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DEVICE-SPECIFIC EQUATIONS FOR THE ESTIMATION OF GLYCATED HAEMOGLOBIN A1C USING CONTINUOUS GLUCOSE MONITORING METRICS

PhD thesis

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List of Abbreviations

ADA: American Diabetes Association
ADAG study: A1c-Derived Average Glucose study
Bergenstal-GMI: GMI calculated by the equation published by Bergenstal et al. in 2018
CGM: continuous glucose monitoring
CI: confidence interval
CV: the coefficient of variation for glucose
DCCT: Diabetes Control and Complications Trial
DG7: Dexcom G7
EDIC: Epidemiology of Diabetes Interventions and Complications
eGFR: estimated glomerular filtration rate calculated by the CKD-EPI equation
FL3: Freestyle Libre 3
GEE: generalised estimating equation
Guardian-3: Medtronic Guardian Sensor 3
Guardian-4: Medtronic Guardian 4 Sensor
Guardian-3 GMI: the device-specific GMI equation for Guardian Sensor 3
Guardian-4 GMI: the device-specific GMI equation for Guardian 4 Sensor
GLUT1: glucose transporter 1
GMI: glucose management indicator
GOx: glucose oxidase
HbA1c: glycated haemoglobin A1c
HbC: haemoglobin C variant

HbS: haemoglobin S, sickle haemoglobin variant
HbSC: haemoglobin S-C variant
HPLC: high-performance liquid chromatography
IDGC-MS method: standard isotope dilution gas chromatography–mass spectrometry method
IFCC: International Federation of Clinical Chemistry and Laboratory Medicine
isCGM: intermittently-scanned continuous glucose monitoring
MARD: mean absolute relative difference
MSP: Medtronic Simplera
rtCGM: real-time continuous glucose monitoring
SD: standard deviation
SMBG: self-monitoring of blood glucose
TAR: time above range, i.e., the percentage of time spent in the glucose range of above 10 mmol/L
TBR: time below range, i.e., the percentage of time spent in the glucose range of below 3.9 mmol/L
TIR: time in range, i.e., the percentage of time spent in the glucose range of 3.9-10 mmol/L
TITR: time in tight range, i.e., the percentage of time spent in the glucose range of 3.9-7.8 mmol/L
TSH: thyroid-stimulating hormone
T1D: type 1 diabetes melliuts
T2D: type 2 diabetes mellitus
UKPDS: United Kingdom Prospective Diabetes Study

Units of measurement

To convert HbA1c[%] and GMI[%] (as absolute values) to mmol/mol, the conversion formula is: HbA1c(mmol/mol)=(HbA1c[%]−2.15)x10.929, and GMI(mmol/mol)=(GMI[%]−2.15)x10.929.

To convert glucose concentration to mg/dl, multiply values in mmol/l by 18.015.

1. Introduction

1.1. Scope of the problem

Type 1 diabetes is a chronic disease caused by the autoimmune destruction of pancreatic beta cells, resulting in relative and, ultimately, absolute insulin deficiency. If untreated, type 1 diabetes is a fatal illness, while with proper treatment, people with type 1 diabetes can live a full life, with a life expectancy approaching or even reaching that of the non-diabetic population. Even today, however, achieving near-normoglycaemia in type 1 diabetes is difficult, as observational data show. In the United States, between 2016 and 2018, just over 21% of adults with type 1 diabetes were able to achieve the HbA1c target of below 7% (1). The situation has improved since then, as rapidly evolving technologies enable more patients to achieve glycaemic targets. For example, real-world data with an advanced hybrid closed-loop system, Minimed 780G, showed that 79% of type 1 diabetes patients using this system achieved an estimated HbA1c (GMI) target of below 7% (2). However, not everyone can afford or find these technologies suitable, and these systems still have their limitations. Thus, despite clear improvements, more recent data showed that by 2021-2022, only 26% of type 1 diabetes patients in the United States had achieved an HbA1c target of below 7% (3).

In a joint paper published by the IDF Atlas and the T1D Index team, it was estimated that in 2025, 9.5 million people worldwide were living with type 1 diabetes, including 1.85 million children, adolescents and young adults under the age of 20 (4). The authors estimated that there would be an additional 4.1 million people living with type 1 diabetes if their life expectancy were equal to that of the general population (the so-called „missing prevalence"). There is a lack of high-quality data on the prevalence of type 1 diabetes in Hungary. The paper mentioned above estimates that approximately 31,000 people (including 4600 under the age of 20) are currently living with type 1 diabetes in Hungary (4), although the real number may be somewhat higher. Importantly, both the incidence and the prevalence of type 1 diabetes are rising worldwide, the reasons for which are multifactorial (4, 5).

Chronic hyperglycaemia is the most important risk factor for the development of chronic diabetic complications. Hyperglycemia adversely affects various metabolic pathways, such as the polyol pathway, the hexosamine biosynthetic pathway, and

glucose autoxidation, and is responsible for increased synthesis of advanced glycation end-products. Additionally, it leads to hexokinase-2-driven glycolytic overload and increased activities of the cyclooxygenase, lipoxygenase, and pyruvate kinase enzymes (6). Through these mechanisms, chronic hyperglycaemia can lead to the development of chronic macrovascular (atherosclerotic cardiovascular diseases) and microvascular (retinopathy, diabetic kidney disease, neuropathy) complications.

The landmark Diabetes Control and Complications Trial (DCCT) and its longitudinal observational follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, demonstrated that targeting near-normoglycemia with intensive insulin therapy reduced the risk of developing (or progression of) chronic micro- and macrovascular complications, as compared to the so-called conventional therapy that aimed to avoid symptomatic hyperglycaemia and ketonuria only (7, 8). In the original DCCT, at a mean follow-up of 6.5 years, intensive insulin therapy reduced the risk of developing retinopathy by 76%, and in the secondary prevention cohort, it slowed the progression of retinopathy by 54% (7).

Based on 20-25 years of follow-up data from the DCCT-EDIC, roughly every 10% increase in the weighted average of a patient's HbA1c values (e.g. from 7% to 7.7% or from 8% to 8.8%) increased the risk of developing proliferative diabetic retinopathy or clinically significant progression of retinopathy by approximately 1.6 times (9). In the Pittsburgh Epidemiology of Diabetes Complications Study, each 1% increase in HbA1c (e.g. from 7% to 8% or from 8% to 9%) was associated with a 13–26% higher relative risk of cardiovascular disease in people with type 1 diabetes (10). The DCCT-EDIC, as well as other large observational studies with several years of follow-up (11, 12), demonstrated not just the deleterious effect of chronic hyperglycaemia but also the strong predictive value of HbA1c for the development of chronic diabetic complications.

1.2. HbA1c: the gold standard glycaemic metric

HbA1c is a subfraction of glycated haemoglobin, which forms through a non-enzymatic glycation process where glucose creates a ketoamine on the N-terminus of the haemoglobin beta chain. This reaction is highly dependent on extracellular glucose concentrations. Consequently, HbA1c reflects the *weighted* average of plasma glucose

levels over the mean lifespan of an individual's erythrocytes, generally 120 days (13, 14). A small study in type 2 diabetes patients showed that the mean plasma glucose concentration of the preceding month accounted for 50% of the HbA1c level. In comparison, the second month accounted for 25%, and the third and fourth months together accounted for another 25% of the HbA1c level (15). This weighted characteristic explains why HbA1c is traditionally considered to reflect the average plasma glucose level over the previous 2-3 months (15).

While the first study reporting elevated levels of glycated haemoglobin A1c in people with diabetes was published in 1969 (16), it were the landmark DCCT and UKPDS studies in type 1 and type 2 diabetes, recpectively (7, 17), published in 1993 and 1998, that utilised HbA1c as the gold standard marker of chronic hyperglycaemia and as the strongest known predictive marker for developing chronic diabetic complications. The median HbA1c reached in the intensive-therapy group of the DCCT was 7% (53 mmol/mol), a value that has become the cornerstone of therapeutic goals for type 1 diabetes over the next 30 years. Even in 2025, major international diabetes organisations recommend a HbA1c goal of less than 7% for most nonpregnant adults, children and adolescents with type 1 diabetes, with a tighter goal of less than 6.5% if it can be safely achieved with a low level of hypoglycaemia and less tight control for elderly or frail individuals or people with a high risk of hypoglycaemic events (18-20).

The emergence of continuous glucose monitoring (CGM) has transformed the way we approach glycaemic control. However, none of the CGM metrics have been investigated in large, prospective clinical trials regarding their predictive value for chronic diabetes complications (21). Thus, even when determining targets for modern CGM metrics, expert committees had to rely indirectly on HbA1c. For example, the recommendation that the percentage of time spent in the glucose range of 3.9-10 mmol/L (TIR) should be more than 70% is based on a study in which, on average, a TIR of 70% corresponded with an HbA1c of 7% (22).

1.3. The benefits and caveats of reporting HbA1c

1.3.1. HbA1c: strengths and benefits

As discussed earlier, HbA1c is strongly associated with mean plasma glucose over the preceding 2-3 months (18) and has a strong predictive value for the development of chronic diabetic complications, validated in large prospective studies and long-term observational studies (7-9, 11, 12, 17, 23). However, HbA1c has other benefits that should be emphasised.

Besides its favourable cost and accessibility, HbA1c measurement is a well-standardised test in laboratories that follow the reference method developed by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) (24).

Furthermore, several small studies suggest that HbA1c may have an additional value in predicting chronic diabetic complications compared to mean plasma glucose alone (25-28). HbA1c is an intracellular, stable, early-stage glycation product of haemoglobin (29), and besides mean plasma glucose, several factors affect its formation. These include transmembrane glucose gradient (e.g., glucose transport by GLUT1 and/or glycolytic enzyme activity) (30, 31), intracellular pH and intracellular environment (30), antioxidant capacity (27), deglycation of haemoglobin, and kinetic differences in HbA1c glycation (32). For example, a study by Dunmore et al. demonstrated that variations in the level of the deglycating enzyme fructosamine-3-kinase can significantly alter the level of HbA1c at a given mean plasma glucose level (33). Many of these factors may also affect the glycation of target tissues, such as retinal, renal, and vascular cells. It is well known that some people have higher HbA1c values than would be expected based on their mean glucose levels (25-27, 30-35). In the literature, these patients are referred to as high glycators, or those with a high glycation index or a high glycemic gap. Several observational studies have shown that having a high-glycation phenotype may be associated with an increased risk of micro- and macrovascular complications (25-28). Although these studies are small and have numerous limitations, they may reflect the fact that increased glycation occurs not only in erythrocytes but also in other target organs in these individuals. Reporting mean glucose levels alone could miss this unique property of HbA1c.

1.3.2. HbA1c: limitations and caveats

1.3.2.1. Factors affecting HbA1c besides mean glucose

Several pathological states are known to affect HbA1c, irrespective of the mean glucose level. These include moderate and severe chronic kidney disease, anaemias and haemoglobinopathias, thyroid diseases, chronic liver disease, acute blood loss, recent blood transfusions, intravenous iron supplementation, and corticosteroid treatment (36). Any state that affects erythrocyte turnover will alter the age distribution of red blood cells and subsequently affect HbA1c levels (36).

However, physiological states and patient characteristics can also independently affect HbA1c. HbA1c levels drop during pregnancy because of increased erythrocyte turnover (37). Race and ethnicity can also significantly affect HbA1c values. HbA1c tends to be 0.3–0.4 percentage points higher among Black patients relative to White patients for a given mean glucose (38, 39). In one study, Kartel et al. reported that the glycation properties of Asians, Latinos, and multi-ethnic patients were not significantly different from those of White patients, and the slope of the association between mean glucose and HbA1c did not differ significantly across racial/ethnic groups (38). Although the jury is still out there, whether race- and ethnicity-specific differences should impact clinical decision-making (38), the American Diabetes Association (ADA) currently recommends against race- and ethnicity-specific assessment of HbA1c in daily clinical practice (18). In its scientific statement, ADA notes that the variability in the HbA1c - mean glucose relationship within races is greater than between races (18, 19, 39).

Altered erythrocyte lifespan is a well-known confounder of HbA1c interpretation in several pathological conditions (36). However, one study has shown that even otherwise healthy individuals can have widely different erythrocyte lifespans, sufficient to alter the HbA1c–mean glucose relationship to a clinically significant extent (40). Using a method of biotin-labelled red blood cells in 6-6 individuals with and without diabetes, free from any condition known to alter erythrocyte lifespan, the authors reported that the mean age of circulating erythrocytes was 38 to 59 days. It corresponded to a mean erythrocyte lifespan of 90 to 125 days. According to their model, if a patient with „average” erythrocyte lifespan (i.e., with a mean age of circulating erythrocytes of 47.9 days) has a HbA1c of 8.6%, that would correspond to a HbA1c of 7.5% if the same

patient would be at the lower end of the spectrum (with a mean age of circulating erythrocytes of 38 days), and to a HbA1c of 9.9% if the patient would be at the higher end of the spectrum (with a mean age of circulating erythrocytes of 59 days). While there are several limitations to this study, including the small sample size, the magnitudes of these differences are comparable to those observed in daily clinical practice between the measured and the estimated HbA1c (41-43). Adjusting HbA1c for the mean age (or lifespan) of the patient's erythrocytes would be extremely beneficial. However, measuring the mean age or lifespan of erythrocytes is complicated and time-consuming, and is currently not an option in daily clinical practice (44).

Haemoglobin variants can interfere with HbA1c determination to a degree that depends on the method used. Haemoglobin A1c determination may lead to highly distorted results in all patients who are homozygous for HbS or HbC, have HbSC disease, or have any condition that significantly affects erythrocyte survival. Heterozygous mutations may remain unnoticed; however, if their presence is known, clinicians should inquire about the limitations of the specific method used for HbA1c determination. (18, 45)

1.3.3.2. The „blind spots" of HbA1c: hypoglycaemia and glucose variability

HbA1c has other important limitations as a marker of glycaemic control. It doesn't reflect hypoglycaemia burden, a critical aspect of diabetes management. Hypoglycaemia, as well as fear of hypoglycaemia, can impair quality of life and increase diabetes-related psychological stress in type 1 diabetes. Hypoglycaemia can lead to serious (sometimes fatal) consequences like transient impairment of cognition, seizures, falls, accidents, arrhythmias and even atherosclerotic plaque ruptures. Hypoglycaemia can be a major obstacle to achieving adequate glycaemic control. (46)

HbA1c also does not inform about glycemic variability, a phenomenon that is increasingly acknowledged as a significant risk factor for both acute and chronic diabetic complications (47-49).

1.4. Glycated serum proteins as glycaemic markers

Given the limitations of HbA1c, particularly how it's influenced by red blood cell turnover and hematologic disorders, there has been interest in other glycated molecules as glycemic markers. Fructosamine measures all glycated proteins in the serum, of

which glycated albumin constitutes the largest part. Nonimmunoglobulin serum proteins have a half-life of approximately 14-21 days; thus, fructosamine and glycated albumin reflect glycaemic control over a significantly shorter period than does HbA1c. Another important difference is that HbA1c is a marker of intracellular glycation, while glycated serum proteins reflects the rate of extracellular glycation. While glycated serum proteins are free from many confounders affecting HbA1c interpretation, they have their own shortcomings. Apart from mean plasma glucose, many factor affects their levels. Perhaps most importantly, there are no large prospective studies linking glycated serum proteins to chronic diabetic complications. Thus, measurement of fructosamine and/or glycated albumin can be helpful in some cases, e.g., when HbA1c is clearly unreliable, or we want to assess glycaemic control over a short, recent period of time. However, glycated serum proteins are not a reasonable alternative to HbA1c for most patients. (18, 50)

1.5. Assessing glycaemic control by self-monitoring of blood glucose (SMBG)

The emergence of SMBG in the late 1970s and early 80s, with the implementation of HbA1c and intensive insulin therapy, revolutionised the clinical care of type 1 diabetes patients (51). While HbA1c strongly correlates with mean plasma glucose over the preceding 2-3 months, self-monitoring of blood glucose allows for the detection of daily fluctuations, hypoglycemic and hyperglycemic events, and consequently, better adjustment of insulin dosages. Register data shows lower HbA1c with increasing numbers of daily fingerprick blood glucose measurements (52). Although the optimal number of daily measurements likely varies from person to person, guidelines indicate that many type 1 diabetes patients require 6-10 fingerprick blood glucose measurements daily for optimal glycemic control, unless continuous glucose monitoring is used (20, 53). However, even with frequent blood glucose measurements using SMBG, many fluctuations remain unnoticed (both nocturnal and daytime), and numerous hypoglycemic events occur, even in patients known to have preserved hypoglycaemia awareness (54). Additionally, performing frequent blood glucose measurements can be a significant burden on patients, and many patients who use SMBG perform only a very limited number of fingerprick measurements. These limitations of SMBG were the driving force behind the development of continuous glucose monitoring (CGM).

1.6. Continuous glucose monitoring

CGM devices measure glucose concentrations subcutaneously in the interstitial fluid every 1-15 minutes (1-5 minutes in the case of most modern devices), and either continuously transmit these values to a smartphone, smartwatch or an insulin pump (real-time CGM, rtCGM) or require intermittent scanning with a reader or smart device (intermittently scanned CGM, isCGM). Interstitial glucose concentrations correlate strongly with blood glucose concentrations. (19)

Continuous glucose monitoring has revolutionised diabetes management and is recommended as the standard, primary glucose measurement method for most children, adolescents, and adults with type 1 diabetes (19, 55). It can be used along with multiple daily insulin injections or can be integrated with an insulin pump or a so-called „smart pen" (56). Some CGM devices require regular calibrations with fingerprick blood glucose measurement, while others are factory-calibrated.

1.6.1. The benefits of CGM in improving glycaemic control

Several randomised clinical trials (57-60), meta-analyses (61, 62), as well as observational data (63, 64), indicate that continuous glucose monitoring improves glycaemic control, reduces HbA1c in adults and may reduce it in children and adolescents (55, 65). It reduces hypoglycaemia burden in all age groups, and, generally, it improves diabetes-related quality of life (55, 57-65). The greatest benefit is seen when continuous glucose monitoring is integrated into an automatic insulin delivery system (66).

1.6.2. The benefits of CGM in assessing glycaemic control

1.6.2.1. CGM-derived glycaemic metrics

The benefits of continuous glucose monitoring are not limited to achieving better glycaemic control and less hypoglycemia; it also enables a more detailed assessment of glycaemia than HbA1c or SMBG alone. CGM metrics that should be part of every CGM report were standardised in a consensus document in 2019 (67). These include mean glucose concentration, percentage of time spent in different glucose ranges (time in range [TIR]: 3.9-10 mmol/L, time below range [TBR]: <3.9 mmol/L, time above

range [TAR]: > 10 mmol/L), coefficient of variation (CV) of glucose values, and sensor usage as a percentage of time. However, while all these metrics are useful in many ways, direct evidence linking them to long-term diabetic complications is still lacking (21). Thus, from the very beginning, there was an apparent demand from patients, caregivers, healthcare professionals, and researchers to link continuous monitoring data to HbA1c, a familiar parameter with a strong predictive value for chronic diabetic complications (42). Estimating HbA1c from CGM data is calculated from the CGM-derived mean glucose value, as it has the strongest correlation with HbA1c among all CGM metrics (68).

1.6.2.2. Estimating HbA1c from CGM data

The way we estimate HbA1c from CGM-derived mean glucose has changed over the years. Although there were some data linking average blood glucose levels to HbA1c based on the DCCT (69), more solid evidence came from the A1c-Derived Average Glucose (ADAG) Study (70). This international study with 507 nondiabetic/T1D/T2D participants revealed a strong linear correlation between HbA1c and mean glucose (CGM and/or blood glucose derived) over a 3-month period, and an equation was derived that enabled the estimation of one from the other (70). In 2017, a new equation was proposed, derived from a larger dataset and utilising newer CGM technology (71). Based on this dataset, as well as additional data from another multicentre, randomised clinical trial (72), Bergenstal et al. published a revised equation in 2018 that estimates HbA1c from CGM-derived mean glucose (42). With all published equations, however, including this latest one, significant differences remained between the estimated HbA1c and the laboratory-measured HbA1c in many individuals (42, 70, 71). Thus, to help patients, caregivers, healthcare professionals and researchers avoid confusion, Bergenstal et al. proposed a new term for the estimated HbA1c value obtained through their equation. Rather than calling it estimated HbA1c, they proposed the term „glucose management indicator" (GMI) (42). The glucose management indicator became part of the 10 standardised CGM metrics that should be reported in every CGM report, according to a landmark consensus document published in 2019 (67).

The currently used GMI equation, developed by Bergenstal et al., is based on data from four clinical trials involving a total of 528 patients (T1D: n=456 [86%], T2D: n=72

[14%]) aged ≥ 18 years (42, 57, 71-74). Importantly, all patients used Dexcom G4 and G5 CGM systems. Their characteristics are only partially available. In a subgroup of 387 patients, the age range (20-78 years) and the proportion of White patients (83%) were reported (71). Known confounding factors regarding HbA1c interpretation, such as anaemias, haemoglobinopathies, and chronic renal disease, were considered as exclusion criteria in some, but not all, substudies.

The so-called GMI equation to estimate HbA1c from CGM-derived mean glucose has been reported by Bergenstal et.al. as follows:

GMI (%)=3.31+0.43×mean glucose (mmol/l)

GMI (%)=3.31+0.0239×mean glucose (mg/dl). (42)

1.7. The glycaemic gap

GMI and laboratory-measured HbA1c strongly correlate with each other. While Bergenstal's original paper didn't report Pearson's r, other studies reported a Pearson's r of 0.82-0.86 (75, 76).

However, the two parameters significantly differ in many individuals (21). Even in Bergenstal's original paper, 28% of the study population had a clinically significant difference of ≥ 0.5% between the GMI and the laboratory-measured HbA1c (42). Significant individual differences were also observed when HbA1c was estimated using other equations (70, 71).

The difference between the laboratory-measured HbA1c and the GMI is called the glycaemic gap (glycation gap). Historically, the glycaemic gap also refers to the difference between the laboratory-measured HbA1c and glycaemia assessed through serum fructosamine measurement (also a marker of extracellular glucose concentrations). Although many transient factors may cause discordance between the HbA1c and the GMI/fructosamine, several studies indicate that the glycation gap is often consistent within an individual (77, 78). A twin study also reported a remarkable hereditary component of the HbA1c – fructosamine gap that may be connected to genes affecting glycation and deglycation processes and/or erythrocyte lifespan (79).

1.7.1. Reasons for the glycaemic gap (HbA1c-GMI gap)

Individual differences between the laboratory-measured HbA1c and the GMI can originate from three primary sources:

1. Factors that affect HbA1c (independently from mean plasma glucose)
2. Factors that affect interstitial glucose measurement (independently from plasma glucose)
3. Factors that affect and limit the applicability of the original GMI equation

1.7.1.1. Factors that affect HbA1 (independently of mean plasma glucose)

These factors have been discussed earlier. Physiological states (e.g., pregnancy) (37), patient characteristics (e.g., race and ethnicity) (38, 39), individual differences in mean erythrocyte age (erythrocyte lifespan) (40), as well as glycation- and deglycation processes (32, 33), and numerous pathological conditions (36) can affect HbA1c apart from mean plasma glucose concentration. Furthermore, HbA1c indicates the weighted average of mean plasma glucose during the preceding 2-3 months, with a larger effect from the preceding month (12). Thus, significant changes in glycaemia during a relatively brief, recent period have a greater impact on HbA1c than on GMI.

1.7.1.2. Factors that affect interstitial glucose measurement (independently of plasma glucose)

Although the interstitial glucose concentrations measured by CGMs correlate strongly with blood glucose levels, some limitations should be noted. Most modern CGM devices measure glucose concentrations using glucose oxidase (GOx) enzyme technology (80). Although it is a highly accurate method, it has certain limitations relative to the gold standard isotope dilution gas chromatography–mass spectrometry (IDGC-MS) method (81), or even to the hexokinase method, which is often considered the gold standard in clinical practice (82). GOx sensors utilise an enzymatic electrochemical reaction in which the oxidation of glucose produces hydrogen peroxide. This generates an electrical current that is directly proportional to the interstitial glucose concentration. A crucial step in every CGM device development, as well as the factory calibration process and/or fingerstick calibration, is to ensure that the electrical signal generated by the enzymatic reaction is accurately converted into a glucose value. Many

factors can affect this process, of which the collection of comparator data seems to be a critical one. The heterogeneous procedures used in CGM development may have a significant impact on why different types of CGM devices can display varying glucose values and CGM metrics, even when worn simultaneously by the same individual. (83)

Fingerprick calibration is not required for most new-generation, factory-calibrated CGM devices; however, it remains optional or even mandatory for some devices, potentially impacting their accuracy.

Other sources of possible errors include, among others, inherent instability and degradation of the GOx enzyme (84), as well as interferences with some chemical substances like paracetamol, hydroxyurea, and high-dose vitamin C (80).

Another source of error is that CGMs measure the interstitial glucose concentration in the subcutaneous tissue. Interstitial glucose concentration follows plasma glucose concentration, with an average lag time of 5-15 minutes (19). Although it can be confusing for patients, it typically doesn't impact long-term glycemic metrics, such as GMI. However, when a CGM device is inserted into the subcutaneous tissue, it causes mechanical injury followed by a healing process, and also provokes an immune response through foreign-body reaction (85). These immunological reactions can affect the accuracy of the CGM device, for example, by forming a so-called cell-based metabolic barrier around the sensor. Thereby, sensors are often somewhat inaccurate in the first days and last days of their wearing time, but sometimes can be affected throughout their lifespan. Furthermore, even subtle bleeding at the insertion site can affect sensor accuracy. (85)

CGM devices can show falsely low glucose values under mechanical stress (80). This well-known phenomenon is called biomechanical hypoglycaemia or „compression low", and, if it happens often, can cause discrepancies between HbA1c and CGM-derived mean glucose values, thereby affecting GMI. Most CGM devices have a mandatory alarm reaction if the interstitial glucose level is below 3 mmol/L, so long-lasting hypoglycemia (false or true) is infrequent with modern sensors (not every patient notices alarms, however, especially during the night).

Given the several difficulties associated with measuring interstitial glucose concentrations, there is an unmet need for better standardization of CGM devices (21, 86-88). Today, approval of CGM devices is mostly based on their mean absolute relative differences (MARDs) and error grid analyses against laboratory blood glucose measurements (89). This process, however, is a limited assessment of sensor accuracy and allows for certain biases. For example, it allows larger errors in the lower and higher ends of the glucose range (90).

1.7.1.3. Factors that affect the applicability of the original GMI equation

The original GMI equation was formulated based on data from Dexcom G4 and G5 CGM systems. Even Bergenstal et al. noted in their original paper that it may not apply equally well for other types of CGM systems (42). Another source of bias can be the application of the original GMI equation to a population that is markedly different from that of the derivative studies (57, 72-74).

2. Objectives

Based on the above and our daily experiences with Medtronic Guardian Sensor 3 (Guardian-3) and Medtronic Guardian 4 Sensor (Guardian-4) CGM systems, we hypothesised that the currently used GMI equation (Bergenstal-GMI) could be suboptimal for other than the Dexcom G4 and Dexcom G5 sensors, and that device-specific GMI equations could lead to better HbA1c estimation. Thus, in an adult population with type 1 diabetes free of known pathophysiological factors affecting HbA1c measurement, we aimed to

1., develop sensor-specific GMI equations for the Guardian-3 and Guardian-4 sensors (Guardian-3 GMI, Guardian-4 GMI);

2., compare overall performance of the Bergenstal-GMI and the sensor-specific GMI equations; as well as

3., investigate the association (using a modified Bland-Altman analysis (91, 92)) between the magnitude of the so-called glycaemic gap (the difference between HbA1c and GMIs with each equation) and HbA1c. (93)

We conducted two studies using the same methodology, given that our first study (Study-1) was underpowered to develop an accurate and precise sensor-specific GMI equation for the Guardian-4 sensor (93). Thus, the second study (Study-2) was essentially an extension of the first study, with a sufficiently large sample size for the Guardian-4 sensors. The results of Study-2 have not yet been published (94).

3. Methods (same for Study-1 and Study-2)

3.1. Study design

We conducted two single-centre, observational cohort studies of adult type 1 diabetes patients receiving care at our tertiary diabetes centre at the Department of Internal Medicine and Oncology, Semmelweis University, Budapest, Hungary in JAN/01/2021-JUN/17/2024 (first study, Study-1) and JAN/01/2021-DEC/09/2025 (second study, Study-2).

At the baseline visit, demographics, anamnestic data, current medications, laboratory data, and CGM metrics for the last 60 to 90 days were collected from electronic health records. To improve modelling, we included (if available) an additional visit with a second HbA1c and preceding CGM metrics ≥ 90 days after baseline. Using the CGM-derived mean glucose, we estimated the measured HbA1c values. (93)

The retrospective studies were approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (SE RKEB number: 273/2023 [Study-1] and 163/2025 [Study-2]).

3.2. Participants

Type 1 diabetes patients aged 18–75 years were eligible for inclusion in the current studies if they had an HbA1c measurement from the Central Laboratory of Semmelweis University, a complete blood count, and a serum creatinine assessment during the baseline visit, and were regular users (≥ 70 % use during the preceding 60 days) of either Guardian-3 or Guardian-4 CGM devices in Study-1 and Guardian-4 CGM devices in Study-2. Exclusion criteria were any co-morbidities or conditions known to affect HbA1c or any significant therapeutic change (including CGM or insulin pump initiation) within six months preceding baseline **(Table 1)**. (93)

Table 1 *– Eligibility and exclusion criteria (93)*

1. **Eligibility criteria**
• Type 1 diabetes
• Age 18 years or older at baseline
• At least 70% use of a Medtronic Guardian Sensor 3 or Medtronic Guardian 4 Sensor continuous glucose monitoring (CGM) device during the 60-day period corresponding to the HbA1c measurement
• At least 6-month experience with continuous glucose monitoring at baseline
• HbA1c determined at the Department of Laboratory Medicine, Semmelweis University with high-performance liquid chromatography (HPLC) method
• Complete blood count and serum creatinine determination at baseline. (If a patient had a second HbA1c – glucose management indicator [GMI] cycle analysed, blood count and serum creatinine were accepted within 1 year.)
2. **Exclusion criteria**
• Anaemia (haemoglobin level below the normal range)
• Micro- or macrocytosis (mean cellular volume [MCV] below or above the normal range)
• Any known haematologic disorder (e.g. thalassaemia)
• Significant therapeutic change (including CGM or pump initiation) in the last six months before baseline
• Pregnancy or delivery in the last six months before baseline
• Ovulation induction treatment or assisted reproduction in the last six months before baseline
• Any major surgery or significant acute illness in the last 3 months before baseline
• Estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 calculated by the CKD-EPI equation
• Liver cirrhosis
• At least 3 fold elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above the upper limit of normal
• Uncontrolled thyroid disease (thyroid-stimulating hormone [TSH] outside the normal range)
• Unknown thyroid function status, defined as no TSH determination on the day of HbA1c determination if the patient has known thyroid disease or lacking TSH determination within one year if the patient has no known thyroid disease
• Venous iron supplementation or haemotransfusion within 6 months before baseline
• Ongoing treatment with hydroxyurea within 6 months before baseline
• Ongoing treatment with systemic corticosteroids within 6 months before baseline
3. Remarks
• Latent iron deficiency was not considered as an exclusion criterion as long as the patient had normal haemoglobin and MCV values
• Prophylactic or maintenance oral iron supplementation was not considered an exclusion criterion if the patient had normal haemoglobin and MCV values
• Mild to moderate haemoconcentration is common when patients present for a blood test. Therefore, moderately elevated red blood cell count or haematocrit (within 10% of the upper limit of normal) was not considered as an exclusion criterion
• None of our patients were known to be regularly taking paracetamol or high doses of vitamin C (more than 500 mg per day). However, these products are available over the counter in Hungary.

- Patients were eligible for the use of a second GMI-HbA1c pair if they satisfied all inclusion and no exclusion criteria at a second timepoint. However, we accepted complete blood count, serum creatinine test, and TSH results within a year before the second timepoint

3.3. Measurements

Using patients' electronic medical records, the following data were obtained: demographics (age, sex, type and duration of diabetes); data on diabetes treatment for the last 6 months (type of insulin preparations, treatment regimen: multiple daily insulin injections or hybrid closed-loop insulin pump – MiniMed 780G), co-morbidities and complications (diabetic retinopathy, albuminuria, coeliac disease, thyroid disease, and hypertension), oral contraceptive, iron, and folic acid supplementation use.

The following laboratory tests were obtained: HbA1c, complete blood cell count, serum creatinine, estimated glomerular filtration rate calculated by the CKD-EPI equation (eGFR), and thyroid function test (TSH). Except for HbA1c, all measures could have been done in local laboratories. HbA1c was measured in the Central Laboratory of Semmelweis University using high-performance liquid chromatography (HPLC) on a Tosoh Automated Glycohemoglobin Analyzer HLC-723G11 device (Tosoh Europe N.V. Tessenderlo, Belgium). The central laboratory follows ISO 9001 standards for quality management.

All patients at our diabetes centre receive a baseline and continuous in-person education on the use of CGM devices and accompanying software. For the current studies, users of Guardian-3 and Guardian-4 CGM systems were included. Guardian-3 is an adjuvant CGM system that requires at least two fingerstick calibrations per day, providing a mean absolute relative difference (MARD) of 8.7-10.6% in adults, depending on the insertion site and the number of calibrations performed (95). Guardian-4 is a factory-calibrated CGM system that does not require fingerstick calibration, but optional calibration is possible. When used without calibration but otherwise appropriately, MARD in adults is 10.6% (90). The following standard CGM metrics were collected from Medtronic CareLink™ system software for 60 to 90 days preceding the HbA1c test: GMI (Bergenstal-GMI), mean glucose, coefficient of variation (CV), time in range (TIR; % of time with glucose 3.9–10.0 mmol/l), time below range (TBR; % of time with glucose

< 3.9 mmol/l), time above range (TAR; % of time with glucose > 10 mmol/l), sensor usage (%).

For further analysis, we selected the 60-day GMI based on a preliminary correlation analysis of 14-, 30-, 60-, and 90-day Bergenstal-GMI and HbA1c for the baseline visit in Study-1, as this value showed the strongest correlation with HbA1c (Table 2). (93) This 60-day interval may reflect the fact that HbA1c reflects the weighted average of plasma glucose levels over the mean lifespan of an individual's erythrocytes (~120 days), where glycaemia during the preceding 1-2 months has a greater effect on HbA1c (15). Consequently, HbA1c is traditionally considered to reflect the average plasma glucose level over the previous 2-3 months (15). However, the correlation between Bergenstal-GMI and HbA1c remained almost equally strong across all investigated timeframes (14, 30, 60, and 90 days), probably reflecting the relative stability of glycemic control in our population (partly explained by the eligibility and exclusion criteria – Table 1) (93).

Table 2 *– Pearson correlation coefficients (r) with their respective 95% confidence intervals (95% CI) between baseline HbA1c and 14-, 30-, 60- and 90-day Bergenstal-GMI. Study-1. (93)*

	GMI 14 days	**GMI 30 days**	**GMI 60 days**	**GMI 90 days**
	r [95% CI]	**r [95% CI]**	**r [95% CI]**	**r [95% CI]**
HbA1c (Guardian-3 users)	0.844 [0.765;0.898]	0.868 [0.8;0.914]	0.879 [0.817;0.922]	0.875 [0.811;0.919]
HbA1c (Guardian-4 users)	0.898 [0.75;0.961]	0.938 [0.843;0.976]	0.95 [0.872;0.981]	0.944 [0.857;0.979]

3.4. Statistical analysis

Baseline characteristics are reported as means and standard deviations (SD) for continuous and counts (percentages) for categorical variables. For comparisons between Guardian-3 and Guardian-4 users, independent sample t-tests for continuous and chi2-tests for categorical variables were used.

First, we modelled laboratory-measured HbA1c (dependent) using CGM-derived mean glucose values (independent) with CGM type both as main effect and its interaction with mean glucose. We tested for non-linearity with the addition of a quadratic term of mean glucose, but given its non-significance, it was dropped from the final model. For graphical representation, we report mean estimated HbA1c and its 95 % confidence interval (CI) for Guardian-3 (Guardian-3 GMI) and Guardian-4 (Guardian-4 GMI) separately. Given that participants could have provided up to 2 HbA1c and mean glucose measurements for the analysis, we used generalised estimating equations (GEE) with individual measurements as units of analysis grouped within individuals.

Second, we saved the errors from the previous model (the difference or so-called "gap" between measured and estimated HbA1c; Guardian-3 gap and Guardian-4 gap) as well as the difference (gap) between Bergenstal-GMI and measured HbA1c (Bergenstal-gap) and compared the proportion of patients with clinically relevant gaps (absolute value ≥ 0.5 %) (21) at the baseline visit for device-specific vs Bergenstal measures with McNemar tests (96).

Third, we investigated the association between the measured HbA1c and the given gaps on a modified Bland-Altman plot by sensor type (91, 92). We also modelled the gaps (using a similar approach to the previous models with GEE) with the Guardian-3 gap, Guardian-4 gap, and Bergenstal-gap as outcomes and laboratory-measured HbA1c as predictor separately for each sensor. Estimates were plotted over HbA1c as a gold standard measure (with 95 %CIs).

All analyses were performed using IBM SPSS Statistics version 29 (IBM Corp, NY, USA) or StataNOW/MP 18.5 (StataCorp LLC, TX, USA), two-sided P-values < 0.05 were considered statistically significant. (93)

4. Results (reported separately for Study-1 and Study-2)

4.1. Results of Study-1

4.1.1. Baseline characteristics

We included 120 patients (n=90 with Guardian-3 sensors and n=30 with Guardian-4 sensors) with type 1 diabetes aged 18 years or older. Altogether, they had 194 measurement points (149 for Guardian-3 users and 45 for Guardian-4 users). The median time between the first and second measurements was 133 days (range: 91–511 days). Both Guardian-3 and Guardian-4 sensor users had similar age (~ 40 years), sex distribution, and diabetes duration (~ 20 years).

Furthermore, Guardian-3 and Guardian-4 users had similar clinical characteristics (eGFR, haemoglobin, mean corpuscular volume, frequency of hypothyroidism, coeliac disease, hypertension, diabetic retinopathy, and diabetic kidney disease, use of iron supplementation and oral anticoncipient), sensor use (~90%), CV of sensor glucose (~33%), difference between HbA1c and Bergenstal-GMI (Bergenstal-gap), and TBR (~2%). (**Table 3**)

In contrast, Guardian-3 users were more frequently on hybrid closed-loop insulin pump therapy (MiniMed 780G; 67 vs 3%). As expected, the Guardian-3 group had significantly lower GMI (mean difference [MD]: 0.51, 95%CI: 0.28-0.74), lower TAR (MD: 14.7%, 95%CI: 8.6-20.9%) and higher TIR (MD: 14.3, 95%CI: 8.4-20.2%) compared to the Guardian-4 group. There was a numerically lower but statistically not significantly different HbA1c in the Guardian-3 group (MD: 0.36, 95% CI: -0.79-0.07%). **(Table 3)** (93)

Table 3 *– Baseline characteristics of included type 1 diabetes patients in Study-1 (93)*

	All	**Guardian-3 sensor users**	**Guardian-4 sensor users**	**p**[#]
	Mean ± SD[¶] **/ n(%)**	**Mean ± SD**[¶] **/ n(%)**	**Mean ± SD**[¶] **/ n(%)**	
n	120	90 (75%)	30 (25%)	
Age (years)	36 ± 13.3	35.1 ± 12.4	38.7 ± 11.2	0.15

Sex				0.21
Female, n (%)	61 (50.8%)	49 (54.4%)	12 (40%)	
Male, n (%)	59 (49.2%)	41 (45.6%)	18 (60%)	
Duration of diabetes (years)	19.2 ± 15.1	18.8 ± 10.9	20.5 ± 13.7	0.49
Insulin treatment				<0.001
MDI*[*], n (%)	59 (49.2%)	30 (33.3%)	29 (96.7%)	
Insulin pump (MM780G)*[†], n (%)	61 (50.8%)	60 (66.7%)	1 (3.3%)	
Sensor use (% of time)	88.4 ± 8.3	88 ± 7.9	89.7 ± 6.9	0.30
Glycated haemoglobin (HbA1c) [%]	7.3 ± 1.2	7.2 ± 0.8	7.6 ± 1.1	0.10
HbA1c (mmol/mol)	56.3 ± 12.8	55.3 ± 9.1	59.3 ± 11.7	
GMI*[‡] *(%)	7.0 ± 0.7	6.9 ± 0.5	7.4 ± 0.6	<0.001
GMI (mmol/mol)	53.1 ± 7.6	51.7 ± 5.6	57.3 ± 6.9	
Coefficient of variation (CV) [%]	32.9 ± 4.1	32.9 ± 4.2	33.2 ± 3.3	0.69
Time in range (TIR) [%]	69.5 ± 17.5	73.1 ± 13.6	58.8 ± 15.6	<0.001
Time below range (TBR) [%]	2.1 ± 2.1	2.2 ± 2.1	1.6 ± 1.7	0.20
Time above range (TAR) [%]	28.5 ± 18.4	24.8 ± 14.1	39.5 ± 16.5	<0.001
Glycaemic gap (HbA1c-GMI) [%]	0.3 ± 0.6	0.3 ± 0.4	0.2 ± 0.6	0.14
eGFR*[§] *(mL/min/1.73 m^2)	87.5 ± 9.3	87.8 ± 7.1	86.6 ± 8.4	0.44
Haemoglobin (g/L)	145.2 ± 17.1	144.7 ± 13.2	146.7 ± 15.4	0.49
Mean cellular volume (MCV) [fL]	87.9 ± 4.6	87.9 ± 3.8	87.8 ± 4	0.92
Hypothyroidism, n (%)	16 (13.3%)	13 (14.4%)	3 (10%)	0.76
Coeliac disease, n (%)	7 (5.8%)	6 (6.7%)	1 (3.3%)	0.68
Hypertension, n (%)	24 (20%)	17 (18.9%)	7 (23.3%)	0.61
Iron supplementation, n (%)	6 (5%)	4 (4.4%)	2 (6.7%)	0.64
Oral anticoncipient, n (%)	10 (8.3%)	6 (6.7%)	4 (13.3%)	0.27
Retinopathy*[‖], n (%)	16 (21.6%)	10 (17.9%)	6 (33.3%)	0.20
Diabetic kidney disease*[‖], n (%)	7 (7.4%)	4 (5.6%)	3 (13.6%)	0.35

** MDI: multiple daily insulin injections, † MM780G: Minimed 780G advanced hybrid closed-loop system, ‡ GMI: glucose management indicator, § eGFR: estimated glomerular filtration rate calculated*

by the CKD-EPI equation. || Forty-six patients had unknown retinopathy status, and twenty-six patients had unknown albuminuria status (no screening within one year). SD: standard deviation.
The percentages are based on the number of patients for whom data are available.
P values are given for the comparison of Guardian-3 and Guardian-4 sensors using 2-sample t-tests or χ2-tests as appropriate.

4.1.2. Sensor-specific GMI equations versus the Bergenstal equation to estimate HbA1c

By modelling laboratory-measured HbA1c using CGM-derived mean glucose values for each sensor separately (see **Table 4** and **Figure 1** for details), the following device-specific GMI equations (Guardian-3 GMI, Guardian-4 GMI) were obtained:

Table 4 – Device-specific and the original GMI equations (93)

Device-specific GMI equations for the Medtronic Guardian Sensor 3 sensors • Guardian-3 GMI (%)=2.32+0.59×mean glucose (mmol/l) • Guardian-3 GMI (%)=2.32+0.033×mean glucose (mg/dl)
Device-specific GMI equations for the Medtronic Guardian 4 Sensors • Guardian-4 GMI (%)=1.565+0.63×mean glucose (mmol/l) • Guardian-4 GMI (%)=1.565+0.035×mean glucose (mg/dl)
Original GMI equation published by Bergenstal *et al.* using Dexcom G4 and G5 sensors (42) • GMI (%)=3.31+0.43×mean glucose (mmol/l) • GMI (%)=3.31+0.0239×mean glucose (mg/dl).

Compared to the original Bergenstal equation, both the Guardian-3- and Guardian-4 specific equations had a steeper slope (Δ HbA1c / Δ mean glucose was 0.43% versus 0.59% and 0.63% / mmol/L for the Bergenstal-equatinon, Guardian-3 GMI and Guardian-4 GMI, respectively [4.7 versus 6.4 and 6.9 mmol/mol / mmol/l]), while the Guardian-3 and Guardian-4 slopes were similar. This translated to the fact that the line of the Bergenstal equation fell below the Guardian-3- and Guardian-4 specific estimations at higher mean sensor glucose values **(Fig. 1)**.

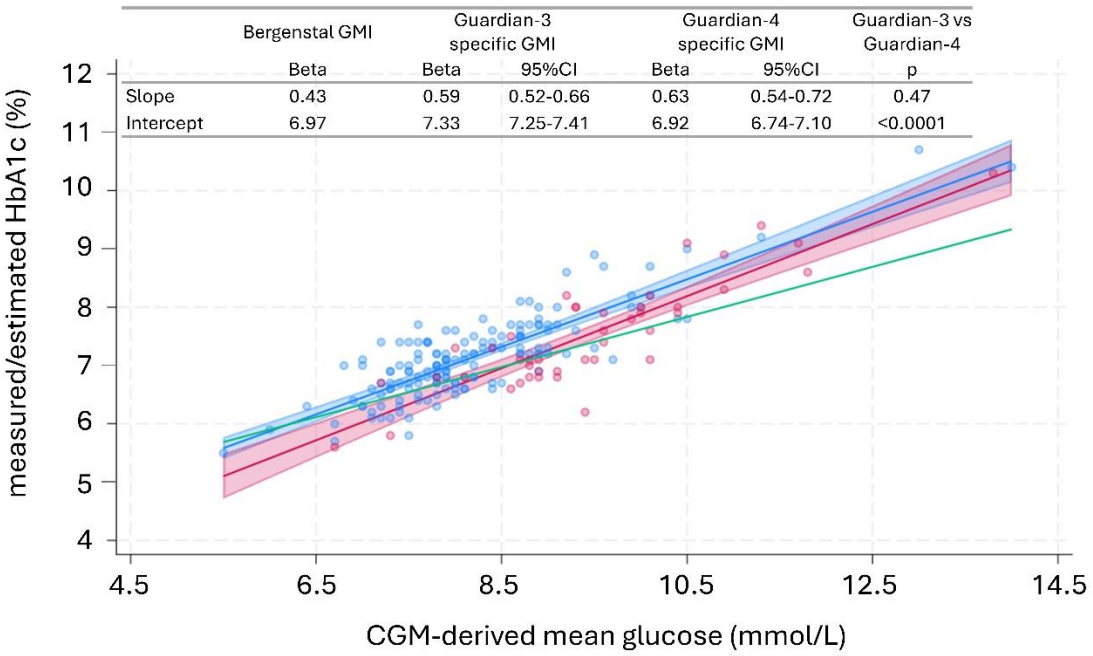


Fig. 1. *Association between CGM-derived mean glucose and laboratory measured HbA1c (raw data and based on the Bergenstal as well as device-specific equations). The table shows slope and intercepts for the association between CGM-derived mean glucose (centred at 8.5 mmol/l) and estimated HbA1c (%, Bergenstal GMI, Guardian-3 specific GMI, Guardian-4 specific GMI). Dots represent raw HbA1c data (%, blue – Guardian-3 sensor users, red – Guardian-4 sensor users) for each measurement point. The green line shows estimated HbA1c(%) based on the Bergenstal-GMI equation. The blue line (and band) displays the estimated HbA1c (%, and 95 % confidence band) for the Guardian-3 sensor-based device-specific GMI equation, the red line (and band) displays the estimated HbA1c (%, and 95 % confidence band) for the Guardian-4 sensor-based device-specific GMI equation based on generalised estimating equations. Details of the derivation of the device-specific GMI can be found under Statistical Analysis. To convert HbA1c [%] and GMI [%] (as absolute values) to mmol/mol, the conversion formula is: HbA1c(mmol/mol) = (HbA1c[%]−2.15)x10.929, and GMI(mmol/mol) = (GMI[%]−2.15)x10.929. To convert glucose concentration to mg/dl, multiply values in mmol/l by 18.015.* (93)

As shown in **Figure 1**, we centred the sensor glucose values around the overall CGM-derived mean of the study population (8.5 mmol/l [153 mg/dl]); thus, the intercept values provided estimated HbA1c values for 60-day mean sensor glucose of 8.5 mmol/l [153 mg/dl]. While the confidence interval for the Guardian-4 sensor contained the recalculated value of the Bergenstal equation, it was lower than the lower bound of the confidence interval of the intercept for the Guardian-3 equation. This means that the Bergenstal equation estimated HbA1c well around the mean (8.5 mmol/l [153 mg/dl])

sensor glucose for the Guardian-4 sensor, while it was significantly underestimating for the Guardian-3 sensor **(Fig. 1)**.

Altogether, this translated into 2 parallel lines for Guardian-3 (higher) and Guardian-4 (lower) that were both steeper than the Bergenstal line. The confidence interval of the Guardian-3 line contained the Bergenstal line for the lowest mean glucose values but it was above the Bergenstal line from approximately 7 mmol/l [126 mg/dl]. The confidence interval of the Guardian-4 line was below the Bergenstal line for the lower range, contained the line between approximately 7 and 9 mmol/l [126 and 162 mg/dl], and was above the Bergenstal line above ~9 mmol/l [162 mg/dl] **(Fig. 1)**.

We found that the proportion of participants with clinically significant GMI-gap (an absolute value of ≥0.5% difference between the estimated and the laboratory-measured HbA1c) was significantly smaller with the use of the device-specific GMI compared to the use of the Bergenstal-GMI for the Guardian-3 sensor (P = 0.043) and numerically smaller for the Guardian-4 sensor (P = 0.125) (**Table 5**). (93)

Table 5*. Crosstabulation of clinically significant glycaemic gap (absolute value of HbA1c-GMI≥0.5 %[5.5mmol/mol]) by the type of GMI equation stratified by type of CGM system at the baseline visit.* (93)

		Absolute value of Guardian-3 gap			Absolute value of Guardian-4 gap		
		<0.5%	≥0.5%	p	<0.5%	≥0.5%	p
Absolute value of Bergenstal-gap	*<0.5%*	n=53 (58.9%)	n=7 (7.8%)	0.043	n=17 (56.7%)	n=1 (3.3%)	0.125
	≥0.5%	n=18 (20.0%)	n=12 (13.3%)		n=6 (20.0%)	n=6 (20.0%)	

P-values are given for McNemar tests.

Bergenstal-gap(%) = HbA1c(%)-GMI_Bergenstal(%).

Guardian-3 gap(%) = HbA1c(%)-GMI_Guardian3(%).

Guardian-4 gap(%) = HbA1c(%)-GMI_Guardian4(%).

GMI_Bergenstal, GMI_Guardian3, and GMI_Guardian4 are calculated with the original, the Guardian-3 specific, and Guardian-4 specific GMI equations, respectively

4.1.3. Bland-Altman analysis of the HbA1c-GMI difference

When we plotted the difference between HbA1c and GMI based on the Bergenstal or the sensor-specific equation, i.e., the Bergenstal-gap, Guardian-3 gap, and Guardian-4 gap with HbA1c for each device separately, we saw a strong relationship between all three gaps and HbA1c, with larger gaps at higher HbA1c values.

Furthermore, the slope of this association was steeper for the Bergenstal-gap versus the sensor-specific Guardian-3 and Guardian-4 gaps **(Table 6, Fig. 2)**. (93)

Table 6 *– Association between glycaemic gap (dependent; based on device-specific and the original GMI) and HbA1c (independent) based on generalised estimating equations (Bland-Altman analysis).* (93)

Guardian-3 sensor				
	Bergenstal-gap(%)		**Guardian-3 gap(%)**	
	Beta	**95% CI**	**Beta**	**95% CI**
Slope(%)	0.47	0.40-0.55	0.27	0.16-0.38
Intercept(%)	0.30	0.25-0.35	0.00	-0.07-0.06
Guardian-4 sensor				
	Bergenstal-gap(%)		**Guardian-4 gap(%)**	
	Beta	**95% CI**	**Beta**	**95% CI**
Slope(%)	0.47	0.38-0.57	0.24	0.09-0.38
Intercept(%)	0.14	0.05-0.23	0.00	-0.13-0.13

Based on generalised estimating equations. HbA1c(%) was centred at 7.14 % for the Guardian-3 sensor and at 7.52 % for the Guardian-4 sensor.

Bergenstal-gap(%) = HbA1c(%)-GMI_Bergenstal(%), calculated with the original GMI equation.

Guardian-3 gap(%) = HbA1c(%)-GMI_Guardian3(%), calculated with the Guardian-3 specific GMI equation.

Guardian-4 gap(%) = HbA1c(%)-GMI_Guardian4(%), calculated with the Guardian- 4 specific GMI equation.

CI: confidence interval.

To convert HbA1c[%] and GMI[%] (as absolute values) to mmol/mol, the conversion formula is: HbA1c(mmol/mol)=(HbA1c[%]−2.15)x10.929, and GMI(mmol/mol)=(GMI[%]−2.15)x10.929.

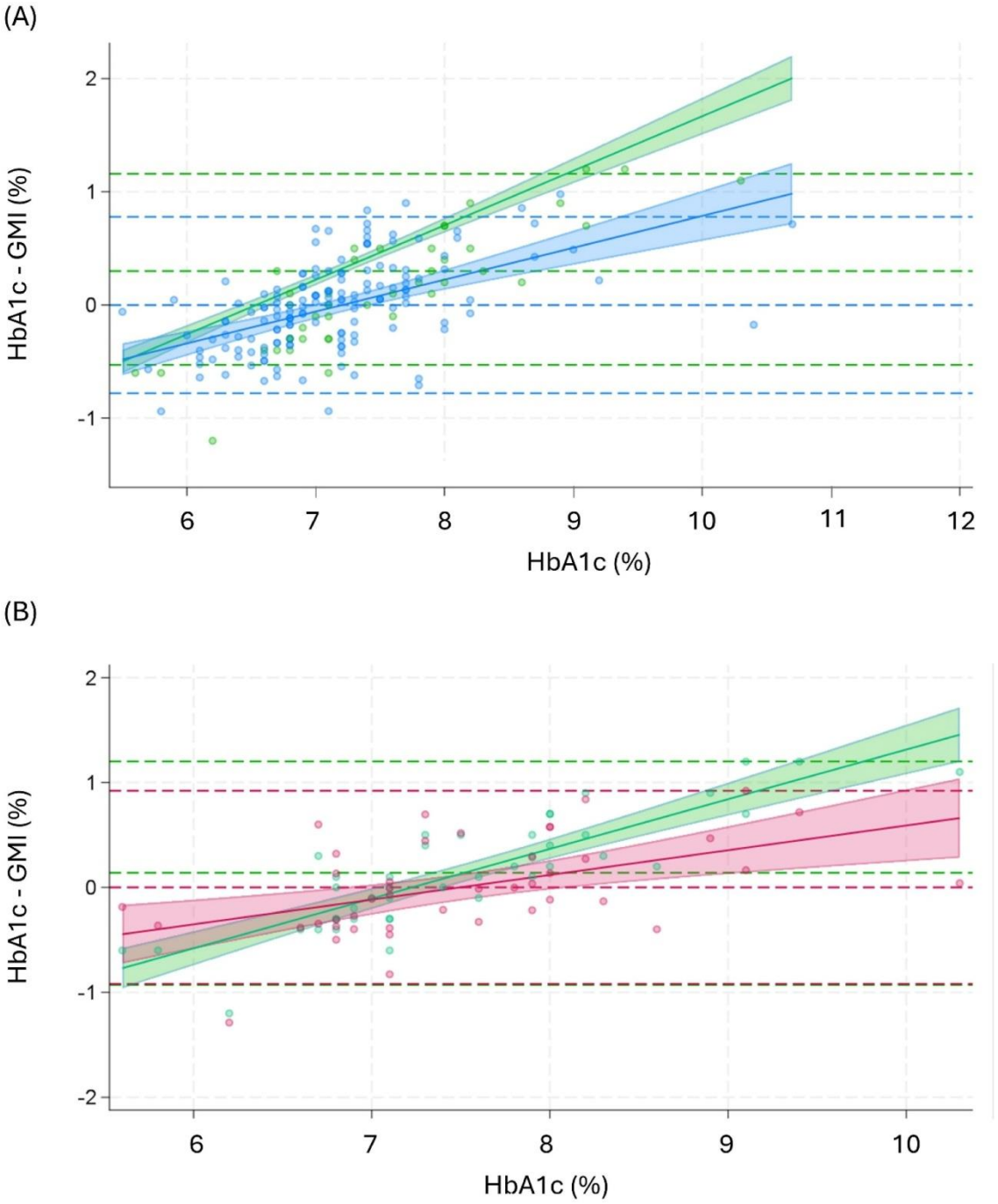


Fig. 2. Modified Bland-Altman plots for the analysis of agreement between laboratory-measured HbA1c and model-derived GMI (using the original and the sensor-specific GMI equations) for the Guardian-3 (A) and Guardian-4 sensors (B). Dots represent raw agreement data (HbA1c[%]-GMI[%]; green – based on original GMI equation, blue – based on Guardian-3 specific GMI equation, red – based on Guardian-4 specific GMI equation). The green line (and band) shows estimated agreement data based on the original GMI equation (and its 95 % confidence band) stratified by CGM device. The blue line (and band) displays the estimated agreement (and 95 % confidence band) data for the Guardian-3 sensor-specific GMI equation, the red line displays the estimated agreement (and 95 % confidence band) data for

the Guardian-4 sensor-specific GMI equation based on generalised estimating equations. Dashed lines mark 1.96 standard deviation and the mean of the raw data. Details of the derivation of the device-specific GMI can be found under Statistical Analysis. To convert HbA1c[%] and GMI[%] (as absolute values) to mmol/mol, the conversion formula is: HbA1c(mmol/mol) = (HbA1c[%]−2.15) x 10.929, and GMI(mmol/mol) = (GMI[%]−2.15) x 10.929. To convert glucose concentration to mg/dl, multiply values in mmol/l by 18.015. (93)

For the Guardian-3 sensor, the only overlap between the confidence intervals was found at the lowest HbA1c values. Above that the GMI based on the Bergenstal equation underestimated significantly more the actual HbA1c values compared to the sensor-specific equation. The difference in overestimation was over 1 % [11 mmol/mol] for HbA1c values above 10 % [86 mmol/mol] **(Table 6, Fig. 2)**.

For the Guardian-4 sensor, a similar pattern emerged. However, the lines crossed each other at an HbA1c of around 7 % [53 mmol/mol], leading to smaller overestimation at lower HbA1c values and smaller underestimation at higher HbA1c values for the sensor-specific GMI equation compared to the Bergenstal-based GMI equation. The largest difference was reached at the highest HbA1c values (10.5 % [91 mmol/mol]), where the Bergenstal equation underestimated HbA1c by approximately 1 % [11 mmol/mol] compared to the sensor-specific equation **(Table 6, Fig. 2)**.

The slopes for the Guardian-3 gap and Guardian-4 gap were similar, and they were substantially (40–50 %) shallower compared to the slope for the Bergenstal-gap. Furthermore, the intercepts for the Bergenstal-gap were different (higher for the Guardian-3 sensor-based mean glucose values compared to the Guardian-4 sensor-based mean glucose values), suggesting that the calibration of the sensor glucose values were different for the Guardian-3 and Guardian-4 sensors in line with the fact that for a given HbA1c value the Guardian-3 sensor reports a lower mean sensor glucose **(Table 6, Fig. 1, Fig. 2)**. (93)

4.2. Results of Study-2

4.2.1. Baseline characteristics

Altogether, we included 145 patients with n=216 measurement points (Minimed 780G n=90, multiple daily injection therapy [MDI] n=126, median time between first and second measurements 138 [range:90–392] days). All patients in Study-2 used

Guardian-4 sensors. The patient population included the 30 Guardian-4 users from Study-1. It also included some patients who used Guardian-3 in Study-1 but had switched to Guardian-4 by the time of Study-2. Pump users were younger, had lower HbA1c and GMI and higher time in range (TIR) and sensor use compared to patients on MDI. (**Table 7**) (94)

Table 7 – Baseline characteristics of included type 1 diabetes patients (94)

	All	**Minimed 780G users**	**Patients on MDI[*] therapy**	**P[#]**
	Mean ± SD[¶] / n(%)	**Mean ± SD[¶] / n(%)**	**Mean ± SD[¶] / n(%)**	
n	145	66 (46%)	79 (54%)	
Age (years)	34.6 ± 11.7	32.2 ± 10.0	36.5 ± 12.8	0.024
Sex				
Female, n (%)	71 (49.0%)	38 (57.6%)	33 (41.8%)	0.068
Male, n (%)	74 (51.0%)	28 (42.4%)	46 (58.2%)	0.068
Duration of diabetes (years)	17.9 ± 11.6	18.4 ± 9.1	17.5 ± 13.3	0.640
Sensor use (% of time)	90.4 ± 7.7	93.1 ± 5.7	88.0 ± 8.4	<0.001
HbA1c[†] (%)	7.4 ± 1.1	7.0 ± 0.7	7.7 ± 1.3	<0.001
HbA1c[†] (mmol/mol)	57.2 ± 12.2	53.3 ± 8.0	60.6 ± 14.0	<0.001
GMI[‡] (%)	7.1 ± 0.7	6.8 ± 0.4	7.4 ± 0.8	<0.001
GMI[‡] (mmol/mol)	53.9 ± 9.8	51.3 ± 3.9	57.0 ± 12.5	<0.001
Coefficient of variation (%)	33.6 ± 4.9	33.6 ± 4.3	33.6 ± 5.0	0.986
Time in range (TIR) [%]	66.1 ± 17.4	75.4 ± 9.1	58.3 ± 18.8	<0.001
Time below range (TBR) [%]	2.3 ± 2.7	1.8 ± 1.5	2.7 ± 3.3	0.045
Time above range (TAR) [%]	31.6 ± 17.7	22.7 ± 9.5	39.0 ± 19.5	<0.001
Serum creatinine (umol/L)	75.1 ± 13.7	74.2 ± 13.5	75.9 ± 13.9	0.457
Haemoglobin (g/L)	145.2 ± 13.2	143.2 ± 13.0	146.8 ± 13.3	0.102
Mean cellular volume (fL)	88.0 ± 3.7	88.2 ± 3.7	87.8 ± 3.7	0.476
Body mass index (BMI) (kg/m^2)	24.6 ± 4.2	24.5 ± 4.3	24.7 ± 4.1	0.805
Hypothyroidism, n (%)	17 (11.7%)	9 (13.6%)	8 (10.1%)	0.607
Coeliac disease, n (%)	10 (6.9%)	3 (4.5%)	7 (8.9%)	0.347
Hypertension, n (%)	22 (15.2%)	8 (12.1%)	14 (17.7%)	0.486
Iron supplementation, n (%)	5 (3.4%)	3 (4.5%)	2 (2.5%)	0.660
Oral anticoncipient, n (%)	14 (9.7%)	7 (10.6%)	7 (8.9%)	0.782
Retinopathy[§], n (%)	18 (22.8%)	8 (21.6%)	10 (23.8%)	1.000

Diabetic kidney diseas[§], n (%)	5 (4.2%)	1 (1.7%)	4 (6.6%)	0.365

** MDI: multiple daily injection, † HbA1c: glycated haemoglobin A1c, ‡ GMI: glucose management indicator based on the original Bergenstal equation. § Sixty-six patients had unknown retinopathy status, and twenty-five patients had unknown albuminuria status (no screening within one year). ¶ SD: standard deviation. # P values are given for the comparison of Minimed 780G users and patients on MDI therapy using 2-sample t-tests or χ2-tests as appropriate.*

4.2.2. Guardian-4 specific versus Bergenstal GMI equation to estimate HbA1c

By modelling laboratory-measured HbA1c using CGM-derived mean glucose values for the Guardian-4 sensor, using a significantly larger sample size compared to Study-1, the following device-specific GMI equation (Guardian-4 GMI) was obtained:

Guardian-4 GMI (%)=2.02+0.6×mean glucose (mmol/L)

Guardian-4 GMI (%)=2.02+0.0333×mean glucose (mg/dL)

Compared to the original Bergenstal equation, the Guardian-4 specific equation had a steeper slope (0.43 versus 0.60% / mmol/l [4.7 versus 6.6 mmol/mol / mmol/l]), and a higher intercept at a mean glucose of 8.5 mmol/l (153 mg/dl). The confidence interval of the Guardian-4 line was below the Bergenstal line for lower mean glucose values, contained the line between approximately 6.8 and 8.1 mmol/l (123 and 146 mg/dl), and was above the Bergenstal line for mean glucose values above ~8.1 mmol/l (146 mg/dl). (**Fig. 3A**)

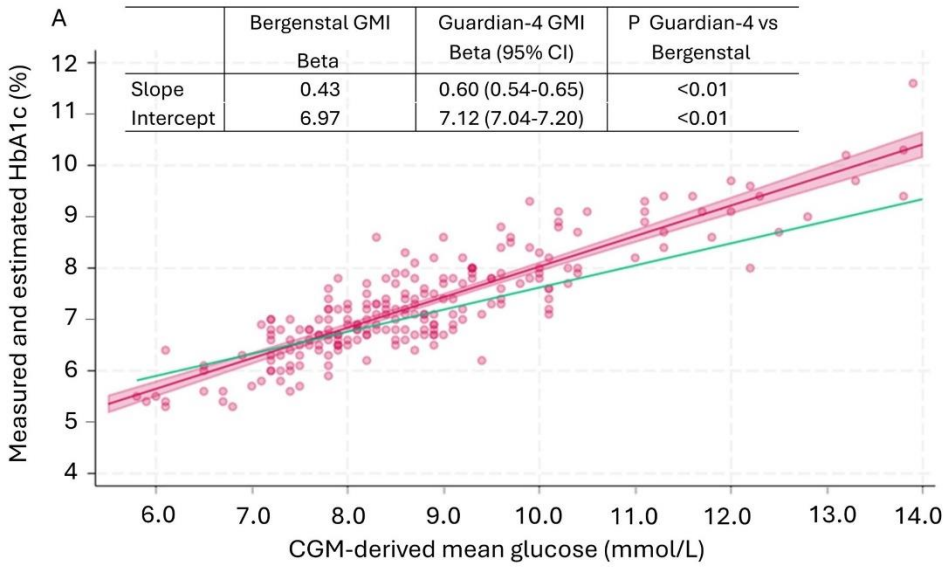
The difference between the Bergenstal-GMI and Guardian-4 specific GMI reached the clinically significant 0.5%(5.5 mmol/mol) difference at a mean glucose level of 10.6 mmol/L (191mg/dl) (95%CI:10.1-11.3mmol/L[182-204mg/dl]). (**Fig. 3A**)

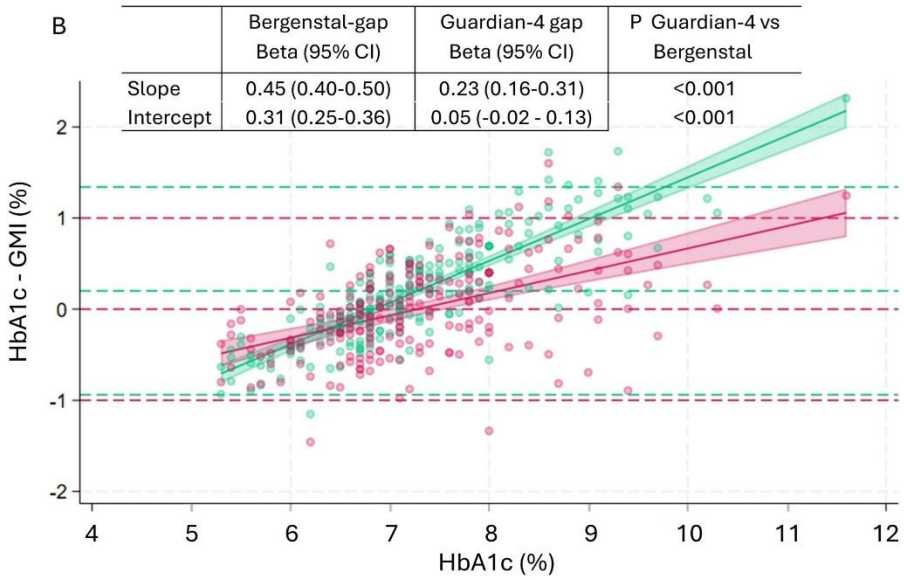
The number of participants with clinically significant GMI-gap (absolute value ≥0.5% [≥5.5 mmol/mol]) was smaller for the Guardian-4 specific vs the Bergenstal equation (Bergenstal-gap ≥0.5% and Guardian-4 gap <0.5%: n=24 [16.6%]; Guardian-4 gap ≥0.5% and Bergenstal-gap <0.5%: n=11 [7.6%]; both gaps ≥0.5%: n=36 [24.8%]; both gaps < 0.5%: n=74 [51.0%]. McNemar test P=0.04). Besides more favourable overall results, it should be noted, however, that some patients had higher GMI-gap when the Guardian-4 vs the Bergenstal equation was used. (94)

Bland-Altman analysis

When we plotted the difference between HbA1c and GMI based on the Bergenstal or the Guardian-4 specific equation (i.e., the Bergenstal-gap and Guardian-4 gap) over HbA1c, we saw a strong positive relationship between both gaps and HbA1c, with larger gaps at higher HbA1c values. The slope was almost twice as steep for the Bergenstal-gap versus the Guardian-4 specific gap. (**Fig. 3B**)

The confidence intervals of the Bergenstal and the sensor-specific gaps overlap only in well-controlled patients with an HbA1c of <7% (53 mmol/mol). Above 7% of HbA1c, the Bergenstal GMI underestimated the actual HbA1c values significantly more compared to the Guardian-4 specific equation. Furthermore, the gap reached the clinically significant threshold of 0.5% at an HbA1c of ~8% (64 mmol/mol) for the Bergenstal and at ~9.3% (78 mmol/mol) for the device-specific GMI-gap. (**Fig. 3B**) (94)





HbA1c (%) (baseline)	5.0-5.4	5.5-5.9	6.0-6.4	6.5-6.9	7.0-7.4	7.5-7.9	8.0-8.4	8.5-8.9	9.0-9.4	9.5-9.9	10.0-10.4	≥10.5
Number of patients	3	8	11	34	31	21	11	10	11	2	2	1

Fig. 3 *Association between CGM-derived mean glucose and laboratory-measured HbA1c (raw data and based on the Bergenstal as well as device-specific equations)* ***(panel A)*** *and modified Bland-Altman plots for the analysis of agreement between laboratory-measured HbA1c and model-derived GMI (using the original and the sensor-specific GMI equations)* ***(panel B)****.*

The table in ***panel A*** *shows slope and intercepts for the association between CGM-derived mean glucose (centred at 8.5 mmol/l) and estimated HbA1c (%, Bergenstal GMI, Guardian-4 specific GMI). Red dots represent raw HbA1c data (%) for each measurement point. The green line shows estimated HbA1c(%)*

based on the Bergenstal-GMI equation. The red line (and band) displays the estimated HbA1c (%, and 95 % confidence band) for the Guardian-4 sensor-based device-specific GMI equation based on generalised estimating equations.

Estimates in the table in ***panel B*** *are based on generalised estimating equations. HbA1c(%) was centred at 7.52%.Dots represent raw agreement data (HbA1c[%]-GMI[%]; green – based on original GMI equation, red – based on Guardian-4 specific GMI equation). The green line (and band) shows estimated agreement data based on the original GMI equation (and its 95 % confidence band). The red line (and band) displays the estimated agreement (and 95 % confidence band) data for the Guardian-4 sensor-specific GMI equation based on generalised estimating equations. Dashed lines mark 1.96 standard deviation and the mean of the raw data. Details of the derivation of the device-specific GMI can be found under Statistical Analysis. To convert HbA1c[%] and GMI[%] (as absolute values) to mmol/mol, the conversion formula is: HbA1c(mmol/mol) = (HbA1c[%]−2.15) x 10.929, and GMI(mmol/mol) = (GMI[%]−2.15) x 10.929. To convert glucose concentration to mg/dl, multiply values in mmol/l by 18.015.* (94)

5. Discussion

5.1. Short Summary

Among adult type 1 diabetes patients on intensified insulin therapy with a wide range of diabetes duration and HbA1c using Guardian-3 and Guardian-4 sensors, we demonstrated that the original GMI equation (Bergenstal-GMI) clinically significantly (≥0.5% [5.5 mmol/mol]) underestimates HbA1c in Guardian-3 users with an HbA1c >7.6%(60 mmol/mol) and in Guardian-4 users with an HbA1c >8 %(64 mmol/mol). Our device-specific GMIs reach this level of inaccuracy at an HbA1c >9%(75 mmol/mol) for Guardian-3 and at an HbA1c >9.3%(78 mmol/mol) for Guardian-4 sensors. **(Fig. 2A and Fig. 3B)** This inaccuracy could potentially lead to undertreatment of patients with moderately elevated HbA1c values when the original GMI equation is used, while this risk is much smaller with the device-specific equation. Furthermore, we found that the proportion of patients with clinically significant GMI-gaps (absolute value ≥0.5% [≥5.5 mmol/mol]) was reduced with the use of the device-specific vs the original GMI equation. **(Table 5).**

The difference between the Bergenstal-GMI and device-specific GMI reached the clinically significant 0.5%(5.5 mmol/mol) difference at a mean glucose level of 9.5 mmol/L (171mg/dl) (95%CI:9.4-9.7mmol/L[169-175mg/dl]) for Guardian-3 sensors and at 10.6 mmol/L (191mg/dl) (95%CI:10.1-11.3mmol/L[182-204mg/dl]) for Guardian-4 sensors. **(Fig. 1 and Fig. 3A)**

The Bland-Altman analysis clearly demonstrates that heteroscedasticity was present between the glycaemic gap (the residual for the HbA1c prediction model) and HbA1c for all three prediction models. Compared to the Bergenstal-GMI, the error of the Guardian-3 GMI and Guardian-4 GMI was mostly significantly smaller and approximately half as large as for the Bergenstal-GMI for HbA1c values > 7 % [53 mmol/mol]. **(Table 6, Fig. 2A and Fig. 3B)** Thus, applying sensor-specific GMI equations significantly improved accuracy in almost all HbA1c ranges.

For Guardian-4 sensors, our discussion is based on the results of Study-2, given the larger sample size (Study-1 vs Study-2: n= 30 vs 145 patients, 45 vs 216 measurement points) and the consequently 40-60% narrower CIs for estimating HbA1c (CI: 0.3-0.9% for HbA1c estimation in the glucose range of 5.5-14 mmol/L in Study-1, vs 0.1-0.5% in Study 2). For Guardian-4 sensors, the proposed device-specific GMI equation is that derived from Study-2. Thus, our proposed device-specific GMI equations for the Guardian-3 and Guardian-4 sensors are as follows:

Guardian-3 GMI (%)=2.32+0.59×mean glucose (mmol/L)

Guardian-3 GMI (%)=2.32+0.033×mean glucose (mg/dL)

Guardian-4 GMI (%)=2.02+0.6×mean glucose (mmol/L)

Guardian-4 GMI (%)=2.02+0.0333×mean glucose (mg/dL) (93, 94)

5.2. Our results in the context of the literature

Numerous studies suggested that the type of CGM system influences the overall association between mean sensor glucose and HbA1c (21, 75, 83, 97-101).

Similarly to our results, studies using Freestyle Libre found that the Bergenstal-GMI underestimates glycaemia at higher and overestimates at lower HbA1c values (75, 98-100). However, heteroscedasticity and intercept bias were rarely investigated.

Among 252 type 1 diabetes patients aged 15-79 years using Freestyle Libre sensors (sensor generation not reported), Alarcón et al. reported that differences between HbA1c and Bergenstal-GMI became greater as HbA1c increased, especially above an HbA1c of 8%, where Bergenstal-GMI significantly underestimated HbA1c. However, a detailed quantitative assessment was not reported. (99). In a markedly different patient population (including type 2 diabetes patients) using Freestyle Libre 1 devices, classical Bland-Altman analysis showed similar tendencies (75).

For the Dexcom G4 and G5 sensors, some indirect evidence suggests that the Bergenstal-GMI equation is appropriate (77). This is consistent with the fact that the original GMI formula was developed with Dexcom G4 and G5 sensors (42).

In contrast, similar data is scarce for Medtronic sensors. Although the Bergenstal-GMI formula has been validated for Guardian 3 sensors, the related study is only descriptive and did not investigate the accuracy of GMI in different HbA1c ranges (102). Using a

mixed population on real-time (rt) and intermittently scanned CGM systems that included > 80 % Medtronic sensor users (sensor generation not indicated), ~75 % of all rtCGM users with HbA1c ≥ 7.5 % [58 mmol/mol] had lower GMI than HbA1c (97), confirming our findings (quantitative assessment of heteroscedasticity was not reported).

Recently, two other studies reported a detailed assessment of how the original Bergenstal equation performed with other CGM systems (100, 101).

Yoo et al. investigated type 1 diabetes patients using Dexcom G6 (n=117) or FreeStyle Libre 1 (n=158) CGM devices (100). For Dexcom G6 users, the original GMI equation significantly overestimated glycaemia when HbA1c was below 8.0%. In patients with Dexcom G6 whose laboratory HbA1c fell into the range of 5.0-5.9% (mean: 5.6%), GMI was, on average, 0.9% higher (mean: 6.5%) than HbA1c. Above an HbA1c of 8%, HbA1c and GMI did not differ significantly; however, the number of patients who fell into this range was small. For Freestly Libre users, the original GMI equation significantly underestimated glycaemia in the higher HbA1c ranges and overestimated glycaemia in the lower HbA1c ranges. In patients with Freestyle Libre 1 whose laboratory HbA1c fell into the range of 5.0-5.9% (mean: 5.6%), GMI was, on average, by 0.5% higher (mean: 6.2%) than HbA1c. In those whose HbA1c fell into the range of 9.0-9.9% (mean: 9.4%), GMI was, on average, by 0.9% lower (mean: 8.5%) than HbA1c. Modified Bland-Altman analysis showed that for Freestyle Libre 1, the original GMI equation estimated HbA1c well around a laboratory HbA1c of 7.1%. However, above and below 7.1%, approximately 0.5% discordance occurred with every 1% change in laboratory HbA1c. It is also important to note that the mean HbA1c and the mean GMI of Freestyle Libre users were identical (7.2%); thus, simply reporting the mean HbA1c and mean GMI would not have captured the aforementioned significant biases. For Dexcom G6 users, the mean HbA1c of the entire subgroup was 0.6% lower than the GMI (6.6 vs. 7.2%, p <.001). Altogether, this study demonstrated similar or partly similar tendencies (overestimating HbA1c in lower ranges with both sensors, and underestimating HbA1c in higher ranges with FreeStyle Libre 1) when the original GMI equation was applied to Dexcom G6 and FreeStyle Libre 1 sensors, as did our study with Guardian-3 and Guardian-4 sensors. (100)

In a study among 147 type 1 diabetes patients in Romania using Medtronic Guardian 3 sensors, Lazar et al. found excellent correlation between HbA1c and GMI in the HbA1c range of 6-8%. However, they reported that the original GMI equation overestimates glycaemia in lower HbA1c values and underestimates glycaemia in higher HbA1c ranges, confirming our findings. The steepness of the Bland-Altman regression line (Δ [HbA1c-GMI] / Δ HbA1c) was approximately 0.6% / % in their report, which is very close to our findings with Guardian 3 sensors. A sensor-specific GMI equation was not reported or investigated in this study. (101)

Freckmann et al. compared the glycaemic metrics derived from three different types of CGMs (Freestyle Libre 3, Dexcom G7 and Medtronic Simplera) worn simultaneously by the same individual, among n=23 adult type 1 diabetes patients (83). Regarding mean values of the entire study population, the agreement between the Freestyle Libre 3 and Dexcom G7 sensors was overall good; they differed significantly only in some hypoglycaemia metrics. However, Freestyle Libre 3 and Dexcom G7 CGMs differed significantly from the Medtronic Simplera sensors in many glycaemic metrics, including the mean TIR (76.3 vs. 76.2 vs. 84.0 %), time in tight range (TITR 3.9-7.8 mmol/L) [54.7 vs. 54.8 vs. 67.5%], TAR, CV, CGM-derived mean glucose, and GMI (6.7 vs. 6.7 vs. 6.3%) of the study population. However, device-specific GMI equations, performance of the GMI equation in different glucose ranges, or the GMI-HbA1c relationship were not investigated (83). This study provides important evidence that CGM metrics may depend on the type of the CGM device itself.

Importantly, Dexcom G4 and G5 CGM devices, which were used to derive the original GMI equation (Bergenstal-GMI), are not reference standards. We still don't know which sensor, if any, should be used to derive a „reference GMI equation", which would reflect the true relationship between laboratory-HbA1c and mean plasma glucose values.

5.3. Potential factors affecting the performance of the GMI equation

Many factors could explain why the Bergenstal-GMI derived from Dexcom G4 and G5 devices does not translate well for the Medtronic Guardian-3 and Guardian-4 sensors

(and possibly for some other CGM devices, as depicted in the literature (21, 75, 83, 97-101)). These factors can be categorised into two main groups:
1. Factors that affect the HbA1c – mean plasma glucose relationship, resulting in a study population that is significantly different from that of the derivative studies of the original GMI equation (57, 72-74)
2. Factors related to CGM accuracy

5.3.1. Factors affecting the HbA1c – mean plasma glucose relationship

Our study controlled for most diseases (e.g. anaemias) and states (e.g. pregnancy) known to bias HbA1c measurements (36), as individuals with such states and diseases were excluded from our study (Table 1). Intrinsic physiological factors, such as differences in erythrocyte lifespan (40), transport of glucose into red blood cells (30, 31), intracellular glycation and deglycation (32), may also have significant effects on the HbA1c – mean glucose relationship. However, the exact association between these factors and HbA1c are not known, and they cannot be measured in routine clinical practice (44).

Demographics are frequently investigated as potential determinants of the HbA1c - mean glucose relationship. Sex did not have a significant effect on the glycaemic gap in a previous study (75), while age may have some effect (27, 75). On the other hand, race and ethnicity can significantly affect the HbA1c – mean glucose relationship, as discussed previously in section 1.3.2.1. (38, 39).

Altogether, the populations included in our study and the derivation cohort of the original Bergenstal equation are unlikely to explain the differences in the performance of the equation, as all participants were non-pregnant adults, mostly Caucasian, most of them had type 1 diabetes, and were free from any severe diseases that might preclude participation in randomizsed trials, although anaemia, haemoglobinopathy, and an eGFR between 45 and 60 ml/min/1.73 m2 were not explicit exclusion criteria in all of these studies (57, 72-74).

Theoretically, any inaccuracy of HbA1c measurement could also impact the HbA1c – mean glucose relationship in our study. However, all HbA1c measurements were performed in the Central Laboratory of Semmelweis University using high-performance

liquid chromatography (HPLC) on a Tosoh Automated Glycohemoglobin Analyzer HLC-723G11 device (Tosoh Europe N.V. Tessenderlo, Belgium). The central laboratory follows ISO 9001 standards for quality management.

5.3.2. Factors related to CGM accuracy

It took decades for HbA1c measurement to become a well-standardised process (24). Such standardisation of measuring interstitial glucose by CGM devices is lacking and is urged by several experts and organisations (21, 86-88). This effort is also reflected in the establishment of the Working Group on Continuous Glucose Monitoring of the IFCC Scientific Division in 2019 (87).

Over the past few years, multiple studies have demonstrated that different types of CGM devices, when worn simultaneously by the same participants, can display consistently discordant glucose values and CGM-derived metrics, likely reflecting differences in sensor accuracy (83, 103-106).

In a recent study that we already mentioned before, Freckmann et al. analyzed the differences in CGM-derived metrics among three new-generation, factory-calibrated CGM systems, FreeStyle Libre 3 (FL3), Dexcom G7 (DG7), and Medtronic Simplera (MSP), worn in parallel by study participants (83). Regarding the mean values of the study population, a significant difference was observed between FL3 and MSP in TBR (2.8% vs. 5.1%, respectively), between FL3/DG7 and MSP in TIR (76.3%/76.2% vs. 84.0%), TITR (54.7%/54.8% vs. 67.5%), and GMI (6.7%/6.7% vs. 6.3%). The study protocol also included an experimentally induced hyperglycaemic and hypoglycaemic episode with a comparator capillary glucose measurement. During these episodes, the profiles of FL3 and DG7 were similar but significantly different from that of the MSP sensor, which displayed lower glucose values. The observed differences were large enough to impact clinical decision-making (83). The performance results of all CGM systems varied depending on the comparator method. However, FL3 and DG7 showed better accuracy in the normoglycemic and hyperglycemic range and tended to be more accurate altogether, while MSP performed better in the hypoglycemic range (107).

In the case of glucose oxidase sensors, the electrical signal generated by the enzymatic reaction must be accurately converted into a glucose value. To ensure this, the collection of comparator data is a critical process during both sensor development and

factory and/or fingerstick calibration of a CGM device. According to an Opinion paper published by the Working Group on Continuous Glucose Monitoring of the IFCC Scientific Division, technical factors, especially differences in the calibration algorithms converting the raw signal to CGM readings, are likely the main factor leading to discordant CGM readings (87). Origin of the comparator sample (capillary, venous or „arterialized"-venous blood), choosing the comparator device, and the study procedures used to obtain validation data (108) are all important factors that can have a significant effect on CGM data, both during sensor development and post-marketing (factory/fingerstick) calibration processes (87). The Working Group on Continuous Glucose Monitoring of the IFCC (87), as well as other scientific working groups (86), aim for better harmonisation of these factors between manufacturers, hopefully leading to better harmonisation of CGM readings between different devices.

For the time being, however, approval of CGM devices is mostly based on their mean absolute relative differences (MARDs) and error grid analyses against blood glucose measurements (89). This process, however, is a limited assessment of sensor accuracy and allows for certain biases. For example, it allows larger errors in the lower and higher ends of the glucose range (90).

As mentioned before, some sensors require fingerstick calibration. The quality of fingerstick calibrations and the devices used could bias accuracy. While this could affect Guardian-3 sensors, Guardian-4 (similarly to other novel sensors) is factory-calibrated.

It should be noted that CGM systems only capture a certain (although wide) glucose range, and values outside this range could be handled differently.

5.4. The benefits and caveats of reporting GMI

HbA1c is still the gold-standard long-term glycaemic metric validated in robust, long-term prospective studies for the prediction of chronic diabetes complications (7, 8, 23, 109). Such studies are lacking and definitely needed for CGM-derived metrics, such as mean glucose, GMI, TIR or TITR (21). Furthermore, proper standardisation of CGM devices is lacking, as demonstrated by several small studies (83, 103-106) and pointed out by recent expert consensus statements (86-88).

Linking CGM metrics to a familiar gold-standard parameter, i.e., HbA1c, is a helpful orientation and educational tool for many patients, caregivers, and healthcare professionals to guide everyday diabetes management (42). It is also reasonable to link CGM metrics to the well-standardised HbA1c until proper standardisation of CGM metrics happens. However, linking CGM-derived mean glucose to HbA1c must take between-device differences into account.

Besides standardisation issues, there are conceptual debates regarding the usefulness of GMI. While GMI and HbA1c correlate strongly at the population level, there are significant individual differences between the two metrics (27, 41, 75, 97, 98, 100, 101, 110). These individual differences exist even when the GMI equation fits a specific device, as was the case with the original GMI equation for Dexcom G4 and G5 sensors (42). The observed individual differences have raised doubts about the utility of GMI as a surrogate for HbA1c and even led some experts to argue for and against its use (21, 111).

The fact that we have two independent measures of chronic glycaemia (HbA1c and CGM-derived mean glucose) allows correction of HbA1c for each individual ('personalized HbA1c') that could be a better reflection of glycaemia than HbA1c (112). However, it is still unknown whether this marker could improve the prediction of chronic complications, given the fact that HbA1c is also a reflection of glycation/deglycation speed (a potential determinant of vascular complications) (26, 27, 33). At this moment, we believe that the combined, rational use of HbA1c and multiple CGM-derived metrics can provide the best care for our patients. For people in whom HbA1c can be markedly confounded (such as anaemias), it is reasonable to assume the superiority of CGM-derived metrics.

Our present study demonstrates that the GMI-HbA1c difference can be reduced using sensor-specific GMI equations that control for different characteristics of unique sensors. Given the exponentially increasing market of CGM systems and number of new devices, we believe that validation (and if necessary, recalibration) of the Bergenstal-GMI equation is warranted for each sensor. This validation could even help the standardisation process of CGM devices, giving light to device-specific bias. However, we acknowledge that CGM certification is currently restricted to glucose

measurements. Based on our data, the addition of an HbA1c measurement and some minor modification of the certification trial protocol might be enough for these purposes.

Furthermore, if device-specific differences truly exist and the Bergenstal-GMI does not reflect these differences, it may not only adversely affect clinical decision-making but also research. For example, GMI will be comparable only between studies using the same device, but between-device comparisons may be biased. This may also mean that meta-analyses of GMI and possibly other CGM data should be stratified by the type of device, and more importantly, the performance of two automated insulin delivery systems cannot be compared using GMI if they are using different CGM systems.

If the accuracy of GMI as a metric is questioned, it is reasonable to hypothesise that, given that it is directly calculated from the CGM-derived mean glucose, the accuracy of other CGM-derived metrics is also questionable. Indeed, several studies have demonstrated that different types of CGM devices, when worn in parallel, can display consistently discordant glucose values and CGM-derived metrics, likely reflecting device-specific differences in sensor accuracy (83, 103-106). Furthermore, one study demonstrated that GMI is strongly related to TIR, TITR and TAR in patients using MiniMed 780G advanced hybrid closed-loop systems (113).

To address this question, we plan a study in which patients will wear different CGM devices simultaneously and measure laboratory HbA1c at the end of the data-collection period. This could also support our findings on the utility of device-specific GMI. (93)

5.5. Strengths and limitations

To the best of our knowledge, this is the first study providing a detailed assessment of the HbA1c–GMI relationship for Medtronic Guardian-3 and Guardian-4 sensors across a wide range of HbA1c values. In this regard, these types of CGM systems are widely used, also as part of an advanced hybrid closed-loop system, MiniMed 780G (66, 114), without detailed investigation of all aspects of their precision and accuracy. Both types of analysis, the McNemar tests (96) for the proportion of patients with clinically relevant glycaemic gaps (absolute value ≥ 0.5%)(21) and the Bland-Altman analyses

(91, 92), confirmed improved HbA1c prediction with the device-specific GMI equations versus the original GMI equation. This confirms the robustness of our findings.

Our study has further strengths that must be acknowledged. Participants had high adherence to sensor use (mean adherence: 88 % of time). For a given HbA1c, the CGM data collection period was relatively long (60 days, corresponding to the use of ~8.5 sets of sensors). Almost two-thirds of participants had a second HbA1c-GMI pair, which improved precision. The narrow CIs around our estimates suggest proper statistical power. We thoroughly screened for common co-morbidities and conditions known to influence HbA1c **(Table 1)**, and patients with such conditions were excluded, limiting the effect of external factors. Participants had a wide range of HbA1c and formed a demographically heterogeneous group, representing the patient population of an adult tertiary outpatient diabetes centre in Hungary, giving good external validity to similar populations.

Our study has important limitations. Among them are the relatively small number of cases, the single-centre design, and the ethnically homogeneous patient population. These limitations clearly demand external validation of our findings. The number of patients with markedly elevated HbA1c values is especially limited; i.e., in Study-2, only 5 patients had an HbA1c value ≥ 9.5%. Our results need validation in a cohort that includes more patients with such high HbA1c values.

Although exclusions related to concurrent medications were based on electronic health records, participants could have taken over-the-counter preparations (e.g., high-dose vitamin C, paracetamol) that could affect sensor reliability. Furthermore, the Guardian-3 sensor requires twice daily calibration, potentially leading to bias. Although all patients received education on proper self-monitoring of blood glucose and calibration techniques, we cannot exclude the potential for incorrect blood glucose measurements or calibration habits leading to discrepancies between sensor data and HbA1c. Finally, we cannot rule out analytical error in HbA1c determination. However, HPLC is a gold standard method and our device is regularly calibrated to IFCC standards. (93)

6. Conclusions

HbA1c is still the gold standard long-term glycaemic metric. However, the importance of CGM-derived glycaemic metrics is increasing. Despite its limitations, we think that an estimate of HbA1c based on CGM-derived mean glucose, i.e., the GMI, is a helpful tool for patients, caregivers, healthcare professionals, and researchers. It should be used along with laboratory-measured HbA1c and other standard CGM metrics.

However, GMI's determination should be accurate. We clearly showed that device-specific equations improved the accuracy of HbA1c estimation based on Medtronic Guardian-3 and Guardian-4 CGM devices. Furthermore, device-specific HbA1c estimates reduced the frequency of clinically significant over- and underestimation of HbA1c, potentially leading to better clinical care. (93) We propose the use of our device-specific GMI equations among Guardian-3 and Guardian-4 users in routine clinical care.

We believe that the lack of proper standardisation of CGM devices is the primary reason for device-specific biases in GMI determination. Therefore, better standardisation of CGM devices is necessary. Until a high degree of standardisation is achieved, we propose validating the original GMI equation for all types of CGM systems and establishing device-specific equations if validation fails. Our results need external validation. Further studies are needed with other CGM systems to determine the performance of the original versus the device-specific GMI equations.

7. Summary

HbA1c is the gold-standard long-term glycaemic metric (7-9, 11, 12, 17, 23); however, the importance of CGM-derived glycaemic metrics is increasing. The glucose management indicator is a standard CGM metric that estimates HbA1c from the CGM-derived mean glucose value (42). It is a helpful tool for patients, caregivers, healthcare professionals, and researchers. Given the lack of standardisation of CGM systems (83, 86-88), the currently used GMI equation, developed with Dexcom G4 and G5 sensors, may underperform for other CGM systems. Thus, we conducted a study aiming to develop and test device-specific GMI for the Medtronic Guardian-3 and Guardian-4 sensors. In two single-centre, observational studies of adult type 1 diabetes patients using Guardian-3 and Guardian-4 CGM devices, we estimated HbA1c using CGM-derived mean glucose for both CGMs using generalised estimating equations. We compared the estimates and their residuals (Guardian-3 gap and Guardian-4 gap to the original GMI and its residuals (Bergenstal-gap) using regression and Bland-Altman plots. We included 201 adult type 1 diabetes patients and 365 (149 with Guardian-3 and 216 with Guardian-4) measurement points. We found that for Guardian-3 and Guardian-4 sensors, GMI significantly underestimated glycaemia in high HbA1c ranges, reaching the clinically significant 0.5%(5.5 mmol/mol) difference at an HbA1c of 7.6%(60 mmol/mol) for Guardian-3 and 8.0%(64 mmol/mol) for Guardian-4 sensors. Our device-specific GMIs reach this level of inaccuracy at an HbA1c >9%(75 mmol/mol) for Guardian-3 and at an HbA1c >9.3%(78 mmol/mol) for Guardian-4 sensors. This inaccuracy could potentially lead to undertreatment of patients with moderately elevated HbA1c values when the original GMI equation is used, while this risk is much smaller with the device-specific equation. Furthermore, we found that the proportion of patients with clinically significant GMI-gaps (absolute value ≥0.5% [≥5.5 mmol/mol]) was reduced with the use of the device-specific vs the original GMI equation.

We concluded that device-specific GMI equations could reduce the risk of clinically significant under- and overestimation of HbA1c, improving clinical decision-making. Our study also underscores the need for better CGM standardisation.

8. References

1. Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA, Maahs DM, Tamborlane WV, Bergenstal R, Smith E, Olson BA, Garg SK. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther. 2019;21(2):66-72.
2. Silva JD, Lepore G, Battelino T, Arrieta A, Castaneda J, Grossman B, Shin J, Cohen O. Real-World Performance of the MiniMed 780G System: First Report of Outcomes from 4120 Users. Diabetes Technol Ther. 2022;24(2):113-9.
3. Ebekozien O, Mungmode A, Sanchez J, Rompicherla S, Demeterco-Berggren C, Weinstock RS, Jacobsen LM, Davis G, McKee A, Akturk HK, Maahs DM, Kamboj MK. Longitudinal Trends in Glycemic Outcomes and Technology Use for Over 48,000 People with Type 1 Diabetes (2016-2022) from the T1D Exchange Quality Improvement Collaborative. Diabetes Technol Ther. 2023;25(11):765-73.
4. Ogle GD, Wang F, Haynes A, Gregory GA, King TW, Deng K, Dabelea D, James S, Jenkins AJ, Li X, Ma RCW, Maahs DM, Oram RA, Pihoker C, Svensson J, Zhou Z, Magliano DJ, Maniam J. Global type 1 diabetes prevalence, incidence, and mortality estimates 2025: Results from the International diabetes Federation Atlas, 11th Edition, and the T1D Index Version 3.0. Diabetes Res Clin Pract. 2025;225:112277.
5. Xie J, Li W, Li X, Zhang X, Liu J, Liu Z, Jing S, Shao H. Global, regional, and national epidemiology of type 1 diabetes in children from 1990 to 2021: trend and health inequality analyses based on the Global Burden of Disease Study 2021. Diabetol Metab Syndr. 2025;17(1):337.
6. Ohiagu FO CP, Chikezie CM. Pathophysiology of diabetes mellitus complications: Metabolic events and control. Biomed Res Ther. 2021;8 No. 3 (2021):4243-57.
7. Diabetes C, Complications Trial Research G, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, Rand L, Siebert C. 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(14):977-86.
8. Cefalu WT, Rodgers GP. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study: Continuing to Build on 40 Years of Diabetes Research. Diabetes Care. 2024;47(9):1518-21.

9. Diabetes C, Complications Trial /Epidemiology of Diabetes I, Complications Research G, Lachin JM, White NH, Hainsworth DP, Sun W, Cleary PA, Nathan DM. Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. Diabetes. 2015;64(2):631-42.
10. Miller RG, Anderson SJ, Costacou T, Sekikawa A, Orchard TJ. Hemoglobin A1c Level and Cardiovascular Disease Incidence in Persons With Type 1 Diabetes: An Application of Joint Modeling of Longitudinal and Time-to-Event Data in the Pittsburgh Epidemiology of Diabetes Complications Study. Am J Epidemiol. 2018;187(7):1520-9.
11. Arnqvist HJ, Westerlund MC, Fredrikson M, Ludvigsson J, Nordwall M. Impact of HbA1c Followed 32 Years From Diagnosis of Type 1 Diabetes on Development of Severe Retinopathy and Nephropathy: The VISS Study. Diabetes Care. 2022;45(11):2675-82.
12. Lind M, Pivodic A, Svensson AM, Olafsdottir AF, Wedel H, Ludvigsson J. HbA(1c) level as a risk factor for retinopathy and nephropathy in children and adults with type 1 diabetes: Swedish population based cohort study. BMJ. 2019;366:l4894.
13. Tahara Y SK. Kinetics of A1C, glycated albumin, and fructosamine and analysis of their weight functions against preceding plasma glucose level. Diabetes Care. 1995;18(4):440-7.
14. Thiagarajan P, Parker CJ, Prchal JT. How Do Red Blood Cells Die? Front Physiol. 2021;12:655393.
15. Tahara Y SK. The response of GHb to stepwise plasma glucose change over time in diabetic patients. Diabetes Care. 1993;16(9):1313-4.
16. Rahbar S, Blumenfeld O, Ranney HM. Studies of an unusual hemoglobin in patients with diabetes mellitus. Biochem Biophys Res Commun. 1969;36(5):838-43.
17. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):837-53.
18. American Diabetes Association Professional Practice C. 6. Glycemic Goals and Hypoglycemia: Standards of Care in Diabetes-2025. Diabetes Care. 2025;48(1 Suppl 1):S128-S45.

19. Holt RIG, DeVries JH, Hess-Fischl A, Hirsch IB, Kirkman MS, Klupa T, Ludwig B, Norgaard K, Pettus J, Renard E, Skyler JS, Snoek FJ, Weinstock RS, Peters AL. The Management of Type 1 Diabetes in Adults. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2021;44(11):2589-625.
20. de Bock M, Agwu JC, Deabreu M, Dovc K, Maahs DM, Marcovecchio ML, Mahmud FH, Novoa-Medina Y, Priyambada L, Smart CE, DiMeglio LA. International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines 2024: Glycemic Targets. Horm Res Paediatr. 2024;97(6):546-54.
21. Selvin E. The Glucose Management Indicator: Time to Change Course? Diabetes Care. 2024;47(6):906-14.
22. Beck RW, Bergenstal RM, Cheng P, Kollman C, Carlson AL, Johnson ML, Rodbard D. The Relationships Between Time in Range, Hyperglycemia Metrics, and HbA1c. J Diabetes Sci Technol. 2019;13(4):614-26.
23. Bebu I, Schade D, Braffett B, Kosiborod M, Lopes-Virella M, Soliman EZ, Herman WH, Bluemke DA, Wallia A, Orchard T, Lachin JM, Group DER. Risk Factors for First and Subsequent CVD Events in Type 1 Diabetes: The DCCT/EDIC Study. Diabetes Care. 2020;43(4):867-74.
24. Consensus C. Consensus statement on the worldwide standardization of the hemoglobin A1C measurement: the American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation. Diabetes Care. 2007;30(9):2399-400.
25. Cohen RM, Holmes YR, Chenier TC, Joiner CH. Discordance between HbA1c and fructosamine: evidence for a glycosylation gap and its relation to diabetic nephropathy. Diabetes Care. 2003;26(1):163-7.
26. Cosson E, Banu I, Cussac-Pillegand C, Chen Q, Chiheb S, Jaber Y, Nguyen MT, Charnaux N, Valensi P. Glycation gap is associated with macroproteinuria but not with other complications in patients with type 2 diabetes. Diabetes Care. 2013;36(7):2070-6.
27. Maran A, Morieri ML, Falaguasta D, Avogaro A, Fadini GP. The Fast-Glycator Phenotype, Skin Advanced Glycation End Products, and Complication Burden Among People With Type 1 Diabetes. Diabetes Care. 2022;45(10):2439-44.

28. Puig-Jove C, Vinals C, Conget I, Quiros C, Vinagre I, Berrocal B, Blanco-Carrasco AJ, Granados M, Mesa A, Seres-Noriega T, Gimenez M, Perea V, Amor AJ. Association between the GMI/HbA1c ratio and preclinical carotid atherosclerosis in type 1 diabetes: impact of the fast-glycator phenotype across age groups. Cardiovasc Diabetol. 2025;24(1):75.
29. Saudek CD, Derr RL, Kalyani RR. Assessing glycemia in diabetes using self-monitoring blood glucose and hemoglobin A1c. JAMA. 2006;295(14):1688-97.
30. Gould BJ, Davie SJ, Yudkin JS. Investigation of the mechanism underlying the variability of glycated haemoglobin in non-diabetic subjects not related to glycaemia. Clin Chim Acta. 1997;260(1):49-64.
31. Hempe JM, Gomez R, McCarter RJ, Jr., Chalew SA. High and low hemoglobin glycation phenotypes in type 1 diabetes: a challenge for interpretation of glycemic control. J Diabetes Complications. 2002;16(5):313-20.
32. Chalew SA, McCarter RJ, Thomas J, Thomson JL, Hempe JM. A comparison of the Glycosylation Gap and Hemoglobin Glycation Index in patients with diabetes. J Diabetes Complications. 2005;19(4):218-22.
33. Dunmore SJ, Al-Derawi AS, Nayak AU, Narshi A, Nevill AM, Hellwig A, Majebi A, Kirkham P, Brown JE, Singh BM. Evidence That Differences in Fructosamine-3-Kinase Activity May Be Associated With the Glycation Gap in Human Diabetes. Diabetes. 2018;67(1):131-6.
34. Leslie RD, Cohen RM. Biologic variability in plasma glucose, hemoglobin A1c, and advanced glycation end products associated with diabetes complications. J Diabetes Sci Technol. 2009;3(4):635-43.
35. Xu Y, Dunn TC, Ajjan RA. A Kinetic Model for Glucose Levels and Hemoglobin A1c Provides a Novel Tool for Individualized Diabetes Management. J Diabetes Sci Technol. 2021;15(2):294-302.
36. Campbell L, Pepper T, Shipman K. HbA1c: a review of non-glycaemic variables. J Clin Pathol. 2019;72(1):12-9.
37. Nielsen LR, Ekbom P, Damm P, Glumer C, Frandsen MM, Jensen DM, Mathiesen ER. HbA1c levels are significantly lower in early and late pregnancy. Diabetes Care. 2004;27(5):1200-1.

38. Karter AJ, Parker MM, Moffet HH, Gilliam LK. Racial and Ethnic Differences in the Association Between Mean Glucose and Hemoglobin A1c. Diabetes Technol Ther. 2023;25(10):697-704.
39. Bergenstal RM, Gal RL, Connor CG, Gubitosi-Klug R, Kruger D, Olson BA, Willi SM, Aleppo G, Weinstock RS, Wood J, Rickels M, DiMeglio LA, Bethin KE, Marcovina S, Tassopoulos A, Lee S, Massaro E, Bzdick S, Ichihara B, Markmann E, McGuigan P, Woerner S, Ecker M, Beck RW, Group TDERDS. Racial Differences in the Relationship of Glucose Concentrations and Hemoglobin A1c Levels. Ann Intern Med. 2017;167(2):95-102.
40. Cohen RM, Franco RS, Khera PK, Smith EP, Lindsell CJ, Ciraolo PJ, Palascak MB, Joiner CH. Red cell life span heterogeneity in hematologically normal people is sufficient to alter HbA1c. Blood. 2008;112(10):4284-91.
41. Perlman JE, Gooley TA, McNulty B, Meyers J, Hirsch IB. HbA1c and Glucose Management Indicator Discordance: A Real-World Analysis. Diabetes Technol Ther. 2021;23(4):253-8.
42. Bergenstal RM, Beck RW, Close KL, Grunberger G, Sacks DB, Kowalski A, Brown AS, Heinemann L, Aleppo G, Ryan DB, Riddlesworth TD, Cefalu WT. Glucose Management Indicator (GMI): A New Term for Estimating A1C From Continuous Glucose Monitoring. Diabetes Care. 2018;41(11):2275-80.
43. Piona C, Marigliano M, Mozzillo E, Di Candia F, Zanfardino A, Iafusco D, Maltoni G, Zucchini S, Piccinno E, Maffeis C. Evaluation of HbA1c and glucose management indicator discordance in a population of children and adolescents with type 1 diabetes. Pediatr Diabetes. 2022;23(1):84-9.
44. Ye L, Ji Y, Zhou C, Luo J, Zhang L, Jing L, Zhao X, Guo J, Gao Q, Peng G, Li Y, Li Y, Li J, Fan H, Yang W, Yang Y, Ma Y, Zhang F. Comparison of Levitt's CO breath test and the (15) N-glycine labeling technique for measuring the lifespan of human red blood cells. Am J Hematol. 2021;96(10):1232-40.
45. Little RR, Roberts WL. A review of variant hemoglobins interfering with hemoglobin A1c measurement. J Diabetes Sci Technol. 2009;3(3):446-51.
46. Amiel SA. The consequences of hypoglycaemia. Diabetologia. 2021;64(5):963-70.
47. Ceriello A, Novials A, Ortega E, Pujadas G, La Sala L, Testa R, Bonfigli AR, Genovese S. Hyperglycemia following recovery from hypoglycemia worsens

endothelial damage and thrombosis activation in type 1 diabetes and in healthy controls. Nutr Metab Cardiovasc Dis. 2014;24(2):116-23.
48. Wilmot EG, Choudhary P, Leelarathna L, Baxter M. Glycaemic variability: The under-recognized therapeutic target in type 1 diabetes care. Diabetes Obes Metab. 2019;21(12):2599-608.
49. Klimontov VV, Saik OV, Korbut AI. Glucose Variability: How Does It Work? Int J Mol Sci. 2021;22(15).
50. Danese E, Montagnana M, Nouvenne A, Lippi G. Advantages and pitfalls of fructosamine and glycated albumin in the diagnosis and treatment of diabetes. J Diabetes Sci Technol. 2015;9(2):169-76.
51. Walford S, Gale EA, Allison SP, Tattersall RB. Self-monitoring of blood-glucose. Improvement of diabetic control. Lancet. 1978;1(8067):732-5.
52. Miller KM, Beck RW, Bergenstal RM, Goland RS, Haller MJ, McGill JB, Rodriguez H, Simmons JH, Hirsch IB, Network TDEC. Evidence of a strong association between frequency of self-monitoring of blood glucose and hemoglobin A1c levels in T1D exchange clinic registry participants. Diabetes Care. 2013;36(7):2009-14.
53. American Diabetes Association Professional Practice C. 7. Diabetes Technology: Standards of Care in Diabetes-2025. Diabetes Care. 2025;48(1 Suppl 1):S146-S66.
54. Henriksen MM, Andersen HU, Thorsteinsson B, Pedersen-Bjergaard U. Asymptomatic hypoglycaemia in Type 1 diabetes: incidence and risk factors. Diabet Med. 2019;36(1):62-9.
55. Tauschmann M, Cardona-Hernandez R, DeSalvo DJ, Hood K, Laptev DN, Lindholm Olinder A, Wheeler BJ, Smart CE. International Society for Pediatric and Adolescent Diabetes Clinical Practice Consensus Guidelines 2024 Diabetes Technologies: Glucose Monitoring. Horm Res Paediatr. 2024;97(6):615-35.
56. MacLeod J, Im GH, Smith M, Vigersky RA. Shining the Spotlight on Multiple Daily Insulin Therapy: Real-World Evidence of the InPen Smart Insulin Pen. Diabetes Technol Ther. 2024;26(1):33-9.
57. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, Kollman C, Kruger D, McGill JB, Polonsky W, Toschi E, Wolpert H, Price D, Group DS. Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1

Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. JAMA. 2017;317(4):371-8.
58. Lind M, Polonsky W, Hirsch IB, Heise T, Bolinder J, Dahlqvist S, Schwarz E, Olafsdottir AF, Frid A, Wedel H, Ahlen E, Nystrom T, Hellman J. Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections: The GOLD Randomized Clinical Trial. JAMA. 2017;317(4):379-87.
59. Pratley RE, Kanapka LG, Rickels MR, Ahmann A, Aleppo G, Beck R, Bhargava A, Bode BW, Carlson A, Chaytor NS, Fox DS, Goland R, Hirsch IB, Kruger D, Kudva YC, Levy C, McGill JB, Peters A, Philipson L, Philis-Tsimikas A, Pop-Busui R, Shah VN, Thompson M, Vendrame F, Verdejo A, Weinstock RS, Young L, Miller KM, Wireless Innovation for Seniors With Diabetes Mellitus Study G. Effect of Continuous Glucose Monitoring on Hypoglycemia in Older Adults With Type 1 Diabetes: A Randomized Clinical Trial. JAMA. 2020;323(23):2397-406.
60. Lind M, Olafsdottir AF, Hirsch IB, Bolinder J, Dahlqvist S, Pivodic A, Hellman J, Wijkman M, Schwarcz E, Albrektsson H, Heise T, Polonsky W. 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. 2021;44(1):141-9.
61. Maiorino MI, Signoriello S, Maio A, Chiodini P, Bellastella G, Scappaticcio L, Longo M, Giugliano D, Esposito K. Effects of Continuous Glucose Monitoring on Metrics of Glycemic Control in Diabetes: A Systematic Review With Meta-analysis of Randomized Controlled Trials. Diabetes Care. 2020;43(5):1146-56.
62. Rizos EC, Markozannes G, Charitakis N, Filis P, Stoimeni AE, Norgaard K, Ntzani EE, Tsilidis KK. Continuous Glucose Monitoring in Type 1 Diabetes, Type 2 Diabetes, and Diabetes During Pregnancy: A Systematic Review with Meta-Analysis of Randomized Controlled Trials. Diabetes Technol Ther. 2025;27(7):537-52.
63. Miller KM, Beck RW, Foster NC, Maahs DM. HbA1c Levels in Type 1 Diabetes from Early Childhood to Older Adults: A Deeper Dive into the Influence of Technology and Socioeconomic Status on HbA1c in the T1D Exchange Clinic Registry Findings. Diabetes Technol Ther. 2020;22(9):645-50.
64. Noor N, Norman G, Sonabend R, Chao L, Kamboj M, Golden L, Bekx MT, Hseih S, Levy C, Sanchez J, Rapaport R, Ebekozien O. An Observational Crossover Study of

People Using Real-Time Continuous Glucose Monitors Versus Self-Monitoring of Blood Glucose: Real-World Evidence Using Electronic Medical Record Data From More Than 12,000 People With Type 1 Diabetes. J Diabetes Sci Technol. 2025;19(1):63-71.
65. Dorando E, Haak T, Pieper D. Correction: Continuous Glucose Monitoring for Glycemic Control in Children and Adolescents Diagnosed with Diabetes Type 1: A Systematic Review and Meta-Analysis. Exp Clin Endocrinol Diabetes. 2022;130(1):e1-e3.
66. Choudhary P, Arrieta A, van den Heuvel T, Castaneda J, Smaniotto V, Cohen O. Celebrating the Data from 100,000 Real-World Users of the MiniMed 780G System in Europe, Middle East, and Africa Collected Over 3 Years: From Data to Clinical Evidence. Diabetes Technol Ther. 2024;26(S3):32-7.
67. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, Bosi E, Buckingham BA, Cefalu WT, Close KL, Cobelli C, Dassau E, DeVries JH, Donaghue KC, Dovc K, Doyle FJ, 3rd, Garg S, Grunberger G, Heller S, Heinemann L, Hirsch IB, Hovorka R, Jia W, Kordonouri O, Kovatchev B, Kowalski A, Laffel L, Levine B, Mayorov A, Mathieu C, Murphy HR, Nimri R, Norgaard K, Parkin CG, Renard E, Rodbard D, Saboo B, Schatz D, Stoner K, Urakami T, Weinzimer SA, Phillip M. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019;42(8):1593-603.
68. Hirsch IB, Welsh JB, Calhoun P, Puhr S, Walker TC, Price DA. Associations between HbA(1c) and continuous glucose monitoring-derived glycaemic variables. Diabet Med. 2019;36(12):1637-42.
69. Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. Diabetes Care. 2002;25(2):275-8.
70. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ, Group Ac-DAGS. Translating the A1C assay into estimated average glucose values. Diabetes Care. 2008;31(8):1473-8.

71. Beck RW, Connor CG, Mullen DM, Wesley DM, Bergenstal RM. The Fallacy of Average: How Using HbA(1c) Alone to Assess Glycemic Control Can Be Misleading. Diabetes Care. 2017;40(8):994-9.
72. Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier D, Hermanns N. 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. Lancet. 2018;391(10128):1367-77.
73. Aleppo G, Ruedy KJ, Riddlesworth TD, Kruger DF, Peters AL, Hirsch I, Bergenstal RM, Toschi E, Ahmann AJ, Shah VN, Rickels MR, Bode BW, Philis-Tsimikas A, Pop-Busui R, Rodriguez H, Eyth E, Bhargava A, Kollman C, Beck RW, Group R-BS. REPLACE-BG: A Randomized Trial Comparing Continuous Glucose Monitoring With and Without Routine Blood Glucose Monitoring in Adults With Well-Controlled Type 1 Diabetes. Diabetes Care. 2017;40(4):538-45.
74. Beck RW, Riddlesworth TD, Ruedy K, Ahmann A, Haller S, Kruger D, McGill JB, Polonsky W, Price D, Aronoff S, Aronson R, Toschi E, Kollman C, Bergenstal R, Group DS. Continuous Glucose Monitoring Versus Usual Care in Patients With Type 2 Diabetes Receiving Multiple Daily Insulin Injections: A Randomized Trial. Ann Intern Med. 2017;167(6):365-74.
75. Fellinger P, Rodewald K, Ferch M, Itariu B, Kautzky-Willer A, Winhofer Y. HbA1c and Glucose Management Indicator Discordance Associated with Obesity and Type 2 Diabetes in Intermittent Scanning Glucose Monitoring System. Biosensors (Basel). 2022;12(5).
76. Diaz-Soto G, Bahillo-Curieses MP, Jimenez R, Nieto MO, Gomez E, Torres B, Lopez Gomez JJ, de Luis D. The relationship between glycosylated hemoglobin, time-in-range and glycemic variability in type 1 diabetes patients under flash glucose monitoring. Endocrinol Diabetes Nutr (Engl Ed). 2021;68(7):465-71.
77. Sterner Isaksson S, Imberg H, Hirsch IB, Schwarcz E, Hellman J, Wijkman M, Bolinder J, Nystrom T, Holmer H, Hallstrom S, Olafsdottir AF, Pekkari S, Polonsky W, Lind M. Discordance between mean glucose and time in range in relation to HbA(1c) in individuals with type 1 diabetes: results from the GOLD and SILVER trials. Diabetologia. 2024;67(8):1517-26.

78. Nayak AU, Holland MR, Macdonald DR, Nevill A, Singh BM. Evidence for consistency of the glycation gap in diabetes. Diabetes Care. 2011;34(8):1712-6.
79. Cohen RM, Snieder H, Lindsell CJ, Beyan H, Hawa MI, Blinko S, Edwards R, Spector TD, Leslie RD. Evidence for independent heritability of the glycation gap (glycosylation gap) fraction of HbA1c in nondiabetic twins. Diabetes Care. 2006;29(8):1739-43.
80. Morales-Dopico L, MacLeish SA. Expanding the horizon of continuous glucose monitoring into the future of pediatric medicine. Pediatr Res. 2024;96(6):1464-74.
81. Hagvik J. Glucose measurement: time for a gold standard. J Diabetes Sci Technol. 2007;1(2):169-72.
82. Olansky L, Kennedy L. Finger-stick glucose monitoring: issues of accuracy and specificity. Diabetes Care. 2010;33(4):948-9.
83. Freckmann G, Wehrstedt S, Eichenlaub M, Pleus S, Link M, Jendrike N, Oter S, Brandt D, Haug C, Waldenmaier D. A Comparative Analysis of Glycemic Metrics Derived From Three Continuous Glucose Monitoring Systems. Diabetes Care. 2025;48(7):1213-7.
84. Hassan MH, Vyas C, Grieve B, Bartolo P. Recent Advances in Enzymatic and Non-Enzymatic Electrochemical Glucose Sensing. Sensors (Basel). 2021;21(14).
85. Klueh U, Frailey JT, Qiao Y, Antar O, Kreutzer DL. Cell based metabolic barriers to glucose diffusion: macrophages and continuous glucose monitoring. Biomaterials. 2014;35(10):3145-53.
86. Scharf M, Feriz K, Yepes C, Contreras A, Lequi L, Sanhueza D, Krakauer M, Marquez E, Re M, Mehta R. Consensus statement on standardizing CGM evaluation metrics in Latin America: an expert approach. Diabetol Metab Syndr. 2025;17(1):291.
87. Pleus S, Eichenlaub M, Eriksson Boija E, Fokkert M, Hinzmann R, Jendle J, Klonoff DC, Makris K, Nichols JH, Pemberton J, Selvin E, Slingerland RJ, Thomas A, Tran NK, Witthauer L, Freckmann G. The Need for Standardization of Continuous Glucose Monitoring Performance Evaluation: An Opinion by the International Federation of Clinical Chemistry and Laboratory Medicine Working Group on Continuous Glucose Monitoring. J Diabetes Sci Technol. 2024:19322968241296097.

88. Pemberton JS, Adolfsson P, Wilmot EG, Choudhary P, Moser O. Urgent Need for Standardization in CGM Performance Assessment. Diabetes Care. 2025;48(10):e126-e7.
89. US Department of Health and Human Services and Food and Drug Administration. Recognized consensus standards: medical devices. Integrated continuous glucose monitoring system, factory calibrated. Regulation Number §862.1355 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=862.1355 Accessed November 23, 2024. 2024.
90. Vigersky RA, Shin J. The Myth of MARD (Mean Absolute Relative Difference): Limitations of MARD in the Clinical Assessment of Continuous Glucose Monitoring Data. Diabetes Technol Ther. 2024;26(S3):38-44.
91. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1(8476):307-10.
92. Twomey PJ. How to use difference plots in quantitative method comparison studies. Ann Clin Biochem. 2006;43(Pt 2):124-9.
93. Javorfi T, Kocsis G, Svebis MM, Ferencz V, Domjan BA, Kezdi A, Hanko H, Putz Z, Tabak AG. Glucose management indicator: Do we need device-specific equations? Diabetes Metab. 2025;51(4):101661.
94. Javorfi T, Kocsis G, Svebis MM, Ferencz V, Domjan BA, Kezdi A, Hanko H, Putz Z, Meszaros S, Selley E, Nagy T, Molnar GA, Tabak AG. Refitting the generic glucose management indicator for the Guardian 4 Sensor significantly improves estimation of glycaemic control – A model development and validation study. Unpublished data, provisionally accepted for publication in PLOS Digital Health. Date of provisional acceptance: 22.09.2026.
95. Christiansen MP, Garg SK, Brazg R, Bode BW, Bailey TS, Slover RH, Sullivan A, Huang S, Shin J, Lee SW, Kaufman FR. Accuracy of a Fourth-Generation Subcutaneous Continuous Glucose Sensor. Diabetes Technol Ther. 2017;19(8):446-56.
96. Mc NQ. Note on the sampling error of the difference between correlated proportions or percentages. Psychometrika. 1947;12(2):153-7.
97. Grimsmann JM, von Sengbusch S, Freff M, Ermer U, Placzek K, Danne T, Hammer E, Holl RW, Initiative DPV. Glucose Management Indicator Based on Sensor Data and

Laboratory HbA(1c) in People With Type 1 Diabetes From the DPV Database: Differences by Sensor Type. Diabetes Care. 2020;43(9):e111-e2.
98. Oriot P, Viry C, Vandelaer A, Grigioni S, Roy M, Philips JC, Prevost G. Discordance Between Glycated Hemoglobin A1c and the Glucose Management Indicator in People With Diabetes and Chronic Kidney Disease. J Diabetes Sci Technol. 2023;17(6):1553-62.
99. Pujante Alarcon P, Alonso Felgueroso C, Ares Blanco J, Morales Sanchez P, Lambert Goitia C, Rodriguez Escobedo R, Rodriguez Rodero S, Delgado Alvarez E, Menendez Torre EL. Correlation between glucose measurement parameters of continuous flash monitoring and HbA1c. Real life experience in Asturias. Endocrinol Diabetes Nutr (Engl Ed). 2022;69(7):493-9.
100. Yoo JH, Moon SJ, Park CY, Kim JH. Differences Between Glycated Hemoglobin and Glucose Management Indicator in Real-Time and Intermittent Scanning Continuous Glucose Monitoring in Adults With Type 1 Diabetes. J Diabetes Sci Technol. 2024:19322968241262106.
101. Lazar S, Potre O, Ionita I, Reurean-Pintilei DV, Timar R, Herascu A, Avram VF, Timar B. The Usefulness of the Glucose Management Indicator in Evaluating the Quality of Glycemic Control in Patients with Type 1 Diabetes Using Continuous Glucose Monitoring Sensors: A Cross-Sectional, Multicenter Study. Biosensors (Basel). 2025;15(3).
102. Leelarathna L, Beck RW, Bergenstal RM, Thabit H, Hovorka R, Apcam APh, Investigators AP. Glucose Management Indicator (GMI): Insights and Validation Using Guardian 3 and Navigator 2 Sensor Data. Diabetes Care. 2019;42(4):e60-e1.
103. Freckmann G, Pleus S, Schauer S, Link M, Jendrike N, Waldenmaier D, Haug C, Stuhr A. Choice of Continuous Glucose Monitoring Systems May Affect Metrics: Clinically Relevant Differences in Times in Ranges. Exp Clin Endocrinol Diabetes. 2022;130(5):343-50.
104. Selvin E, Wang D, Rooney MR, Fang M, Echouffo-Tcheugui JB, Zeger S, Sartini J, Tang O, Coresh J, Nisha Aurora R, Punjabi NM. Within-Person and Between-Sensor Variability in Continuous Glucose Monitoring Metrics. Clin Chem. 2023;69(2):180-8.

105. Kumagai R, Muramatsu A, Fujii M, Katakura Y, Ito K, Fujie K, Nakata Y, Hashimoto K, Yagyu H. Comparison of glucose monitoring between Freestyle Libre Pro and iPro2 in patients with diabetes mellitus. J Diabetes Investig. 2019;10(3):851-6.
106. Michalak A, Pagacz K, Mlynarski W, Szadkowska A, Fendler W. Discrepancies between methods of continuous glucose monitoring in key metrics of glucose control in children with type 1 diabetes. Pediatr Diabetes. 2019;20(5):604-12.
107. Eichenlaub M, Waldenmaier D, Wehrstedt S, Pleus S, Link M, Jendrike N, Öter S, Haug C, Schinz M, Braunack-Mayer V, Schneider R, Brandt D, Freckmann G. Performance of Three Continuous Glucose Monitoring Systems in Adults With Type 1 Diabetes. Journal of Diabetes Science and Technology.0(0):19322968251315459.
108. Freckmann G, Eichenlaub M, Waldenmaier D, Pleus S, Wehrstedt S, Haug C, Witthauer L, Jendle J, Hinzmann R, Thomas A, Eriksson Boija E, Makris K, Diem P, Tran N, Klonoff DC, Nichols JH, Slingerland RJ. Clinical Performance Evaluation of Continuous Glucose Monitoring Systems: A Scoping Review and Recommendations for Reporting. J Diabetes Sci Technol. 2023;17(6):1506-26.
109. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577-89.
110. Monzon AD, Patton SR, Clements M. An Examination of the Glucose Management Indicator in Young Children with Type 1 Diabetes. J Diabetes Sci Technol. 2022;16(6):1505-12.
111. Bergenstal RM, Beck RW. The Glucose Management Indicator: Time to Change Course? Diabetes Care 2024;47:906-914. Diabetes Care. 2024;47(6):e48-e9.
112. Dunn TC, Xu Y, Bergenstal RM, Ogawa W, Ajjan RA. Personalized Glycated Hemoglobin in Diabetes Management: Closing the Gap with Glucose Management Indicator. Diabetes Technol Ther. 2023;25(S3):S65-S74.
113. Castaneda J, de Galan BE, van Kuijk SMJ, Arrieta A, van den Heuvel T, Cohen O. The interdependence of targets for continuous glucose monitoring outcomes in type 1 diabetes with automated insulin delivery. Diabetes Obes Metab. 2024;26(12):5836-44.
114. Thrasher JR, Arrieta A, Niu F, Cameron KR, Cordero TL, Shin J, Rhinehart AS, Vigersky RA. Early Real-World Performance of the MiniMed 780G Advanced Hybrid Closed-Loop System and Recommended Settings Use in the United States. Diabetes Technol Ther. 2024;26(S3):24-31.

9. Bibliography of the candidate's publications

9.1. Publications directly related to this thesis

1., Jávorfi Tamás, Kocsis Győző, Svébis Márk M, Ferencz Viktória, Domján Beatrix A, Kézdi Árpád, Hankó Hanna, Putz Zsuzsanna, Tabák Ádám G
Glucose management indicator: Do we need device-specific equations?
DIABETES & METABOLISM 51: 4 Paper: 101661, 8 p. (2025)
Közlemény: 36163744 | Szakcikk (Folyóiratcikk) | Tudományos
Scopus - Medicine (miscellaneous) SJR indikátor: D1
Scopus - Endocrinology SJR indikátor: Q1
Scopus - Endocrinology, Diabetes and Metabolism SJR indikátor: Q1
Scopus - Internal Medicine SJR indikátor: Q1
IF: 5,8

9.2. Publications not directly related to this thesis

1., Kézdi Árpád, Horváth Viktor J, Vass Viktor, Svébis Márk M, Kocsis Győző, Ferencz Viktória, Jávorfi Tamás, Domján Beatrix A, Tabák Ádám G
Changes of the cardiac electrical cycle in type 1 diabetes during hypoglycaemia – a prospective observational study
FRONTIERS IN ENDOCRINOLOGY 16 Paper: 1690371, 14 p. (2026)
Közlemény: 36855454 | Szakcikk (Folyóiratcikk) | Tudományos
Scopus - Endocrinology, Diabetes and Metabolism SJR indikátor: Q1
IF: 5,7

2., Panykó István, Kun Attila, Visolyi Gergely A, Domján Beatrix A, Svébis Márk M, Ferencz Viktória, Kézdi Árpád, Jávorfi Tamás, Kocsis Győző, Szabó Eszter, Kerényi Zsuzsa, Tabák Ádám
Trends in Gestational Diabetes Identified through Universal Screening: A Population-Based Observational Study
BJOG: AN INTERNATIONAL JOURNAL OF OBSTETRICS AND GYNAECOLOGY
2026 Paper: DOI: 10.1111/1471-0528.70261, 10 p. (2026)
Közlemény: 37170195 | Szakcikk (Folyóiratcikk) | Tudományos

Scopus - Obstetrics and Gynecology SJR indikátor: D1
IF: 4,8

9.3. Abstracts (not directly related to this thesis)

1., Hankó H, Lee Y, Tóth B, Garam N, Jávorfi T, Svébis M, Tabák G, Kocsis G
A MINIMED 780G INZULINPUMPARENDSZER ANYAGCSERÉRE GYAKOROLT HATÁSA MAGYAR BELORVOSI ARCHIVUM 77: 5-6 pp. 339-339. (2024)
Közlemény: 35707528 | Absztrakt | Kivonat (Folyóiratcikk) | Tudományos Jávorfi T,

2., Garam N, Kocsis G, Svébis M, Tóth B, Ferenci T, Eigner G, Barkai S, Kovács L
A MINIMED™ 780G INZULINPUMPA-RENDSZER HATÁSA AZ ANYAGCSERÉRE – EGY-CENTRUMOS PROSPEKTÍV OBSZERVÁCIÓS VIZSGÁLATUNK EREDMÉNYE
MAGYAR BELORVOSI ARCHIVUM 76: 5-6 pp. 313-314. (2023)
Közlemény: 34561937 | Absztrakt | Kivonat (Folyóiratcikk) | Tudományos

3., Jávorfi Tamás, Kocsis Győző
Adjuváns kezelések 1-es típusú diabetes mellitusban – elméleti háttér és esetbemutatás
DIABETOLOGIA HUNGARICA 28: Suppl. 1 pp. 53-54. (2020)
Közlemény: 32784737 | Absztrakt | Kivonat (Folyóiratcikk) | Tudományos

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