning with FGM is correlated with improved outcomes, with reference to our study amongst others [31]. It stands to reason that a high motivation for diabetes self-care and the capability of adequate interpretation and action based on glucose values and trends will be of importance for the ultimate outcomes of more frequent scanning. Physicians and patients can be trained to use FGM data to make timely and effective treatment decisions to improve glycemic control [32]. Patient education also plays an important role in reducing fear of hypoglycemia and related strategies to maintain higher glucose levels [33].

In **chapter 6** we performed a longitudinal analysis among Europeans with T1DM or T2DM who initiated FGM, to assess the effects of FGM on glycemic parameters in persons with DM with different treatment modalities and different levels of glycemic (dys)regulation (TIR <70%, TAR >25% or TBR >4%). In contrast to the previous chapter, we were able to include information about users characteristics and diabetes type to provide more detailed information. We found an association between FGM use for 24 weeks and improvement of glycemic parameters in all subgroups of persons with DM, irrespective of pre-use glycemic dysregulation or treatment modality.

In persons with T1DM or T2DM treated with basal-bolus insulin and with an initial TIR <70% we observed improvement of TIR, time in hyperglycemia, time in hypoglycemia, and CV. In the T1DM subgroup with >4% TBR, a significant reduction of time in hypoglycemia was observed, along with less time in level 2 hyperglycemia and only a small decrease in TIR.

We observed improvement in eHbA1c, TIR, and time in hyperglycemia in persons with T2DM on basal insulin with an initial TIR <70%. The ADA standard of care of 2024 states the advice to offer FGM or rt-CGM to adults who are treated with basal insulin, if they are capable of using the device safely and to determine the choice of the device on individuals circumstances and preferences [31]. Our study results emphasize the benefits of FGM with regards to glycemic control in persons with T2DM on basal insulin with suboptimal glucose regulation. Other (retrospective) studies also showed improvement of HbA1c after FGM initiation in persons with suboptimal controlled T2DM on basal insulin [34,35]. Notably, FGM is not reimbursed in the Netherlands for persons with a less intensive (basal insulin only) insulin treatment or persons with T2DM without insulin use.

In persons with T2DM without insulin use, routine glucose monitoring is regarded of limited benefit by the ADA, because of limited improvement in outcomes, although glucose monitoring can provide more insight into the impact of nutrition, physical activity, and medication on glucose levels [31]. In our study, the number of persons with T2DM without insulin use and with suboptimal glycemic control (TIR <70% or TAR >25%) was too small (n= 21) to draw a firm conclusion regarding the benefits of FGM, although we observed improvement of TIR, TAR and eHbA1c in this group. In an RCT among persons with T2DM without insulin use (mean HbA1c 62 mmol/mol (7.8%)) the benefits of FGM were shown compared to those randomized to fingerprick measurements [36]. FGM significantly improved HbA1c, mean glucose levels, CV, time in hyperglycemia and treatment satisfaction after 12 weeks. However, in the SMBG group HbA1c was also lower after 12 weeks ((−3.3 mmol/mol (-0.3%) compared to −4.7 mmol/ mol (−0.43%)). After 24 weeks the between-group difference in HbA1c was −3.2 mmol/mol (−0.29%). Future longer-term studies are needed to evaluate if these HbA1c reductions are of clinical relevance in persons with T2DM without insulin use and to determine if FGM is cost-effective in T2DM without insulin use. Unfortunately, lifestyle changes were not evaluated, so it is undetermined if FGM use leads to lifestyle improvement. However, since there were no significant differences with respect to changes in blood glucose lowering drugs, lifestyle improvement could be expected to be a factor contributing to improved glycemia.

In a pilot study among persons with T2DM without insulin use and an HbA1c ≥ 64 mmol/mol (≥8.0%) who initiated FGM, the effect of a personalized and interactive diabetes self-management education and support (DSMES) program was assessed [37]. After 3 months

of a “discovery learning” approach to education centered on FGM, TIR rose from 55% to 74%, TAR declined from 44% to 25% and well-being improved. Furthermore, participants reported improvements in healthy eating and physical activity. Although the study lacked a control group, it suggests that when providing a FGM is accompanied by sufficient and interactive education, patients with suboptimal regulated T2DM can reach improvements in (short-term) glycemic control and wellbeing.

In the previous chapters of this thesis, benefits of FGM for a broad population of persons with T1DM and T2DM have been shown. Given the association between use of FGM and improved glycemic control and quality of life, it is imperative to strive for equitable access to diabetes technology. As reimbursement of FGM and CGM has expanded over het past years in developed countries, financial barriers for FGM uptake are expected to be reduced. Nevertheless, persons with a lower socio-economic status (SES) and ethnic minorities have less access to CGM technology and experience worse diabetes-related health-outcomes [38]. A recent overview of disparities with regards to FGM and CGM use in developed countries by persons with differences in SES and ethnicity – in the light of recent changes in reimbursement criteria - was lacking in current literature. Therefore, in **chapter 7** we evaluated the impact of SES and ethnicity on the use of glucose sensor technology in developed countries and analyzed differences between healthcare systems with regards to reimbursement and uptake of FGM and CGM.

Via a review of available evidence, we found that income (available financial resources) was a main driver behind disparities in CGM use. These disparities in use of and access to CGM technology resulted in disproportionately higher HbA1c levels among persons with a lower SES and ethnic minorities. As expected based on previous literature [39], extension of reimbursement coverage increased CGM utilization. However, income and lack of reimbursement of CGM are not the sole drivers for disparities in CGM use. Other possibly important explanatory factors for these disparities, often outside patient control, are bias by healthcare providers against persons with a lower SES and ethnic minorities, lack of objective criteria for CGM prescription and limited training resources. Disturbingly, the majority of providers with bias based on the ethnicity and insurance status of their patients, don’t seem to be aware of their bias [40]. Due to this implicit bias, with automatic and unconscious prejudices and preferences affecting recommendations regarding the use of technology, diabetes technology is withheld from persons with a lower SES and ethnic minorities. Therefore, there is a need to address (implicit) ethnic- and insurance-mediated bias to overcome inequities in diabetes care. Another discrepancy was found in the field of educational levels of persons with diabetes. Educational attainment and higher (health) literacy are associated with better glycemic control [41]. However, in cases where physicians believed that information provided by CGM would be too difficult to

understand, this opinion was not endorsed by the majority of persons with diabetes [42]. These findings highlight opportunities for education of caregivers targeting their own unawareness of bias with regards to SES, ethnicity, insurance status and educational level, to bridge disparities and increase access to diabetes technology via adequate counselling of their patients. Furthermore, objective and uniform criteria for CGM reimbursement and prescription are needed, with less bureaucratic burden, to facilitate the prescription process. Lastly, improved education of patients targeting awareness of possibilities with regards to diabetes technology could help to empower them to ask for the desired technology and to improve communication around device barriers. For persons with lower literacy, appropriate education should be available.

Future perspectives

Evaluation of FGM with alarm function versus rt-CGM

To date, it is unclear if persons with diabetes using MDI benefit more from rt-CGM as compared to the second generation FGM (FSL 2) with alarm function. Only studies comparing the first generation FGM (FSL 1) - without alarm function - with rt-CGM exist at present. In T1DM, studies comparing the FSL 1 with rt-CGM have shown benefits of rt-CGM over FGM with regards to glycemic control and quality of life [43–46]. It remains unclear if this difference still exists if an FGM with alarm function will be compared with rt-CGM. In T2DM, both FGM and rt-CGM lowered HbA1c, but only FGM improved patient satisfaction according to a meta-analysis with mostly studies with FGM systems without alarm function [47]. However, sample sizes were small, the follow-up period was relatively short and rt-CGM systems were less user friendly at that time (e.g. more frequent calibration requirements). Over the years, rt-CGM systems have undergone large improvements and became more user-friendly. Providing adequate support and education when recommending FGM or rt-CGM will be of influence on user satisfaction and needs to be considered. Besides the use of rt-CGM as stand-alone device, it is important to note that most rt-CGM sensors can be connected to an insulin pump to create a hybrid closed-loop system, in contrast to FGM sensors, which has important implications for glycemic control and quality of life (as discussed in more detail in a next section of this thesis) [48].

Only one study with a limited number of patients (n=38) examined the switch from FGM without alarm function to FGM with alarm function and showed benefits of the latter with regards to improvement of TIR (from 53% to 57%) and reduction of TBR (from 6.2% to 3.4%) after 4 weeks, especially in persons with > 4% time in hypoglycemia at baseline [49].

Future studies are needed to evaluate the differences between FGM with alarm functionality and rt-CGM systems with regards to glycemic control, quality of life and user satisfaction. Because of the higher costs of rt-CGM, cost-effectiveness should also be evaluated. In a Dutch prospective observational study, the FSL1 was most cost-effective among persons with diabetes with an occupation that requires avoiding finger pricks or hypoglycemia and in persons with a high baseline HbA1c [50]. In the subgroup of individuals with frequent hypoglycemia, the probability of being cost-effective was low, which might suggest that these persons benefit more from a sensor with alarm functionality. In Belgium rtCGM was likely to be cost-effective compared with the FSL1 in persons with reasonably well-controlled T1DM (mean HbA1c 57.8 mmol/mol (7.4%)), when both devices were priced similarly (€3.92/day), at a willingness-to-pay (WTP) threshold of €30,000/QALY [51]. The main drivers favoring rt-CGM were lower HbA1c (6-month between group difference: -3.6 mmol/mol (0.36 %), fewer severe hypoglycemic events and reduced fear of hypoglycemia. Rt-CGM was cost-neutral at a price of €5.11/day compared with FGM. With regards to the FSL2, cost-effectiveness against rt-CGM has not been evaluated yet. However, a review analyzing cost-effectiveness of different CGM devices in T1DM is expected [52].

Increasing use of CGM systems and cloud databases

Concerning future steps in glucose monitoring, it is expected that CGM will replace SMBG for all insulin-requiring persons with diabetes. If higher costs of CGM devices are not a barrier anymore, CGM will probably also become a standard instrument for managing T2DM, irrespective of treatment regimen [53]. Future technological improvements could further reduce burdens for persons with diabetes, e.g. a smaller sensor design, a shorter warm-up period, longer sensor duration, less lag time and improved accurateness. Future CGM devices should also be suitable for integration in different systems for automated insulin delivery (AID), instead of a limited number of options to combine these systems. Next to increased use in outpatient setting, CGM can be incorporated in hospital settings to replace SMBG and to support a decrease in dysglycemia in hospitalized patients with diabetes [54].

Increasing use of CGM systems implicates that evaluation of CGM data including TIR will become standard in clinical practice and TIR will largely replace HbA1c measurements to evaluate glycemic control. As a result of increasing CGM use, cloud databases to support data sharing and remote access to data from glucose sensors and insulin pumps will play an essential role in diabetes care [55]. These cloud-based programs offer healthcare providers, persons with diabetes and family members the ability to visualize integrated glucose and insulin delivery data, which allows identification of patterns that can be used to modify settings and behavior [6]. To obtain such goals, it seems imperative that data can be assessed in a standardized manner and can be integrated into electronic health

records, taking data safety and privacy into account. Data sharing via the cloud with remote monitoring also enables remote consultations instead of an in-person visit to the diabetes clinic. This supports dematerialization, by saving materials needed for on-site enterprise hardware, which will eventually contribute to reduction of CO_2 emissions [56].

Implantable glucose sensors

Apart from sensors that are placed as a patch on the skin and have to be replaced every 7-14 days, an implantable CGM system known as the Eversense which lasts for 180 days has been developed [57]. The Eversense is inserted in the upper arm, intended to decrease the burden of repeated transcutaneous sensor insertions. In contrast to FGM and most rt-CGM systems, daily calibrations are needed. The accuracy of this system is comparable to other CGM systems, with a mean absolute relative difference (MARD) of 8.5% [57]. No device related or insertion/removal procedure-related severe adverse events were reported. Unfortunately, connection to an insulin pump to create a hybrid closed-loop system is not possible, which is an important limitation of the usability of this sensor. Future developments are needed to make this sensor more widely applicable.

Recently the development of another implantable CGM system has been announced. The “glucotrack” sensor is implanted subcutaneously and connected to a lead that is placed directly into a blood vessel, to facilitate continuous blood glucose measurements with zero lag time [58]. This makes the sensor more accurate as compared to other CGM systems that measure glucose in the interstitial fluid, which lags behind blood glucose values. The company reported a MARD of 8.1% at day 30 and a MARD of 4.5% at day 60. The first-in-human studies are expected later in 2024.

Emerging possibilities of advanced hybrid closed-loop insulin therapy with further improvement of glycemic parameters and reduced diabetes burden.

Although improvements in HbA1c and quality of life are observed among FGM users, it remains difficult for persons with T1DM to achieve the recommended target HbA1c of < 53 mmol/mol (<7%), with a TIR of 70%, TBR of < 4% and TAR < 25% [18], even with frequent glucose monitoring via FGM. Currently, rapid developments in advanced hybrid closed-loop (AHCL) therapy with automated insulin delivery (AID) have taken the possibility of improvement of glycemic control an important step further. AHCL initiation results in greater achievement rates of the international glycemic targets among persons with T1DM as compared to MDI or sensor-augmented pump therapy [59–61]. Recent studies in persons with T1DM who switched from FGM to AHCL also showed improvements in glycemic parameters and quality of life in the latter [48,62]. Furthermore, in persons with

T1DM at high risk for hypoglycemia, initiation of AHCL reduced time in hypoglycemia, while TIR improved and time in hyperglycemia was lower after 12 months as compared to use of CGM and an insulin pump without connection [63]. As AHCL therapy increases the likelihood of achieving recommended glycemic targets with less diabetes burden, it is imperative to make this therapy available for all persons with T1DM [55].

However, current limited reimbursement criteria for rt-CGM in The Netherlands impede this goal. Since closed-loop therapy is only possible with an rt-CGM that can be connected to an insulin pump, it is essential to make rt-CGM systems available for all persons with T1DM, via unrestricted reimbursement criteria. This is supported by the ADA standards of care, including the recommendation to initiate rt-CGM and AID early in the disease, even at time of diagnosis [31]. In the future, CSII without the ability to create AID via a connected CGM will be regarded outdated. Reimbursement of rt-CGM should also be available for persons with T2DM who are expected to gain benefit from AHCL therapy.

As more and more AHCL systems with different features are emerging, healthcare providers need to be aware of the different available systems and their benefits and limitations to be able to support persons with diabetes to realize the clinical benefits of AHCL. To maximize clinical benefits of AHCL therapy, including realistic expectations for AHCL system user requirements, specific training and support for users and healthcare providers is important [55]. Persons with diabetes still need to be trained on general diabetes management, carbohydrate counting, insulin pump use, and CGM use to use an AHCL system safely. Eventually, with optimal device use, AHCL systems are used to focus on reducing time spent on diabetes self-management and increasing well-being. Training of healthcare professionals should also focus on implicit bias about several attributes required to use AHCL technology effectively to ensure fair and equitable access to AHCL systems [55].

Further improvement of AID algorithms can eliminate the requirement to announce meals to the system and the need to calculate basal rates, carbohydrate ratios, and insulin sensitivity factors. The iLet bionic pancreas is a recently developed AID system that determines all insulin doses on the basis of body weight, which makes the system more easy to use [64]. Meal announcements consist of a qualitative estimate of carbohydrate content (usual, more, or less for breakfast, lunch and dinner) rather than carbohydrate counts at mealtime. The control algorithms adapt continuously and autonomously to the individual's insulin needs. In children and adults with T1DM in the US, use of this system for 13 weeks resulted in a greater reduction of HbA1c than standard care (MDI, AHCL or pump without automation). No important safety concerns were reported, although there were more episodes of hyperglycemia in the bionic-pancreas group as compared to the standard-care group, mostly due to infusion-set failure.

Dual hormone automated insulin delivery systems

Currently, dual hormone AID systems incorporating glucagon and insulin are also in development [65,66]. The addition of glucagon to an AID system may confer additional protection from hypoglycemia, without meal or exercise announcements [67]. However, barriers to implement this technique are the need for a second chamber in the pump, lack of stable glucagon formulations approved for long term subcutaneous delivery and gastrointestinal side effects of glucagon [68]. In a short (76-hour) study among 23 persons with T1DM comparing a dual-hormone AID system with an insulin-only AID system and a predictive low glucose suspend system, the dual-hormone system reduced hypoglycemia during and after exercise as compared to the other systems, with some increase in hyperglycemia as compared to the insulin-only closed-loop system [69]. When compared to or sensor-augmented pump (SAP) therapy in a home-use setting, use of a dual-hormone AID system for 11 days resulted in an increase in TIR (78% vs 62%) and less time in hypoglycemia (0.6% vs 1.9%) [70]. In another small (n=23) study, use of a dual-hormone AID system for 2 weeks by adults with T1DM resulted in superior glucose control (TIR 87% versus 54%) compared to open loop therapy (insulin pump with CGM or FGM) [71].

Larger and longer-term studies are needed to establish the long-term benefits and risks of dual-hormone AID systems, as compared to currently available advanced insulin-only AID systems (instead of SAP or open loop therapy). The burden of wearing a larger pump and the need for daily replacement of glucagon should also be taken into account. In the near future, a dual-hormone AID system developed by Inreda Diabetic will be tested for 12 months in 240 adults with T1DM in The Netherlands, to assess the longer-term effects of this system on glycemic control, PROMs and cost-effectiveness compared with usual care (MDI with CGM or HCL) [72]. This system consists of a wearable device integrating two pumps (for insulin and glucagon) and an algorithm, with two infusion sets and two sensors.

Time in tight range

Time in tight range (TITR), defined as a glucose level between 3.9 and 7.8 mmol/l, has recently been presented as a new metric to evaluate glucose control, because TITR more closely approximates normoglycemia [73]. When advanced AID systems have the improved ability to reduce hyperglycemia, TITR may become a more relevant metric in clinical practice for establishing goals for therapy than TIR. For T2DM, TITR can also be relevant for patients who have the ability to achieve near-normal glycemic levels, for example after commencement of GLP-1 receptor agonists or SGLT2 inhibitors. Although TIR and TITR are correlated, the relationship is nonlinear. The ratio of TITR:TIR is higher as TIR increases [73]. The standard TIR goal of 70% corresponds on average to a TITR goal of 45%. This glycemic target could be increased for persons with diabetes who are able to

achieve tighter glucose control (supported by more advanced treatment options). A TITR of > 50% has recently been shown as achievable goal in persons with T1DM on AHCL therapy with optimal system settings in a large real-world study [74]. However, the impact of this tighter glycemic target on diabetes burden ("time in happiness") and the effect on long-term complications remains to be investigated.

Pancreas (islet) transplantation and transplantation of beta cells

Despite current technological improvements, a substantial part of persons with diabetes does not achieve the glycemic targets and still experience severe hypoglycemic events, although this is less with AID therapy as compared to users of MDI with CGM and non-CGM users [75]. These findings indicate an ongoing need for improved treatment strategies, including beta-cell replacement therapy.

Pancreas or pancreatic islet transplantation can be considered for persons with T1DM who meet specific clinical criteria. Benefits include cessation of insulin therapy, normoglycemia, avoidance of hypoglycemia and stabilization of complications [76]. However, chronic immunosuppression is needed to prevent graft rejection after pancreas transplantation or pancreas islet allo-transplantation. Pancreas transplantation is usually reserved for persons with insulin-requiring diabetes who already committed to immunosuppression for another reason, and is most commonly performed in combination with kidney transplantation or transplantation of another organ. The pancreas graft survival rate at 5 years after simultaneous pancreas-kidney transplant is 80%, which is superior to pancreas transplantation alone (62%) [76].

Pancreas islet allotransplantation can be considered for persons with T1DM experiencing severe hypoglycemia accompanied by hypoglycemia unawareness or marked glycemic lability, or who already receive immunosuppressive drugs for a kidney transplant [77]. In recipients of pancreas islet transplants, recovery of the physiologic responses to insulin-induced hypoglycemia has been observed, whereby endogenous insulin secretion is appropriately suppressed and glucagon secretion is partially restored [78]. For pancreas islet transplantation multiple donor pancreas are needed to provide enough islet cells to overcome loss of islet cells during transplantation. After isolation and purification of islet cells, the cells are administered to the patient via intraportal infusion for intrahepatic engraftment. Current limitations of this procedure are a limited donor pancreas supply, lifelong need for immunosuppressant therapy and limited survival of islet grafts. Pancreas islet auto-transplantation following total pancreatectomy, is most commonly performed in the setting of recurrent acute or chronic pancreatitis. These persons are dependent on the number and health of isolated islets from their own pancreas. Insulin independence

was experienced by about one-third of persons after auto-islet transplantation and by about half of allo-islet transplant recipients [77]. In a recent retrospective cohort study, the 5-year cumulative incidence of unsuccessful islet transplantation, defined by an HbA1c of ≥53 mmol/mol (7·0%), severe hypoglycemia or a fasting C-peptide concentration of < 0.2 ng/mL, was 70.7% [79]. This indicates the need for future developments enhancing the survival and function of transplanted islets or other beta-cell replacement strategies.

The past decades, stem cell transplantation has been investigated to intervene in disease progression in T1DM, to eliminate the need for pancreas donor tissue and use of immunosuppressive therapy. Different approaches have been attempted, including treatment of patients with newly diagnosed T1DM with mesenchymal stromal cells [80] and autologous hematopoietic stem cells [81,82]. Mesenchymal stromal cells have the capability to specifically home to damaged islets and local pancreatic lymph nodes. Treatment with autologous hematopoietic stem cells preserves the remaining beta-cell function by destroying pathogenic memory T-cells [82]. However, side effects of this treatment are cytotoxic drug-related nausea, vomiting, fever and alopecia. Although still investigational, progress has been made in the development of stem cell derived beta-cells, which provides a renewably supply of insulin-producing cells and could be a potentially curative therapy in the future [83,84]. Strategies to protect these beta-cells from immune attack, via encapsulation or gene therapy techniques, are also under investigation [84].

Disease modifying treatments to preserve β-cell function

Beta-cell mass rapidly declines during the first 1–2 years following the onset of T1DM. Several disease modifying therapies have recently been evaluated to prevent or delay the loss of functional beta-cell mass in T1DM. Preservation of residual beta-cell function, represented by higher levels of C-peptide, facilitates better glycemic control. Teplizumab is a humanized monoclonal antibody against the CD3 molecule on T-cells. It modifies CD8+ T lymphocytes; the autoreactive cells that mediate beta-cell death. When administered (daily for 14 days at baseline and again after 26 weeks) to persons with new onset T1DM, teplizumab reduced the rate of decline of C-peptide after 2 years, as compared to placebo [85]. This effect was strongest in persons treated within 6 weeks after the diagnosis of T1DM. However, teplizumab was unable to restore normoglycemia. Side effects of teplizumab were mostly limited to the dosing period and included transient cytopenia and transient manifestations of cytokine release such as rash, headache, nausea, and vomiting.

In individuals susceptible for T1DM (a first degree relative with T1DM, ≥2 positive autoantibodies and an abnormal oral glucose tolerance test), a single 14-day course of treatment with teplizumab intravenously delayed progression to T1DM by 2 years [86].

Based on these results, teplizumab is approved for persons at high risk of T1DM in the US [87]. Future studies are needed to evaluate if a 2-year delay in the onset of clinical diabetes will translate into lasting benefit, not least because the high costs (US $ 193900 for a 14-day course) of teplizumab [88].

Golimumab is a monoclonal antibody against tumor necrosis factor α (TNF- α); a proinflammatory cytokine that plays a role in the development and progression of several autoimmune diseases, including autoimmune diabetes. It has been tested in children and young adults with newly diagnosed T1DM. Treatment with subcutaneous golimumab (every 2 weeks) for 52 weeks resulted in better endogenous insulin production, as assessed by the area under the concentration-time curve for C-peptide level in response to a 4-hour mixed-meal tolerance test, and less exogenous insulin use than placebo [89].

Baricitinib, a JAK1 and JAK2 inhibitor, is another disease modifying drug which has recently been investigated in a phase 2 study to preserve β-cell function [90]. JAK inhibition impairs the activation of autoreactive CD8+ T-cells involved in the destruction of β-cells. Persons recently (< 100 days) diagnosed with T1DM with a C-peptide level of a least 0.2 mmol/L were included in the RCT. After 48 weeks of treatment with baricitinib, the mixed-meal test stimulated C-peptide level was higher in the baricitinib group as compared to the placebo group and glucose variability was lower. Treatment with baricitinib consist of daily use of a single tablet, in contrast to treatment with teplizumab or golimumab, which require intravenous infusion or subcutaneous injection, and a lower percentage of side effects was reported. Future trials are needed to investigate loss of β-cell function after cessation of baricitinib. It is also of interest to investigate the effects of continuation of baricitinib on C-peptide levels for as long as evidence of β-cell function persists.

References

1. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. N Engl J Med 1993;329:977–86. https://doi.org/10.1056/NEJM199309303291401.
2. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). The Lancet 1998;352:854–65. https://doi.org/10.1016/S0140-6736(98)07037-8.
3. Bebu I, Schade D, Braffett B, Kosiborod M, Lopes-Virella M, Soliman EZ, et al. Risk Factors for First and Subsequent CVD Events in Type 1 Diabetes: The DCCT/EDIC Study. Diabetes Care 2020;43:867–74. https://doi.org/10.2337/dc19-2292.
4. Fokkert M, van Dijk P, Edens M, Barents E, Mollema J, Slingerland R, et al. Improved well-being and decreased disease burden after 1-year use of flash glucose monitoring (FLARE-NL4). BMJ Open Diabetes Res Care 2019;7:e000809. https://doi.org/10.1136/bmjdrc-2019-000809.
5. Evans M, Welsh Z, Seibold A. Reductions in HbA1c with Flash Glucose Monitoring Are Sustained for up to 24 Months: A Meta-Analysis of 75 Real-World Observational Studies. Diabetes Ther 2022;13:1175–85. https://doi.org/10.1007/s13300-022-01253-9.
6. Hughes MS, Addala A, Buckingham B. Digital Technology for Diabetes. N Engl J Med 2023;389:2076–86. https://doi.org/10.1056/NEJMra2215899.
7. Liakos A, Karagiannis T, Avgerinos I, Tsapas A, Bekiari E. Burden and Coping Strategies of Hypoglycemia in People with Diabetes. Current Diabetes Reviews n.d.;20:1–7.
8. Leelarathna L, Sutton CJ, Evans ML, Neupane S, Rayman G, Lumley S, et al. Intermittently scanned continuous glucose monitoring in adults with type 1 diabetes: A subgroup analysis from the FLASH-UK study. Diabet Med 2023:e15249. https://doi.org/10.1111/dme.15249.
9. Jeyam A, Gibb FW, McKnight JA, O'Reilly JE, Caparrotta TM, Höhn A, et al. Flash monitor initiation is associated with improvements in HbA1c levels and DKA rates among people with type 1 diabetes in Scotland: a retrospective nationwide observational study. Diabetologia 2022;65:159–72. https://doi.org/10.1007/s00125-021-05578-1.
10. Leelarathna L, Evans ML, Neupane S, Rayman G, Lumley S, Cranston I, et al. Intermittently Scanned Continuous Glucose Monitoring for Type 1 Diabetes. N Engl J Med 2022;387:1477–87. https://doi.org/10.1056/NEJMoa2205650.
11. Ang E, Lee ZX, Moore S, Nana M. Flash glucose monitoring (FGM): A clinical review on glycaemic outcomes and impact on quality of life. Journal of Diabetes and Its Complications 2020;34:107559. https://doi.org/10.1016/j.jdiacomp.2020.107559.
12. Duarte DB, Fonseca L, Santos T, Silva VB, Puga FM, Saraiva M, et al. Impact of intermittently scanned continuous glucose monitoring on quality of life and glycaemic control in persons with type 1 diabetes: A 12-month follow-up study in real life. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2022;16:102509. https://doi.org/10.1016/j.dsx.2022.102509.
13. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. The Lancet 2016;388:2254–63. https://doi.org/10.1016/S0140-6736(16)31535-5.
14. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline J-P, Rayman G. Flash Glucose-Sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-Treated Type 2 Diabetes: a Multicenter, Open-Label Randomized Controlled Trial. Diabetes Ther 2017;8:55–73. https://doi.org/10.1007/s13300-016-0223-6.

15. Roussel R, Riveline J-P, Vicaut E, de Pouvourville G, Detournay B, Emery C, et al. Important Drop in Rate of Acute Diabetes Complications in People With Type 1 or Type 2 Diabetes After Initiation of Flash Glucose Monitoring in France: The RELIEF Study. Diabetes Care 2021;44:1368–76. https://doi.org/10.2337/dc20-1690.

16. Deshmukh H, Wilmot EG, Gregory R, Barnes D, Narendran P, Saunders S, et al. Effect of Flash Glucose Monitoring on Glycemic Control, Hypoglycemia, Diabetes-Related Distress, and Resource Utilization in the Association of British Clinical Diabetologists (ABCD) Nationwide Audit. Diabetes Care 2020;43:2153–60. https://doi.org/10.2337/dc20-0738.

17. Charleer S, De Block C, Van Huffel L, Broos B, Fieuws S, Nobels F, et al. Quality of Life and Glucose Control After 1 Year of Nationwide Reimbursement of Intermittently Scanned Continuous Glucose Monitoring in Adults Living With Type 1 Diabetes (FUTURE): A Prospective Observational Real-World Cohort Study. Diabetes Care 2020;43:389–97. https://doi.org/10.2337/dc19-1610.

18. 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;42:1593–603. https://doi.org/10.2337/dci19-0028.

19. Beck RW, Bergenstal RM, Riddlesworth TD, Kollman C, Li Z, Brown AS, et al. Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials. Diabetes Care 2019;42:400–5. https://doi.org/10.2337/dc18-1444.

20. Lu J, Ma X, Zhou J, Zhang L, Mo Y, Ying L, et al. Association of Time in Range, as Assessed by Continuous Glucose Monitoring, With Diabetic Retinopathy in Type 2 Diabetes. Diabetes Care 2018;41:2370–6. https://doi.org/10.2337/dc18-1131.

21. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. J Affect Disord 2012;142 Suppl:S8-21. https://doi.org/10.1016/S0165-0327(12)70004-6.

22. Khaledi M, Haghighatdoost F, Feizi A, Aminorroaya A. The prevalence of comorbid depression in patients with type 2 diabetes: an updated systematic review and meta-analysis on huge number of observational studies. Acta Diabetol 2019;56:631–50. https://doi.org/10.1007/s00592-019-01295-9.

23. Tyndall V, Stimson RH, Zammitt NN, Ritchie SA, McKnight JA, Dover AR, et al. Marked improvement in HbA1c following commencement of flash glucose monitoring in people with type 1 diabetes. Diabetologia 2019;62:1349–56. https://doi.org/10.1007/s00125-019-4894-1.

24. Vilagut G, Forero CG, Pinto-Meza A, Haro JM, Graaf R de, Bruffaerts R, et al. The Mental Component of the Short-Form 12 Health Survey (SF-12) as a Measure of Depressive Disorders in the General Population: Results with Three Alternative Scoring Methods. Value in Health 2013;16:564–73. https://doi.org/10.1016/j.jval.2013.01.006.

25. Deshmukh H, Wilmot EG, Gregory R, Barnes D, Narendran P, Saunders S, et al. Predictors of diabetes-related distress before and after FreeStyle Libre-1 use: Lessons from the Association of British Clinical Diabetologists nationwide study. Diabetes, Obesity and Metabolism 2021;23:2261–8. https://doi.org/10.1111/dom.14467.

26. Kathe N, Hayes CJ, Bhandari NR, Payakachat N. Assessment of Reliability and Validity of SF-12v2 among a Diabetic Population. Value Health 2018;21:432–40. https://doi.org/10.1016/j.jval.2017.09.007.

27. van Dijk SEM, Adriaanse MC, van der Zwaan L, Bosmans JE, van Marwijk HWJ, van Tulder MW, et al. Measurement properties of depression questionnaires in patients with diabetes: a systematic review. Qual Life Res 2018;27:1415–30. https://doi.org/10.1007/s11136-018-1782-y.

28. Hohendorff J, Gumprecht J, Mysliwiec M, Zozulinska-Ziolkiewicz D, Malecki MT. Intermittently Scanned Continuous Glucose Monitoring Data of Polish Patients from Real-Life Conditions: More Scanning and Better Glycemic Control Compared to Worldwide Data. Diabetes Technol Ther 2021;23:577–85. https://doi.org/10.1089/dia.2021.0034.

29. Dunn TC, Xu Y, Hayter G, Ajjan RA. Real-world flash glucose monitoring patterns and associations between self-monitoring frequency and glycaemic measures: A European analysis of over 60 million glucose tests. Diabetes Research and Clinical Practice 2018;137:37–46. https://doi.org/10.1016/j.diabres.2017.12.015.

30. Cryer PE. Hypoglycemia: Still The Limiting Factor in the Glycemic Management of Diabetes. Endocrine Practice 2008;14:750–6. https://doi.org/10.4158/EP.14.6.750.

31. American Diabetes Association Professional Practice Committee. 7. Diabetes Technology: Standards of Care in Diabetes-2024. Diabetes Care 2024;47:S126–44. https://doi.org/10.2337/dc24-S007.

32. Wright EE, Subramanian S. Is Continuous Glucose Monitoring a Tool, an Intervention, or Both? Diabetes Technol Ther 2023;25:S48–55. https://doi.org/10.1089/dia.2023.0025.

33. Przezak A, Bielka W, Molęda P. Fear of hypoglycemia—An underestimated problem. Brain Behav 2022;12:e2633. https://doi.org/10.1002/brb3.2633.

34. Carlson AL, Daniel TD, DeSantis A, Jabbour S, Karslioglu French E, Kruger D, et al. Flash glucose monitoring in type 2 diabetes managed with basal insulin in the USA: a retrospective real-world chart review study and meta-analysis. BMJ Open Diab Res Care 2022;10:e002590. https://doi.org/10.1136/bmjdrc-2021-002590.

35. Elliott T, Beca S, Beharry R, Tsoukas MA, Zarruk A, Abitbol A. The impact of flash glucose monitoring on glycated hemoglobin in type 2 diabetes managed with basal insulin in Canada: A retrospective real-world chart review study. Diab Vasc Dis Res 2021;18:14791641211021374. https://doi.org/10.1177/14791641211021374.

36. Wada E, Onoue T, Kobayashi T, Handa T, Hayase A, Ito M, et al. Flash glucose monitoring helps achieve better glycemic control than conventional self-monitoring of blood glucose in non-insulin-treated type 2 diabetes: a randomized controlled trial. BMJ Open Diab Res Care 2020;8:e001115. https://doi.org/10.1136/bmjdrc-2019-001115.

37. Polonsky WH, Fortmann AL, Soriano EC, Guzman SJ, Funnell MM. The AH-HA! Project: Transforming Group Diabetes Self-Management Education Through the Addition of Flash Glucose Monitoring. Diabetes Technology & Therapeutics 2023;25:194–200. https://doi.org/10.1089/dia.2022.0419.

38. Hill-Briggs F, Adler NE, Berkowitz SA, Chin MH, Gary-Webb TL, Navas-Acien A, et al. Social Determinants of Health and Diabetes: A Scientific Review. Diabetes Care 2020;44:258–79. https://doi.org/10.2337/dci20-0053.

39. Auzanneau M, Rosenbauer J, Maier W, von Sengbusch S, Hamann J, Kapellen T, et al. Heterogeneity of Access to Diabetes Technology Depending on Area Deprivation and Demographics Between 2016 and 2019 in Germany. J Diabetes Sci Technol 2021;15:1059–68. https://doi.org/10.1177/19322968211028608.

40. Odugbesan O, Addala A, Nelson G, Hopkins R, Cossen K, Schmitt J, et al. Implicit Racial–Ethnic and Insurance-Mediated Bias to Recommending Diabetes Technology: Insights from T1D Exchange Multicenter Pediatric and Adult Diabetes Provider Cohort. Diabetes Technology & Therapeutics 2022;24:619–27. https://doi.org/10.1089/dia.2022.0042.

41. Schillinger D, Barton LR, Karter AJ, Wang F, Adler N. Does Literacy Mediate the Relationship Between Education and Health Outcomes? A Study of a Low-Income Population with Diabetes. Public Health Rep 2006;121:245–54.

42. Tanenbaum ML, Adams RN, Hanes SJ, Barley RC, Miller KM, Mulvaney SA, et al. Optimal Use of Diabetes Devices: Clinician Perspectives on Barriers and Adherence to Device Use. J Diabetes Sci Technol 2017;11:484–92. https://doi.org/10.1177/1932296816688010.

43. Visser MM, Charleer S, Fieuws S, De Block C, Hilbrands R, Van Huffel L, et al. Effect of switching from intermittently scanned to real-time continuous glucose monitoring in adults with type 1 diabetes: 24-month results from the randomised ALERTT1 trial. The Lancet Diabetes & Endocrinology 2023;11:96–108. https://doi.org/10.1016/S2213-8587(22)00352-7.

44. Hásková A, Radovnická L, Petruželková L, Parkin CG, Grunberger G, Horová E, et al. Real-time CGM Is Superior to Flash Glucose Monitoring for Glucose Control in Type 1 Diabetes: The CORRIDA Randomized Controlled Trial. Diabetes Care 2020;43:2744–50. https://doi.org/10.2337/dc20-0112.

45. Préau Y, Galie S, Schaepelynck P, Armand M, Raccah D. Benefits of a Switch from Intermittently Scanned Continuous Glucose Monitoring (isCGM) to Real-Time (rt) CGM in Diabetes Type 1 Suboptimal Controlled Patients in Real-Life: A One-Year Prospective Study §. Sensors (Basel) 2021;21:6131. https://doi.org/10.3390/s21186131.

46. Radovnická L, Hásková A, Do QD, Horová E, Navrátilová V, Mikeš O, et al. Lower Glycated Hemoglobin with Real-Time Continuous Glucose Monitoring Than with Intermittently Scanned Continuous Glucose Monitoring After 1 Year: The CORRIDA LIFE Study. Diabetes Technology & Therapeutics 2022;24:859–67. https://doi.org/10.1089/dia.2022.0152.

47. Seidu S, Kunutsor SK, Ajjan RA, Choudhary P. Efficacy and Safety of Continuous Glucose Monitoring and Intermittently Scanned Continuous Glucose Monitoring in Patients With Type 2 Diabetes: A Systematic Review and Meta-analysis of Interventional Evidence. Diabetes Care 2023;47:169–79. https://doi.org/10.2337/dc23-1520.

48. Choudhary P, Kolassa R, Keuthage W, Kroeger J, Thivolet C, Evans M, et al. Advanced hybrid closed loop therapy versus conventional treatment in adults with type 1 diabetes (ADAPT): a randomised controlled study. The Lancet Diabetes & Endocrinology 2022;10:720–31. https://doi.org/10.1016/S2213-8587(22)00212-1.

49. Boscari F, Ferretto S, Cavallin F, Fadini GP, Avogaro A, Bruttomesso D. Effectiveness of adding alarms to flash glucose monitoring in adults with type 1 diabetes under routine care. Acta Diabetol 2022;59:921–8. https://doi.org/10.1007/s00592-022-01884-1.

50. Emamipour S, van Dijk PR, Bilo HJG, Edens MA, van der Galiën O, Postma MJ, et al. Personalizing the Use of a Intermittently Scanned Continuous Glucose Monitoring Device in Individuals With Type 1 Diabetes: A Cost-Effectiveness Perspective in the Netherlands (FLARE-NL 9). J Diabetes Sci Technol 2024;18:135–42. https://doi.org/10.1177/19322968221109841.

51. Visser MM, Van Muylder A, Charleer S, Isitt JJ, Roze S, De Block C, et al. Cost-utility analysis of Dexcom G6 real-time continuous glucose monitoring versus FreeStyle Libre 1 intermittently scanned continuous glucose monitoring in adults with type 1 diabetes in Belgium. Diabetologia 2024. https://doi.org/10.1007/s00125-023-06084-2.

52. de Jong LA, Li X, Emamipour S, van der Werf S, Postma MJ, van Dijk PR, et al. Model and Empirical Data-Based Cost-Utility Studies of Continuous Glucose Monitoring in Individuals with Type 1 Diabetes: A Protocol of a Systematic Review on Methodology and Quality. Pharmacoecon Open 2023;7:1007–13. https://doi.org/10.1007/s41669-023-00428-9.

53. Garg SK. Past, Present, and Future of Continuous Glucose Monitors. Diabetes Technology & Therapeutics 2023;25:S-1. https://doi.org/10.1089/dia.2023.0041.

54. Gothong C, Singh LG, Satyarengga M, Spanakis EK. Continuous glucose monitoring in the hospital: an update in the era of COVID-19. Curr Opin Endocrinol Diabetes Obes 2022;29:1–9. https://doi.org/10.1097/MED.0000000000000693.

55. Phillip M, Nimri R, Bergenstal RM, Barnard-Kelly K, Danne T, Hovorka R, et al. Consensus Recommendations for the Use of Automated Insulin Delivery Technologies in Clinical Practice. Endocr Rev 2022;44:254–80. https://doi.org/10.1210/endrev/bnac022.

56. Here's how healthcare can reduce its carbon footprint. World Economic Forum 2022. https://www.weforum.org/agenda/2022/10/cop27-how-healthcare-can-reduce-carbon-footprint/ (accessed February 10, 2024).

57. Garg SK, Liljenquist D, Bode B, Christiansen MP, Bailey TS, Brazg RL, et al. Evaluation of Accuracy and Safety of the Next-Generation Up to 180-Day Long-Term Implantable Eversense Continuous Glucose Monitoring System: The PROMISE Study. Diabetes Technol Ther 2022;24:84–92. https://doi.org/10.1089/dia.2021.0182.

58. Home - glucotrack 2022. https://glucotrack.com/ (accessed February 14, 2024).

59. Karakus KE, Akturk HK, Alonso GT, Snell-Bergeon JK, Shah VN. Association Between Diabetes Technology Use and Glycemic Outcomes in Adults With Type 1 Diabetes Over a Decade. Diabetes Care 2023;46:1646–51. https://doi.org/10.2337/dc23-0495.

60. Nørgaard K, Ranjan AG, Laugesen C, Tidemand KG, Green A, Selmer C, et al. Glucose Monitoring Metrics in Individuals With Type 1 Diabetes Using Different Treatment Modalities: A Real-World Observational Study. Diabetes Care 2023:dc231137. https://doi.org/10.2337/dc23-1137.

61. Lablanche S, Delagenière J, Jalbert M, Sonnet E, Benichou M, Arnold N, et al. 12-Month Real-Life Efficacy of the MiniMed 780G Advanced Closed-Loop System in Patients Living with Type 1 Diabetes: A French Observational, Retrospective, Multicentric Study. Diabetes Technology & Therapeutics 2024. https://doi.org/10.1089/dia.2023.0414.

62. Crabtree TSJ, Griffin TP, Yap YW, Narendran P, Gallen G, Furlong N, et al. Hybrid Closed-Loop Therapy in Adults With Type 1 Diabetes and Above-Target HbA1c: A Real-world Observational Study. Diabetes Care 2023;46:1831–8. https://doi.org/10.2337/dc23-0635.

63. Renard E, Joubert M, Villard O, Dreves B, Reznik Y, Farret A, et al. Safety and Efficacy of Sustained Automated Insulin Delivery Compared With Sensor and Pump Therapy in Adults With Type 1 Diabetes at High Risk for Hypoglycemia: A Randomized Controlled Trial. Diabetes Care 2023:dc230685. https://doi.org/10.2337/dc23-0685.

64. Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes. New England Journal of Medicine 2022;387:1161–72. https://doi.org/10.1056/NEJMoa2205225.

65. Castellanos LE, Balliro CA, Sherwood JS, Jafri R, Hillard MA, Greaux E, et al. Performance of the Insulin-Only iLet Bionic Pancreas and the Bihormonal iLet Using Dasiglucagon in Adults With Type 1 Diabetes in a Home-Use Setting. Diabetes Care 2021;44:e118–20. https://doi.org/10.2337/dc20-1086.

66. Nwokolo M, Hovorka R. The Artificial Pancreas and Type 1 Diabetes. J Clin Endocrinol Metab 2023;108:1614–23. https://doi.org/10.1210/clinem/dgad068.

67. Zeng B, Jia H, Gao L, Yang Q, Yu K, Sun F. Dual-hormone artificial pancreas for glucose control in type 1 diabetes: A meta-analysis. Diabetes, Obesity and Metabolism 2022;24:1967–75. https://doi.org/10.1111/dom.14781.

68. Ware J, Hovorka R. Metabolism Clinical & Experimental – Recent advances in closed-loop insulin delivery. Metabolism 2022;127:154953. https://doi.org/10.1016/j.metabol.2021.154953.

69. Wilson LM, Jacobs PG, Ramsey KL, Resalat N, Reddy R, Branigan D, et al. Dual-Hormone Closed-Loop System Using a Liquid Stable Glucagon Formulation Versus Insulin-Only Closed-Loop System Compared With a Predictive Low Glucose Suspend System: An Open-Label, Outpatient, Single-Center, Crossover, Randomized Controlled Trial. Diabetes Care 2020;43:2721–9. https://doi.org/10.2337/dc19-2267.

70. El-Khatib FH, Balliro C, Hillard MA, Magyar KL, Ekhlaspour L, Sinha M, et al. 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;389:369–80. https://doi.org/10.1016/S0140-6736(16)32567-3.

71. 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;44:836–8. https://doi.org/10.2337/dc20-2106.

72. Jancev M, Snoek FJ, Frederix GWJ, Knottnerus H, Blauw H, Witkop M, et al. Dual hormone fully closed loop in type 1 diabetes: a randomised trial in the Netherlands - study protocol. BMJ Open 2023;13:e074984. https://doi.org/10.1136/bmjopen-2023-074984.

73. Beck RW, Raghinaru D, Calhoun P, Bergenstal RM. A Comparison of Continuous Glucose Monitoring-Measured Time-in-Range 70–180 mg/dL Versus Time-in-Tight-Range 70–140 mg/dL. Diabetes Technology & Therapeutics 2023. https://doi.org/10.1089/dia.2023.0380.

74. Castañeda J, Arrieta A, van den Heuvel T, Battelino T, Cohen O. Time in Tight Glucose Range in Type 1 Diabetes: Predictive Factors and Achievable Targets in Real-World Users of the MiniMed 780G System. Diabetes Care n.d. https://doi.org/10.2337/dc23-1581.

75. Sherr JL, Laffel LM, Liu J, Wolf W, Bispham J, Chapman KS, et al. Severe Hypoglycemia and Impaired Awareness of Hypoglycemia Persist in People With Type 1 Diabetes Despite Use of Diabetes Technology: Results From a Cross-Sectional Survey. Diabetes Care 2024:dc231765. https://doi.org/10.2337/dc23-1765.

76. Fridell JA, Stratta RJ, Gruessner AC. Pancreas Transplantation: Current Challenges, Considerations, and Controversies. The Journal of Clinical Endocrinology & Metabolism 2023;108:614–23. https://doi.org/10.1210/clinem/dgac644.

77. Rickels MR, Robertson RP. Pancreatic Islet Transplantation in Humans: Recent Progress and Future Directions. Endocrine Reviews 2019;40:631–68. https://doi.org/10.1210/er.2018-00154.

78. Rickels MR, Fuller C, Dalton-Bakes C, Markmann E, Palanjian M, Cullison K, et al. Restoration of Glucose Counterregulation by Islet Transplantation in Long-standing Type 1 Diabetes. Diabetes 2015;64:1713–8. https://doi.org/10.2337/db14-1620.

79. Chetboun M, Drumez E, Ballou C, Maanaoui M, Payne E, Barton F, et al. Association between primary graft function and 5-year outcomes of islet allogeneic transplantation in type 1 diabetes: a retrospective, multicentre, observational cohort study in 1210 patients from the Collaborative Islet Transplant Registry. The Lancet Diabetes & Endocrinology 2023;11:391–401. https://doi.org/10.1016/S2213-8587(23)00082-7.

80. Carlsson P-O, Schwarcz E, Korsgren O, Blanc KL. Preserved b-Cell Function in Type 1 Diabetes by Mesenchymal Stromal Cells 2015;64.

81. Couri CEB, Oliveira MCB, Stracieri ABPL, Moraes DA, Pieroni F, Barros GMN, et al. C-Peptide Levels and Insulin Independence Following Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in Newly Diagnosed Type 1 Diabetes Mellitus. JAMA 2009;301:1573–9. https://doi.org/10.1001/jama.2009.470.

82. Li L, Shen S, Ouyang J, Hu Y, Hu L, Cui W, et al. Autologous Hematopoietic Stem Cell Transplantation Modulates Immunocompetent Cells and Improves β-Cell Function in Chinese Patients with New Onset of Type 1 Diabetes. The Journal of Clinical Endocrinology & Metabolism 2012;97:1729–36. https://doi.org/10.1210/jc.2011-2188.

83. Hogrebe NJ, Maxwell KG, Augsornworawat P, Millman JR. Generation of insulin-producing pancreatic β cells from multiple human stem cell lines. Nat Protoc 2021;16:4109–43. https://doi.org/10.1038/s41596-021-00560-y.

84. Karpov DS, Sosnovtseva AO, Pylina SV, Bastrich AN, Petrova DA, Kovalev MA, et al. Challenges of CRISPR/Cas-Based Cell Therapy for Type 1 Diabetes: How Not to Engineer a "Trojan Horse." Int J Mol Sci 2023;24:17320. https://doi.org/10.3390/ijms242417320.

85. Hagopian W, Ferry RJ, Sherry N, Carlin D, Bonvini E, Johnson S, et al. Teplizumab preserves C-peptide in recent-onset type 1 diabetes: two-year results from the randomized, placebo-controlled Protégé trial. Diabetes 2013;62:3901–8. https://doi.org/10.2337/db13-0236.

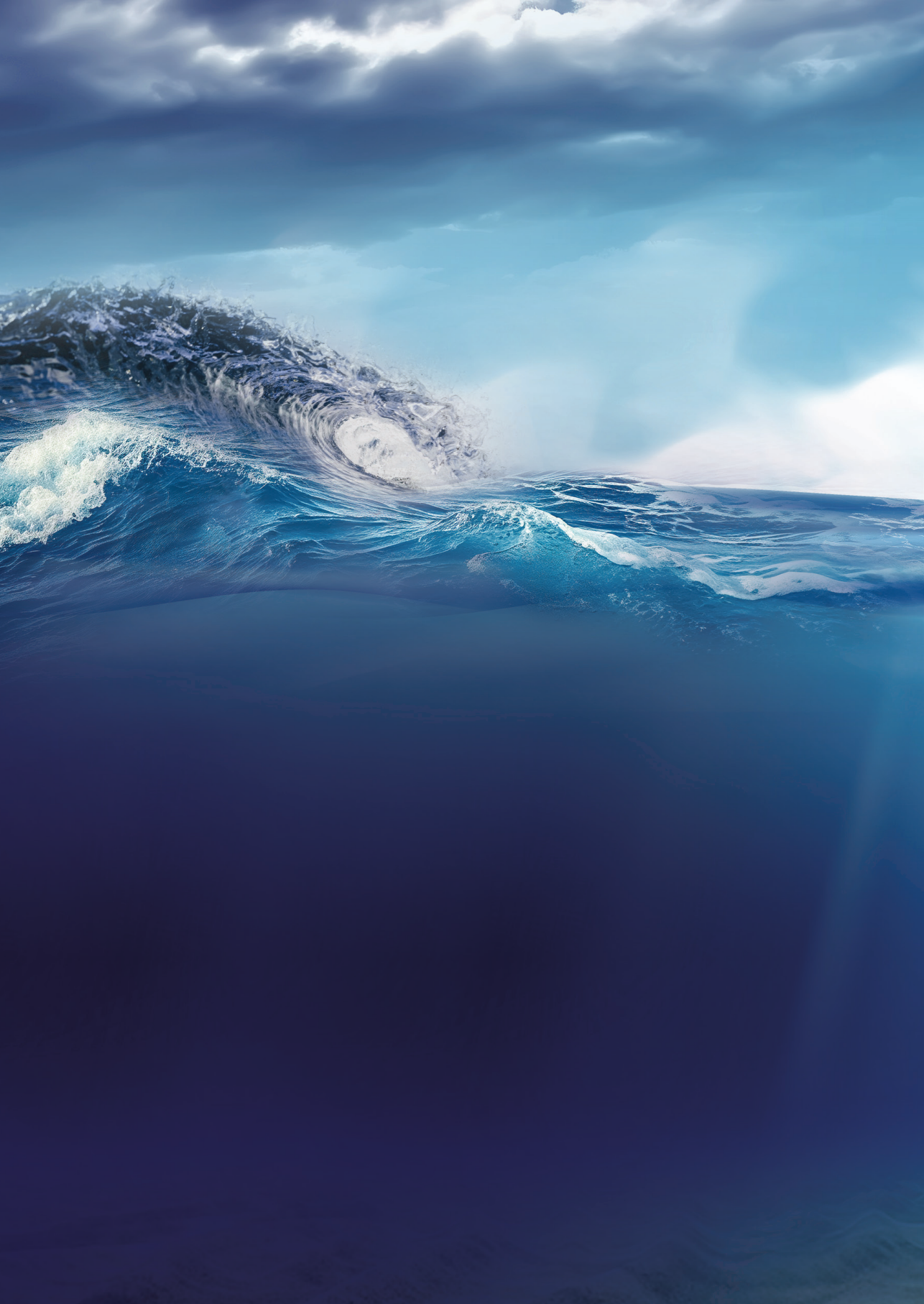
86. Herold KC, Bundy BN, Long SA, Bluestone JA, DiMeglio LA, Dufort MJ, et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. New England Journal of Medicine 2019;381:603–13. https://doi.org/10.1056/NEJMoa1902226.

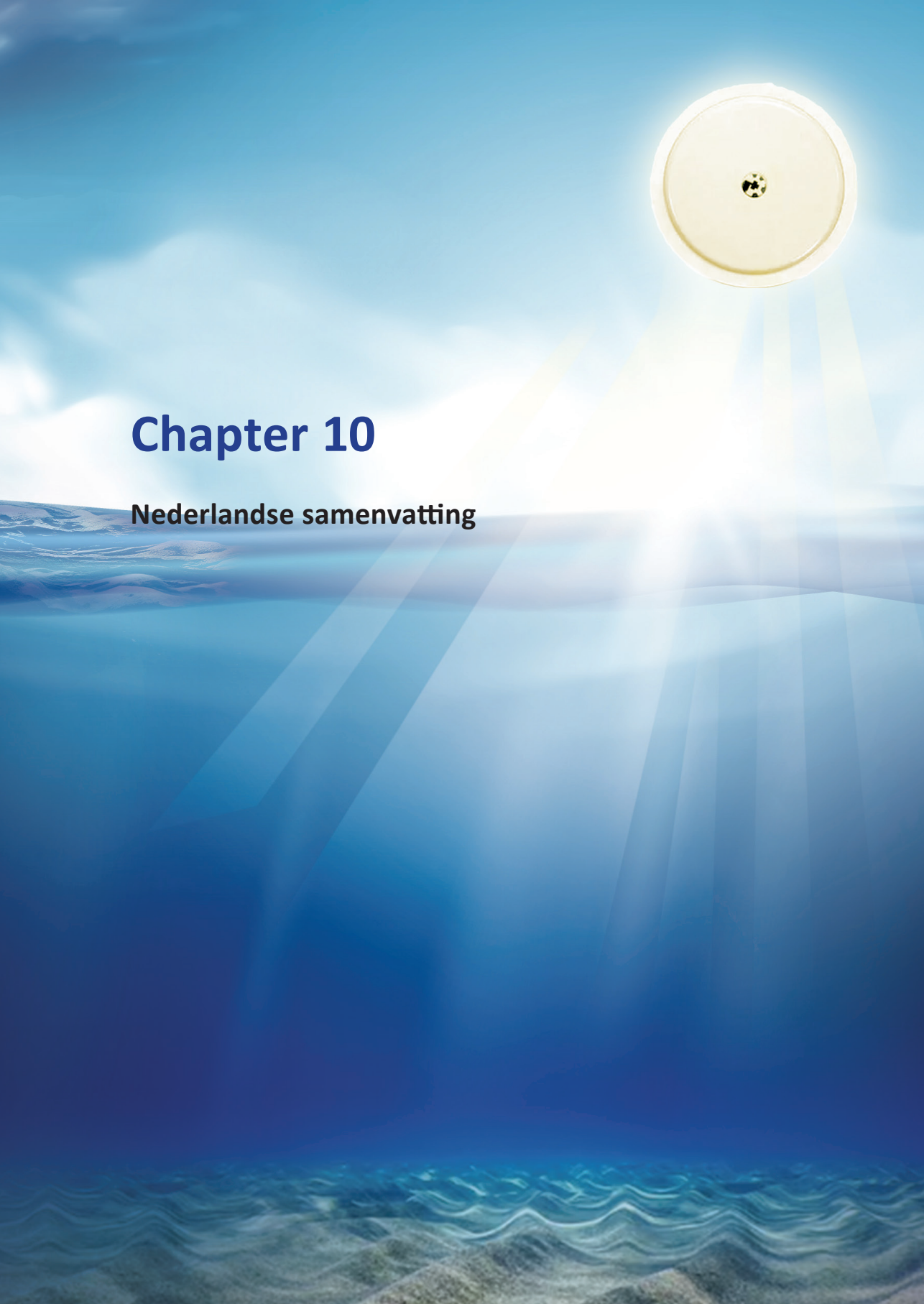
87. FDA approves first drug that can delay onset of type 1 diabetes n.d.

88. Beran D, Abidha C, Adler A, De Beaufort C, Lepeska M, Levitt N, et al. Teplizumab approval for type 1 diabetes in the USA. The Lancet Diabetes & Endocrinology 2023;11:78–80. https://doi.org/10.1016/S2213-8587(22)00384-9.

89. Quattrin T, Haller MJ, Steck AK, Felner EI, Li Y, Xia Y, et al. Golimumab and Beta-Cell Function in Youth with New-Onset Type 1 Diabetes. New England Journal of Medicine 2020;383:2007–17. https://doi.org/10.1056/NEJMoa2006136.

90. Waibel M, Wentworth JM, So M, Couper JJ, Cameron FJ, MacIsaac RJ, et al. Baricitinib and β-Cell Function in Patients with New-Onset Type 1 Diabetes. New England Journal of Medicine 2023;389:2140–50. https://doi.org/10.1056/NEJMoa2306691.





Chapter 10

Nederlandse samenvatting

Diabetes mellitus

Diabetes mellitus (DM) wordt gekenmerkt door een verhoogde glucosewaarde (hyperglycemie) ten gevolge van een tekort aan de productie van het hormoon insuline, onvoldoende werking van insuline of een combinatie hiervan. Het (relatieve) insulinetekort leidt ertoe dat glucose onvoldoende uit de bloedbaan in de weefsels kan worden opgenomen. Kenmerkende symptomen van DM zijn polyurie, polydipsie, gewichtsverlies, vermoeidheid en wazig zicht. De diagnose DM wordt gesteld op basis van de volgende criteria: een nuchter glucose ≥7 mmol/L, een random glucose ≥11 mmol/L in combinatie met klachten passend bij hyperglycemie, een HbA1c ≥48 mmol/mol (≥6.5%) of een glucose ≥11 mmol/L 2 uur na een glucose belastingtest met inname van 75 gram glucose (gemeten op een willekeurig tijdstip van de dag).

DM kan grofweg in 2 categorieën worden onderscheiden:

- Type 1 diabetes (T1DM, 5-10%) inclusief Latent Auto-immune Diabetes in Adults (LADA); een auto-immuunziekte waarbij de insuline producerende bètacellen in de alvleesklier worden aangetast, hetgeen leidt tot een absoluut insulinetekort, waarbij toediening van insuline van vitaal belang is. T1DM presenteert zich meestal op jonge leeftijd en is geassocieerd met het voorkomen van andere auto-immuunziekten.
- Type 2 diabetes (T2DM, > 90%); een aandoening gekenmerkt door insulineresistentie in combinatie met onvoldoende insuline afgifte door de alvleesklier, vaak in het kader van een metabool syndroom (de combinatie van overgewicht, hypertensie, hypercholesterolemie en hyperglycemie).

Overige (zeldzamere) vormen van DM zijn bijvoorbeeld maturity onset diabetes of the young (MODY), neonatale diabetes, medicatie geïnduceerde diabetes (o.a. door steroïden gebruik), diabetes t.g.v. een alvleesklierontsteking of zwangerschapsdiabetes.

T1DM wordt behandeld met insuline. Dit kan worden toegediend door middel van injecties via insulinepennen, of via een insulinepomp. Bij het injecteren van insuline is een basaal-bolusschema gebruikelijk, met eenmaal daags (basale) langwerkende insuline in combinatie met kortwerkende insuline bij de maaltijden en eventueel tussentijds ter correctie van hyperglycemie. Een insulinepomp geeft continu een basale hoeveelheid insuline af en daarnaast wordt (handmatig) een insulinebolus toegediend bij de maaltijden die onder andere gebaseerd is op het aantal koolhydraten die de maaltijd bevat. Tevens wordt een insulinedosis correctie advies gegeven op basis van het actuele glucose en de ingestelde insulinegevoeligheid.

T2DM wordt behandeld met leefstijlmaatregelen (gewichtsverlies, lichaamsbeweging en dieet) al dan niet in combinatie met glucose verlagende medicatie zoals metformine, sulfonylureumderivaten, thiazolidinedionderivaten, DPP4-remmers, GLP1-agonisten en SGLT2-remmers. Afhankelijk van de mate van ernst van de hyperglycemie kan insulinetherapie worden toegevoegd in de vorm van eenmaal daags basale insuline toediening, een basaal-bolusschema of via een insulinepomp.

Het belang van glucosemonitoring en uitdagingen bij het optimaliseren van de glucoseregulatie

Adequate monitoring van glucosewaarden is essentieel bij het streven naar optimale glucoseregulatie, hetgeen uiteindelijk tot doel heeft om micro- en macrovasculaire complicaties te voorkomen danwel uit te stellen. Het doel voor niet-zwangere personen met diabetes is om een HbA1c (een maat voor de glucosewaarde van de afgelopen 6-8 weken) van ≤53 mmol/mol (≤7%) te behalen. Voor mensen met een beperkte levensverwachting zijn hogere HbA1c streefwaarden (53-69 mmol/mol (7%-8.5%)) acceptabel. Tevens wordt tegenwoordig bij mensen met een glucosesensor de tijd binnen het glucose doelbereik (time-in-range (TIR); glucose 3.9-10 mmol/L) beoordeeld als aanvulling op het HbA1c, evenals de tijd in hyper- en hypoglycemie. Deze gegevens verschaffen meer informatie over de stabiliteit van glucosewaarden en de dag-tot-dag variatie. In 2019 zijn de volgende internationale doelen opgesteld met betrekking tot de tijdsduur in een bepaald glucosebereik: tijd binnen doelbereik (TIR; glucose 3,9-10 mmol/l) >70%, tijd beneden doelbereik (TBR; glucose <3.9 mmol/L) <4%, tijd in ernstige hypoglycemie (glucose <3.0 mmol/L) <1%, tijd boven doelbereik (TAR; glucose >10 mmol/L) <25%, en tijd in ernstige hyperglycemie (>13.9 mmol/L) <5%. Een TIR van 70% is gerelateerd aan een HbA1c van 7% en net als HbA1c geassocieerd met micro- en macrovasculaire schade. Voor iedere 10% daling van de TIR neemt het risico op retinopathie en microalbuminurie toe met respectievelijk 64% en 40%.

De meerderheid van de mensen met T1DM behaalt de streefdoelen momenteel niet. Dat is gerelateerd aan het feit dat diabetesmanagement een intensief proces is, met ruim 42 factoren die van invloed zijn op het glucosegehalte. Naast tijdige meting van het glucose is het van belang om de insulinedosis aan te passen aan o.a. de actuele glucosewaarde, het aantal koolhydraten in een maaltijd, geplande activiteiten, veranderingen in insulinegevoeligheid (tijdens sport of ziekte bijvoorbeeld) en de reeds eerder toegediende hoeveelheid insuline. Dit is een uitdagende taak, met invloed op het psychosociaal welbevinden en interferentie met sociale activiteiten, sport en werk. Tevens vormt angst voor hypoglycemie vaak een belemmering bij het behalen van de streefwaarden.

Vormen van glucosemonitoring

Sinds de jaren ’70 kan glucose in capillair bloed gemeten worden m.b.v. een vingerprikmeting. Dit is echter pijnlijk, tijdrovend en de handeling interfereert met dagelijkse activiteiten. Tevens verschaft een dergelijke puntmeting geen informatie over de glucosetrend oftewel een naderende glucose daling of stijging. De afgelopen jaren worden vingerprikmetingen bij mensen met diabetes en intensieve (basaal-bolus) insulinetherapie veelal vervangen door glucosemonitoring met behulp van glucosesensoren die de glucoseconcentratie in het onderhuidse weefselvocht meten en aanvullende informatie verschaffen over de glucoseregulatie.

Er zijn twee manieren van continue glucosemonitoring (CGM) met behulp van glucosesensoren beschikbaar: 1. Flash Glucose Monitoring (FGM) m.b.v. de FreeStyle Libre sensor waarbij de glucosewaarde zichtbaar wordt door de sensor te scannen met een reader of een telefoonapplicatie en 2. real-time Continue Glucose Monitoring (rt-CGM) waarbij het interstitiële glucosegehalte automatisch wordt gemeten en weergegeven op een telefoonapplicatie. Beide systemen bieden de mogelijkheid om het glucose in korte tijd, pijnloos en zo frequent als gewenst te controleren. Bovendien verschaffen glucosesensoren inzicht in het beloop van de glucosewaarden gedurende 24 uur, de tijd in een bepaald glucose (doel)bereik en de glucosevariabiliteit. Deze informatie is van grote meerwaarde bij het optimaliseren van de insulinedosering en bij het evalueren van aanpassingen in leefstijl en voeding. Tevens biedt de tweede generatie FGM, de FreeStyle Libre 2, de mogelijkheid om alarmen in te stellen voor een hoge en lage glucosewaarden. Rt-CGM systemen hebben naast deze alarmen ook een optioneel alarm voor een naderend laag of hoog glucose. Ook kunnen de meeste rt-CGM systemen gekoppeld worden aan een (hybride) insulinepomp. rt-CGM is duurder dan FGM, daarom gelden er striktere vergoedingscriteria voor dit soort systemen. In Nederland wordt rt-CGM alleen vergoed voor kinderen, volwassenen met T1DM en hypo-unawareness (lage glucosewaarden niet tijdig voelen aankomen) of een HbA1c >64 mmol/mol (>8%), zwangere vrouwen met T1DM of T2DM en vrouwen met T1DM of T2DM en een zwangerschapswens.

FGM is momenteel de meeste gebruikte glucosesensor in Nederland en Europa. In 2014 werd de Freestyle Libre sensor (versie 1, zonder alarmen) voor het eerst geïntroduceerd. In Nederland is het gebruik hiervan sterk gestegen vanaf 2019, aangezien de sensor sindsdien vergoed wordt vanuit zorgverzekeraars voor alle mensen met diabetes en een intensief (basaal-bolus) insuline schema en voor mensen met type 2 diabetes die zwanger zijn of een zwangerschapswens hebben. Sinds december 2020 is de FreeStyle Libre versie 2 (met alarmfunctie) beschikbaar.

Doelen van dit proefschrift

Dit proefschrift beschrijft de effecten van FGM op de glucoseregulatie en het welzijn van mensen met diabetes op de langere termijn, aangezien voorgaande studies een beperkte follow-up duur hebben en met name gericht zijn op verandering in HbA1c als uitkomst. Het eerste deel van dit proefschrift richt zich op de lange termijn effecten van FGM op glucoseregulatie, kwaliteit van leven, mentaal welzijn, ziektelast en overige patiënt-gerelateerde uitkomstmaten. Tevens is onderzocht welke factoren van invloed zijn op HbA1c daling. In het tweede deel van dit proefschrift zijn de effecten van FGM op verschillende glycemische parameters bij mensen met T1DM en T2DM in meer detail onderzocht. In het bijzonder is geanalyseerd hoe glycemische parameters veranderen in groepen met verschillende vormen van suboptimale glucoseregulatie bij de start met FGM en in groepen met een verschillende vorm en intensiteit van diabetesbehandeling (basaal-bolus schema, alleen basale insuline of behandeling zonder insuline). Het doel hiervan is het verschaffen van meer inzicht in de effectiviteit van FGM bij mensen met verschillende regulatie en behandeling, hetgeen o.b.v. voorgaande studies slechts beperkt mogelijk was. Verder is de relatie tussen de frequentie van glucosemonitoring via FGM en de glucoseregulatie geëvalueerd, omdat de optimale frequentie van monitoring niet bekend was. Tot slot is het effect van de socio-economische achtergrond en etniciteit van een persoon met diabetes op de toegang tot en het gebruik van glucosesensoren onderzocht. Door het inzicht in de impact van FGM op de glucoseregulatie en het welzijn van mensen met diabetes te verbeteren, heeft dit proefschrift als uiteindelijk doel om bij te dragen aan verbetering van de behandeling en kwaliteit van leven van mensen met diabetes - met diverse achtergronden - en (continuering) van vergoeding van FGM te ondersteunen.

Effecten van flash glucosemonitoring op glucoseregulatie, kwaliteit van leven en mentaal welzijn

In **hoofdstuk 2** hebben we onderzocht welke factoren gerelateerd zijn aan verbetering van HbA1c bij personen met diabetes die starten met FGM. Hiervoor hebben we gebruik gemaakt van de FlAsh monitor REgister in The NetherLands (FLARE-NL) database; een prospectieve studie die is opgezet in 2016 in samenwerking met de Diabetes Vereniging Nederland (DVN) om meer informatie te verkrijgen over de effectiviteit en veiligheid van FGM in Nederland. We zagen een relatie tussen de hoogte van het HbA1c bij aanvang van FGM en HbA1c daling over een periode van 12 maanden; bij mensen met het hoogste HbA1c was de HbA1c daling het sterkst. Ten aanzien van de overige factoren die we hebben onderzocht (leeftijd, geslacht, type diabetes, mentale en fysieke gezondheid, aanwezigheid van micro- of macrovasculaire complicaties) vonden we geen relatie met verandering in HbA1c.

Om meer inzicht te verkrijgen in de effecten van FGM op de langere termijn hebben we in **hoofdstuk 3** het effect van 2 jaar FGM gebruik op de glucoseregulatie, kwaliteit van leven en ziektelast bij mensen met diabetes onderzocht. Tevens is een vergelijking gemaakt tussen mensen die FGM gedurende 2 jaar continueerden en mensen die met FGM zijn gestopt na 1 jaar. In de groep personen met diabetes die FGM 2 jaar hebben gecontinueerd, observeerden we aanhoudende verbetering van HbA1c en kwaliteit van leven, waaronder gevoelens van angst en depressie, conform de verbetering na 1 jaar gebruik van FGM. In de groep mensen die waren gestopt met het gebruik van FGM zagen we dat het HbA1c aan het einde van de periode van 2 jaar follow-up vergelijkbaar was met het HbA1c van voor de start met FGM. Tevens was in deze groep het aantal diabetes gerelateerde ziekenhuisopnames en het arbeidsverzuim hoger ten opzichte van de groep die FGM 2 jaar continueerde. Samenvattend benadrukt deze studie de waardevolle invloed van FGM gebruik over een langere periode en de resultaten onderschrijven het continueren van vergoeding van FGM.

In hoofdstuk 3 zagen we dat personen die FGM 2 jaar continueerden minder gevoelens van angst en depressie rapporteerden ten opzichte van de periode voor de start met FGM toen zij hun glucose met behulp van vingerprikmetingen bepaalden. Depressieve aandoeningen komen relatief vaker voor bij mensen met diabetes, vergeleken met mensen zonder diabetes. Er zijn echter weinig studies gedaan naar de invloed van FGM gebruik op het mentale welzijn en depressieve aandoeningen bij mensen met diabetes, daarom hebben we dit onderzocht in **hoofdstuk 4.** Hiertoe hebben we de mental component scores (MCS), een afgeleide score van de 12-Item Short Form Health Survey (SF-12) vragenlijst, geanalyseerd van deelnemers van de FLARE-NL studie. Een SF-12 MCS score ≤ 45 is indicatief voor de aanwezigheid van een depressieve aandoening. We vonden dat het aantal depressieve aandoeningen afnam bij mensen met diabetes die FGM gedurende 6 en 12 maanden gebruikten. Tevens verbeterde het mentale welzijn van FGM gebruikers, gebaseerd op de MCS. Er was een associatie tussen een lagere MCS bij aanvang van FGM en verbetering van MCS na 12 maanden. De mate van verandering van HbA1c was niet van invloed op verbetering van de MCS. Toekomstige studies zijn nodig om de effecten van verandering van overige sensor-gerelateerde glycemische parameters, zoals tijd in normo-, hyper- en hypoglycemie en glucose variabiliteit op verandering in mentaal welzijn te onderzoeken. Deze gegeven waren niet beschikbaar ten tijde van onze studie.

Veranderingen in glycemische parameters na de start met FGM bij mensen met type 1 of 2 diabetes met verschillende glycemische controle en verschillende behandelmodaliteiten

Om een vollediger beeld te krijgen van de effecten van FGM is het belangrijk om naast HbA1c verandering ook de invloed op TIR, TAR, TBR en glycemische variabiliteit te onderzoeken, omdat deze parameters een betere weerspiegeling geven van de dag-tot-dag variatie van de glucosewaarden en HbA1c slechts een weerspiegeling is van de gemiddelde glucosewaarde over langere tijd. Aangezien FGM frequente glucosemonitoring mogelijk maakt, onderzochten wij allereerst in **hoofdstuk 5** de vraag hoe vaak FGM gebruikers hun glucose controleren en of er een relatie is tussen de FGM (scan) frequentie en verbetering van bovengenoemde glycemische parameters. Hiervoor hebben wij gebruik gemaakt van 'real-life' data van Nederlandse FGM gebruikers. O.b.v. hun gemiddelde scanfrequentie werden mensen verdeeld in 20 gelijke groepen (817 personen per groep). In de periode september 2014 tot maart 2020 was de gemiddelde frequentie van glucosemonitoring met behulp van FGM in Nederland 13 keer per dag. We vonden dat frequentere glucosecontrole via FGM geassocieerd was met verbetering van TIR, afname van tijd in hyperglycemie en verbetering van de glycemische variabiliteit. De groep met de laagste scan frequentie controleerde het glucosegehalte gemiddeld 3.7 keer per dag en had een (op basis van de van de gemiddelde glucosewaarde gemeten met FGM) geschat HbA1c (eHbA1c) van 71 mmol/mol (8.6%), de groep met de hoogste scan frequentie controleerde 40 keer per dag, geassocieerd met een eHbA1c van 52 mmol/mol (6.9%). Een eHbA1c van 53 mmol/mol (7%) correspondeerde met 15 scans per dag, 65% TIR, 30% tijd in hyperglycemie en 5% tijd in hypoglycemie. Tevens zagen we dat mensen met een slechtere glycemische instelling die met een lage frequentie scannen relatief vaker hun glucose monitoren tijdens hypoglycemie en minder frequent tijdens hyperglycemie. Hoewel het een cross-sectionele analyse betreft waarbij causaliteit niet bewezen is, leveren onze bevindingen interessante nieuwe inzichten op voor de klinische praktijk. Het lijkt aangewezen om mensen die weinig frequent hun glucose controleren te wijzen op de positieve effecten van frequentere glucose monitoring. Dit kan hen helpen om meer voordeel te behalen van FGM gebruik en dichter bij de glycemische doelstellingen te komen.

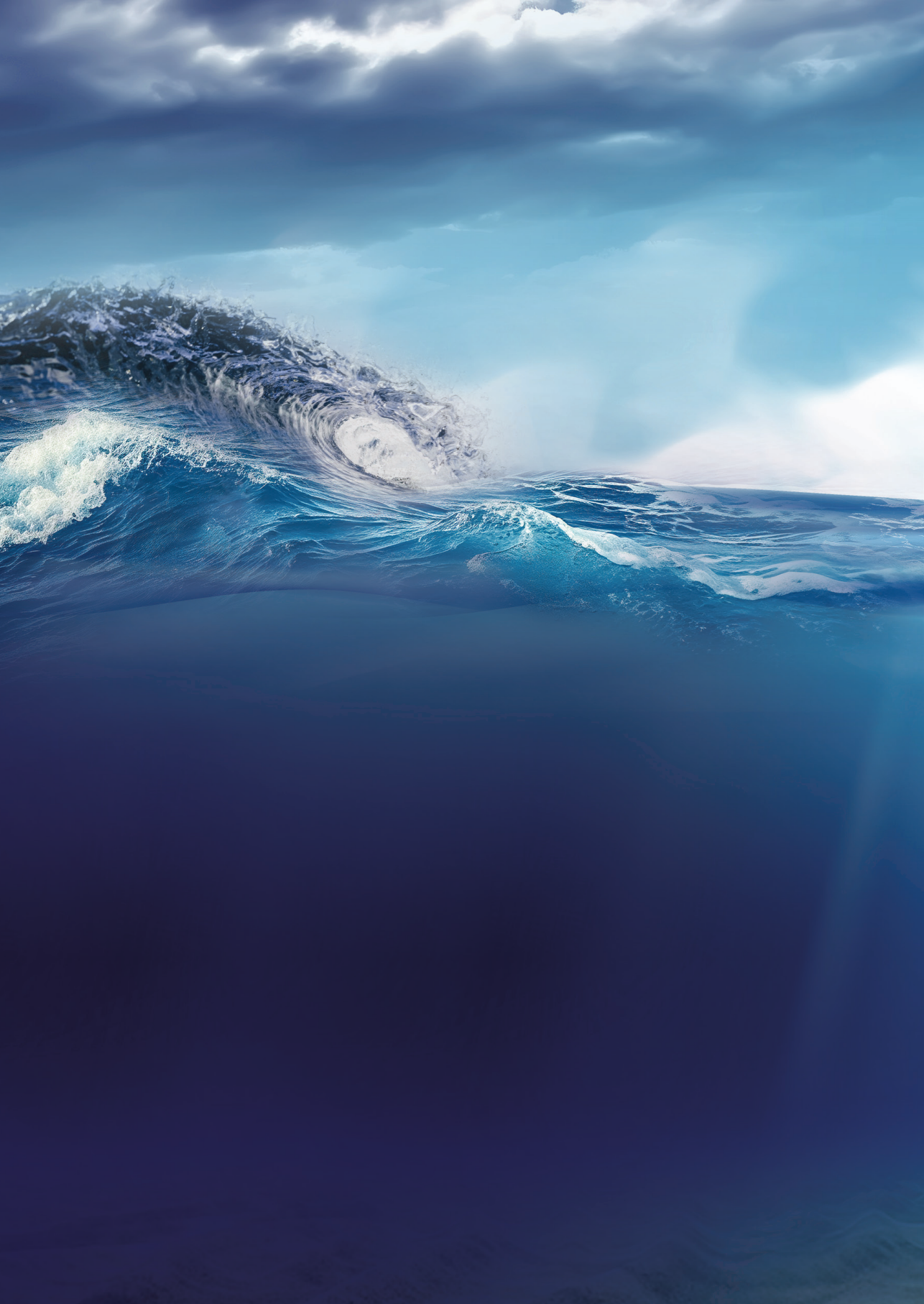
Vervolgens hebben we in **hoofdstuk 6** de 'real-life' effecten van FGM nader onderzocht met behulp van data van Europese gebruikers van FGM om kennis te vergroten ten aanzien van de invloed van FGM op glycemische parameters bij mensen met T1DM en T2DM met verschillende vormen van (suboptimale) glucoseregulatie. Tevens is onderscheid gemaakt ten aanzien verschillen in diabetesbehandeling (insulinepomp, basaal-bolusschema, basale insuline of behandeling zonder insuline) om de effecten in diverse groepen te kunnen beoordelen. Het gebruik van FGM gedurende 24 weken was geassocieerd met verbetering van glycemische parameters bij de meerderheid van de gebruikers van FGM,

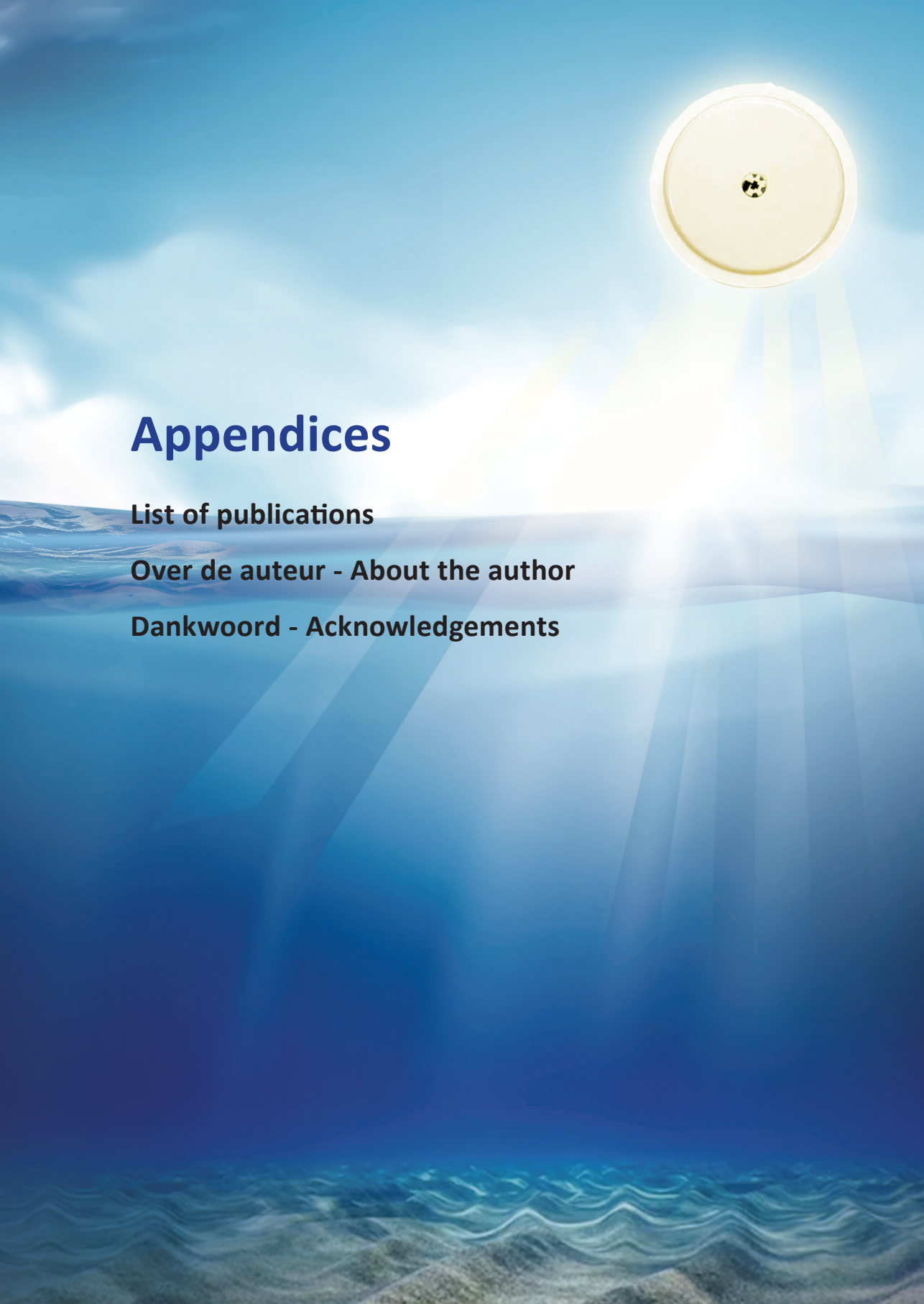
ongeacht de regulatie voor de start met FGM of de behandelmethode. Bij mensen met T1DM of T2DM die werden behandeld met een basaal-bolusschema die een TIR <70% hadden bij aanvang van FGM werd een gelijktijdige verbetering van TIR, tijd in hyper- en hypoglycemie en glucosevariabiliteit geobserveerd, hetgeen stabielere glucosewaarden na 24 weken impliceert. Bij mensen met T1DM met relatief veel tijd in hypoglycemie (>4% TBR), werd een afname van de tijd in hypoglycemie geobserveerd, gepaard met slechts een kleine afname van TIR en minder tijd in ernstige hyperglycemie (glucose > 13.9 mmol/L). Bij mensen met T2DM en behandeling met basale insuline die suboptimaal gereguleerd waren (TIR <70%) voor de start met FGM nam de tijd in hyperglycemie af in combinatie met verbetering van eHbA1c en TIR. Ook in de kleine groep mensen met T2DM die niet met insuline behandeld werden, zagen we in de groep met suboptimale regulatie verbetering van tijd in hyperglycemie, eHbA1c en TIR. Hoewel meer data nodig is om een stellige conclusie te trekken uit deze observatie, suggereren we dat FGM ook van meerwaarde kan zijn bij mensen met T2DM zonder insulinebehandeling die suboptimale glucosewaarden hebben. FGM kan bijdragen aan een verbeterd inzicht in onder andere de effecten van voedingsmiddelen, fysieke activiteit en stress op de glucosewaarden, hetgeen vervolgens kan leiden tot levensstijlmaatregelen om de glycemische instelling te verbeteren.

Verschillen in gebruik van continue glucosemonitoring gerelateerd aan sociaal-economische achtergrond

In de voorgaande hoofdstukken zijn de voordelen van FGM voor een brede populatie mensen met T1DM en T2DM getoond, ongeacht de regulatie bij aanvang van FGM en diverse patiëntkarakteristieken. Gezien de associatie tussen gebruik van FGM en verbetering van glycemische regulatie en kwaliteit van leven is het van groot belang dat mensen met diabetes een gelijke toegang ervaren tot het gebruik van glucosesensoren, ongeacht sociaal-economische en etnische achtergrond. Dit is mede van belang omdat de glucoseregulatie over het algemeen slechter is bij mensen met een lagere sociaal-economische positie. **Hoofdstuk 7** heeft als doel om de invloed van sociaal-economische status (SES) en etniciteit op het gebruik van CGM beter in kaart te brengen. Door middel van een review van beschikbare literatuur beschrijven wij dat mensen met een lagere SES en etnische minderheden minder gebruikmaken van CGM. Een lager inkomen gepaard met beperkte vergoeding van CGM lijkt de belangrijkste factor die deze ongelijkheid verklaart. Verruiming van de vergoedingscriteria leidt tot toename van CGM gebruik in deze groepen, er blijft echter een ongelijkheid in CGM gebruik bestaan als deze factor buiten beschouwing wordt gelaten. Overige geïdentificeerde beïnvloedende factoren zijn het opleidingsniveau en de sociale context van de persoon met diabetes, vooroordelen van artsen tegen mensen met een lagere SES en etnische minderheden, een gebrek aan objectieve criteria voor het voorschrijven van CGM, tijdrovende administratie rondom het voorschrijven van CGM en

beperkte educatie van zorgverleners en patiënten ten aanzien van CGM gebruik. Hieruit vloeien de volgende aanbevelingen voort om het streven naar gelijke beschikbaarheid van CGM te ondersteunen: verruiming van de vergoedingscriteria voor CGM, heldere afspraken over indicaties voor CGM vergoeding, vermindering van de administratielast bij het voorschrijven van CGM, verbeterde educatie van zorgverleners ten aanzien van het gebruik van CGM bij mensen met diverse achtergronden en hun eigen vooroordelen en meer educatieve steun voor mensen met diabetes die starten met CGM. Het verschilt per land welk van deze aanbevelingen het meest relevant is.





Appendices

List of publications

Over de auteur - About the author

Dankwoord - Acknowledgements

List of publications

Lameijer A, Fokkert MJ, Edens MA, Slingerland RJ, Bilo HJG, Van Dijk PR. Determinants of HbA1c reduction with FreeStyle Libre flash glucose monitoring (FLARE-NL 5). J Clin Transl Endocrinol. 2020 Dec;22:100237.

Lameijer A, Fokkert MJ, Edens MA, Gans ROB, Bilo HJG, Van Dijk PR. Two-year use of flash glucose monitoring is associated with sustained improvement of glycemic control and quality of life (FLARE-NL-6). BMJ Open Diabetes Res Care. 2021 Sep;9(1):e002124.

Bakker JJ, **Lameijer A**, Flores Guerrero JL, Bilo HJG, van Dijk PR. Commencement of flash glucose monitoring is associated with a decreased rate of depressive disorders among persons with diabetes (FLARE-NL7). BMJ Open Diabetes Res Care. 2022 Jun;10(3):e002769.

Lameijer A, Lommerde N, Dunn TC, Fokkert MJ, Edens MA, Kao K, et al. Flash Glucose Monitoring in the Netherlands: Increased monitoring frequency is associated with improvement of glycemic parameters. Diabetes Res Clin Pract. 2021 Jul;177:108897.

Lameijer A, Bakker JJ, Kao K, Xu Y, Gans ROB, Bilo HJG, et al. Real-life 24-week changes in glycemic parameters among European users of flash glucose monitoring with type 1 and 2 diabetes and different levels of glycemic control. Diabetes Res Clin Pract. 2023 Jul;201:110735.

Been RA, **Lameijer A**, Gans ROB, van Beek AP, Kingsnorth AP, Choudhary P, van Dijk PR. The impact of socioeconomic factors, social determinants, and ethnicity on the utilization of glucose sensor technology among persons with diabetes mellitus: a narrative review. Ther Adv Endocrinol Metab. 2024 Mar 11;15:20420188241236289.

Over de auteur - About the author

Annel Lameijer is geboren op 19 juli 1988 in het Isala Ziekenhuis in Zwolle en groeide op in Drenthe. Na afronding van haar middelbare school, het Willem Lodewijk Gymnasium te Groningen, studeerde ze geneeskunde aan de Rijksuniversiteit Groningen. Haar artsendiploma behaalde ze in 2013, waarna ze startte met de opleiding tot ziekenhuisarts in het Amsterdam UMC, locatie VUmc. Zij realiseerde zich tijdens deze opleiding dat ze zich verder wilde specialiseren binnen de Interne Geneeskunde en solliciteerde daarom voor de opleiding tot internist in de regio Groningen. In 2016 startte ze als internist in opleiding in ZGT Almelo, waar haar interesse voor de Endocrinologie werd gewekt. Na 2,5 jaar in Twente vervolgde zij haar opleiding in het UMC Groningen om in 2019 te starten als fellow bij de afdeling Endocrinologie.

Via dr. Peter van Dijk en prof. dr. Henk Bilo raakte ze betrokken bij wetenschappelijk onderzoek naar de effecten van het gebruik van glucosesensoren bij mensen met diabetes. Na publicatie van haar eerste artikel op dit onderzoeksgebied startte ze met een promotietraject in 2020. Haar opleiding tot internist-endocrinoloog rondde ze af in 2021 en sindsdien werkt ze als staflid bij de afdeling Endocrinologie in het UMC Groningen. De afgelopen jaren heeft ze haar klinische werkzaamheden gecombineerd met wetenschappelijke activiteiten. De uitkomsten van haar promotietraject worden gepresenteerd in dit proefschrift. Vanaf februari 2024 is ze zowel bij Diabeter als in het UMCG werkzaam als internist-endocrinoloog.

Dankwoord – Acknowledgements

Het is zover! Tijd om mijn dank uit te spreken aan iedereen die, direct of indirect, een bijdrage heeft geleverd aan dit proefschrift. Tevens is dit het moment om terug te blikken op het traject dat achter me ligt. Wat is er veel veranderd de afgelopen 4 jaar, zowel op persoonlijk vlak - met inmiddels een jong gezin - als ten aanzien van de ontwikkelingen op het gebied van diabetestechnologie. Promoveren in combinatie met het laatste deel van mijn opleiding en mijn baan als endocrinoloog was niet gemakkelijk, maar het was zeker van meerwaarde om de onderzoeksuitkomsten direct te kunnen koppelen aan de praktijk op de diabetespoli en vice versa.

Allereerst wil ik alle mensen met diabetes bedanken die hebben deelgenomen aan de studies en bereid waren om relevante gegevens en ervaringen te delen.

Ten tweede wil ik mijn promotieteam bedanken; prof. dr. H.J.G. Bilo, prof. dr. R.O.B. Gans en dr. P.R. van Dijk.

Prof. dr. Bilo, beste Henk, je bevlogenheid, doorzettingsvermogen en toewijding aan het verbeteren van diabeteszorg – op diverse terreinen – vind ik bewonderenswaardig en inspirerend. Hartelijk dank voor je vertrouwen om dit traject te starten en het constructieve meedenken.

Prof. dr. Gans, beste Rijk, veel dank voor je brede visie en het grondig doornemen van de manuscripten om deze naar een hoger niveau te tillen.

dr. van Dijk, beste Peter, ik ben je zeer dankbaar voor de manier waarop je me hebt geënthousiasmeerd om dit traject te starten en je steun gaandeweg. Daarnaast hecht ik veel waarde aan onze prettige samenwerking als collega's. Je bent iemand waar je echt op kunt bouwen, met een hart voor goede zorg, naast een indrukwekkende wetenschappelijke carrière. Ik hoop nog lang met je te kunnen samenwerken.

Graag dank ik de leden van de leescommissie, prof. dr. B.H.R. Wolffenbuttel, prof. dr. T.L. Feenstra en prof. dr. G.D. Laverman voor hun bereidheid om dit proefschrift te beoordelen.

Verder gaat mijn dank uit naar alle medeauteurs voor hun bijdragen. Dear José Luis, Tim, Kalvin and Yongjin, many thanks for the fruitful collaboration.

Ook wil graag mijn collega's van de endocrinologie, interne geneeskunde en Diabeter bedanken voor de prettige samenwerking en gezellige bijeenkomsten.

Lieve vrienden, waaronder mijn paranimfen Sigrid en Jolien, samen mijlpalen vieren, lief en leed delen, genieten van gezellige etentjes en sportieve momenten is goud waard. Lieve Sigrid, wat mooi dat je nu als paranimf naast me staat, na onze avonturen als buurmeisjes vroeger. Inmiddels wonen we verder uit elkaar, maar de basis voor onze vriendschap die in Peize is gelegd maakt dat we aan een half woord genoeg hebben. Lieve Jolien, jij herkent als geen ander hoe fijn het is om weer op te laden tijdens een rondje (samen) hardlopen.

Lieve familie, dank voor jullie onvoorwaardelijke steun en betrokkenheid de afgelopen jaren. Pap, jouw trotse reactie als ik een stap verder was gekomen, op welk front dan ook, deed mij ook even stilstaan bij deze momenten. Fijn dat ik altijd bij je terecht kan. Mam, ik heb veel bewondering voor je doorzettingsvermogen, ondanks alle tegenslagen. Ik wou dat de huidige technologische mogelijkheden beschikbaar waren toen jij jong was. Lieve Egbert en Tineke, het is geweldig hoe jullie altijd voor anderen klaar staan. Dank voor alle hartverwarmende momenten in Peize.

Lieve Lars, na vele hardloopkilometers en omzwervingen door Nederland viel opeens alles op zijn plek in 2020. Dank voor je liefde. Op naar een mooie toekomst samen met onze prachtige zoon Boris. Ik hou van je.

Lieve Boris, ik ben zo gelukkig dat jij er bent! Bijzonder om je bij me te dragen tijdens de afronding van dit proefschrift en geweldig dat je er in volle gezondheid bij bent op de dag van de promotie.