The Relationship between Continuous Glucose Monitor (CGM) Derived Metrics and Indices of Glycemic Control

by

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Abstract

Introduction: Both hypoglycemia (low blood glucose) and hyperglycemia (high blood glucose) are common among individuals with type 1 diabetes and are associated with severe medical complications, therefore it is essential that health care providers are able to accurately measure glycemic control. Measures derived from continuous glucose monitoring (CGM) may provide more accurate measurements of glycemia than the commonly used HbA1c blood test.

Methods: Data from the Juvenile Diabetes Research Foundation (JDRF) clinical trial to assess the efficacy of continuous glucose monitoring was used to estimate the ability of CGM composite scores to predict time in range, time in hyperglycemia and time in hypoglycemia. Spearman partial correlation coefficients were calculated between composite measures and thresholds of glycemia.

Results: HbA1c showed week correlations with time below 54 mg/dL (R = -0.05) and time below 70 mg/dL (R = -0.21). HbA1c was moderately correlated with time in range (R = -0.62), however, most other CGM derived metrics had stronger correlations. HbA1c was also moderately correlated with time above 180 mg/dL (R = 0.68) and time above 250 mg/dL (R = 0.64), however several CGM derived composite scores including the J-index, GRADE, the Q-score, GMI, CGP, and PGS all had stronger correlations with time in hyperglycemia (Table 3).

Conclusions: HbA1c is a poor predictor of time in hypoglycemia and moderately correlated with time in hyperglycemia. Several composite metrics had stronger correlations with both hypo and hyperglycemia than HbA1c and were better predictors of meeting clinical targets.

Introduction and Review of Literature

Type 1 diabetes (T1D) is a chronic disease in which the immune system attacks the body's insulin producing beta cells (Marca, Gianchecchi, & Fierabrachi, 2018). Without these cells the body cannot produce insulin, which is needed to convert glucose into energy (Marca et al., 2018). Therefore, people with T1D must manually administer insulin using either an insulin pump or through daily injections (Danne et al., 2017). If an insufficient quantity of insulin is administered this will result in an excess of glucose in the blood, known as hyperglycemia (Beck et al., 2019). Hyperglycemia is associated with several long-term complications including diabetic retinopathy, nephropathy, autonomic and peripheral neuropathy, and cardiovascular disease (Beck et al., 2019; Nathan, 2013; Vigersky et al., 2018). If excess insulin is administered, this results in an insufficient amount of glucose in the blood, known as hypoglycemia (American Diabetes Association [ADA], 2019; Hirsch et al., 2017). Hypoglycemia is associated with several short-term complications such as rapid heart rate, dizziness, shortness of breath, seizures, loss of consciousness and in serious cases death (ADA, 2019). Administering the correct amount of insulin can be a challenge for those with T1D as the amount of insulin required changes based on changes in diet and physical activity (ADA, 2019). Therefore, it is essential for T1D patients to continuously monitor their glucose in order to administer the appropriate amount of insulin and prevent long- and short-term complications from hypoglycemia and hyperglycemia, and it is important for providers to assess the glycemic control of their patients.

Currently the gold standard for measuring glycemic control is hemoglobin A1c (HbA1c) (Beck, Connor, Mullen, Wesley, & Bergenstal, 2017; Bergenstal et al., 2018; Khonert, 2015). Overtime, small amounts of glucose will attach to hemoglobin molecules in the red blood cells. Researchers found that concentrations of glycated hemoglobin are directly proportional to an individual's mean glucose over a three month period, with a higher HbA1c indicating a higher mean glucose over time (Beck et al., 2017). The Diabetes Control and Complications Trial (DCCT), a ten year trial conducted from 1983 – 1993 among individuals with type 1 and 2 diabetes, established that HbA1c was a strong predictor of long term diabetes complications (Nathan, 2013). However, there are several disadvantages to using HbA1c as a measure of glycemic control.

One disadvantage is that a single value of HbA1c can be associated with a wide range of mean glucose values. Beck et al. (2017) showed that those with an HbA1c of 6% could have a mean glucose anywhere between 101 mg/dL - 163 mg/dL, those with an HbA1c of 7% could have a mean from 128 mg/dL to 190 mg/dL, and those with an HbA1c of 8% could have a mean from 155 mg/dL to 218 mg/dL. Therefore, it is difficult to identify from the HbA1c alone if a person's average glucose has been in a healthy range. HbA1c is only moderately correlated with the time spent in range and time spent in hyperglycemia, and weekly correlated with time spent in hypoglycemia (Beck et al., 2017; Beck et al., 2019). Another disadvantage of HbA1c is that inter-individual variability in red blood cell lifespan can alter A1c levels even when blood glucose levels are constant (Cohen et al., 2008). For two people with the same mean glucose over time, the person with a higher red blood cell lifespan will have a higher HbA1c, as their cells have been exposed to glucose for longer. Abnormally low or high red blood cell lifespans can be caused by medical conditions such as anemia, high triglyceride levels, pregnancy, and red

blood cell transfusion, however even in the absence of these conditions there is still some inter-individual variation in life span (Cohen et al., 2008).

Alternative methods of measuring glycemic control that do not have the same disadvantages as A1c are possible through the use of continuous glucose monitoring (CGM) devices. The continuous glucose monitor is a device worn by T1D patients and records a measurement of glucose every 5 minutes (Danne et al., 2017; Henriques, Munshi, Segal, Costa, & Goldberger, 2014). The device consists of three components; a sensor, which is inserted under the skin to measure glucose, the transmitter, which is attached to the sensor and transmits the glucose reading to the receiver, and a device which displays the individual's glucose levels in real time (Danne et al., 2017). In addition to helping those with T1D better control their glucose, data from CGM devices can be used to calculate various measures of glycemic control such as mean glucose, glucose variability, percent time spent in a healthy range (70-180 mg/dL), percent time spent in hyperglycemia (>180 mg/dL), and percent time spent in hypoglycemia (<70 mg/dL) (Beck et al., 2019; Service, 2013). The indices on which physicians most rely when evaluating a patient's glucose control are the time spent in thresholds of hypoglycemia, hyperglycemia and a healthy glycemic range (Beck et al., 2019; Costa, Enriques, Munshi, Segal, & Goldberger, 2014). While these individual indices provide quality information on different aspects of a person's glycemic control, it is challenging for clinicians to assess a patients overall control from so many different metrics (Hirsch et al., 2017; Khonert, 2015) and up to date there is no single standard measure for evaluating an individual's glycemic control using CGM data, though many metrics have been proposed (Khonert, 2015; Peyser, Balo, Buckingham, Hirsch, & Garcia, 2018). This also poses a challenge for clinical research as the primary end point in diabetes clinical trials is usually glucose control, and none of these indices used alone can

appropriately reflect a person's overall control. Therefore, a measurement that is sensitive to hyperglycemia risk, hypoglycemia risk, and time spent in a healthy range is needed.

There are many proposed metrics calculated using CGM that are intended to measure a patient's overall glucose control. These include the following: Comprehensive glucose pentagon (Vigersky et al., 2018), Personal Glycemic State (Hirsch et al., 2017), Average Daily Risk Range (ADRR) (Khonert, 2015; Kovatchev, Otto, Cox, Gonder-Fredrick, & Clark, 2006; McCall et al., 2009), Glycemic Risk Assessment Diabetes Equation (GRADE) (Hill, 2007; Khonert, 2015), Q-score (Augustein et al., 2015; Khonert, 2017), J-index (Service, 2013), Glucose Management Indicator (GMI) (Bergenstal et al., 2018), Glycemic Variability Percentage (GVP) (Peyser et al., 2018), Mean Amplitude of Glycemic Excursions (MAGE) (Rawlings et al., 2011; Service, 2013), Mean of Daily Differences (MODD) (Rawlings et al., 2011; Service, 2013), and Continuous Overall Net Glycemic Action (CONGA) (Rawlings et al., 2011; Marics, 2015; Service, 2013). The purpose of this study will be to assess the correlation of CGM derived composite metrics of glucose control with the commonly used CGM indices of time in range, time in hypoglycemia, and time in hyperglycemia.

Hypothesis

In this study the primary analysis will test how well HbA1c and each of the CGM metrics listed above are correlated with the following glycemic indices

- Time in a healthy range (70 mg/dL to 180 mg/dL)
- Time in hyperglycemia (>180 mg/dL)
- Time in severe hyperglycemia (>250 mg/dL)
- Time in hypoglycemia (<70 mg/dL)

- Time in severe hypoglycemia (<54 mg/dL)

In 2019 the Advanced Technologies and Treatments for Diabetes (ATTD) congress established clinical targets for commonly used CGM indices (Battelino et al., 2019). For individuals with type 1 diabetes the clinical targets are outlined below:

- Time in Range (70-180 mg/dL): > 70%
- Time > 180 mg/dL: <25%
- Time > 250 mg/dL: <10%
- Time < 70 mg/dL: <4%
- Time < 54 mg/dL: <1%

As a secondary analysis, ROC curves will be used to assess the ability of each of the CGM metrics under study to predict whether or not an individual is meeting the clinical guidelines established by ATTD.

Methods

Data Collection

This analysis used data collected from the Juvenile Diabetes Research Foundation (JDRF) randomized clinical trial to assess the efficacy of real time continuous glucose monitoring in the management of type 1 diabetes (U.S., National Library of Medicine, 2017; Tamborlane et al., 2008). This trial enrolled 451 participants and consisted of two phases, each phase lasting six months. In phase 1, participants were randomized to the treatment group, which was to wear an unblinded CGM device, or the control group, which consisted of wearing a blinded CGM device (a device with no receiver). In phase 2, participants in the control group were given an unblinded CGM device, and both groups were followed for an additional six months. The dataset is publicly available at http://diabetes.jaeb.org/RT_CGMRCTProtocol.aspx.

Participants enrolled in this study were 8 years old or older, had a clinical diagnosis of T1D for at least 1 year, and a baseline HbA1c of <10%. Participants were using either pump or multiple daily injections to administer insulin in order to be eligible. Individuals were excluded if they used corticosteroids, had a diagnosis of asthma or cystic fibrosis, or received psychiatric treatment in the previous 6 months. Those who had used a CGM device in the previous 6 months or who were pregnant were also excluded (U.S., National Library of Medicine, 2017; Tamborlane et al., 2008).

List of Measures

Data on participant's age, gender, duration of T1D, insulin delivery method, BMI, socio-economic status and other demographic and clinical characteristics were obtained through

participant questionnaires and medical chart data. Values for HbA1c were collected from a central laboratory every 3 months, with a maximum of five values for each participant (U.S., National Library of Medicine, 2017; Tamborlane et al., 2008). The glucose indices were calculated by taking the percentage of CGM records that fall within each specified range (70 – 180 mg/dL, >180 mg/dL, etc.) out of all valid CGM records. Details on the calculation of CGM composite scores are provided in published literature (Augustein et al., 2015; Bergenstal et al., 2018; Hill, 2007; Hirsch et al., 2017, Khonert, 2015; Khonert, 2017; Kovatchev et al., 2006; Marics, 2015; McCall et al., 2009; Peyser et al., 2018; Rawlings et al., 2011; Service, 2013; Vigersky et al., 2018).

Statistical Methods

Summary statistics were tabulated for demographic variables, clinical characteristics, glucose indices, and CGM metrics (Tables 1 and 2). Median and interquartile range were reported for continuous variables and frequencies and proportions were reported for categorical variables.

Spearman partial correlations were used to assess the relationship between each CGM composite metric and the glycemic indices (Table 3). This method is appropriate as the glycemic indices time > 180 mg/dL, time > 250 mg/dL, time < 70 mg/dL, and time <54 mg/dL tend to be non-normally distributed, requiring a non-parametric test (Beck et al., 2019). P-values testing the null hypothesis that correlation coefficients are not significantly different from 0 were reported. Correlations were adjusted for age, sex, race, highest education level, pump use, diabetes duration, and treatment group.

Receiver Operating Characteristics (ROC) curves plot the sensitivity by 1 minus the specificity of logistic regression models and the area under the curve. ROC curves measure the

model's ability to predict an event versus a non-event. ROC curves were produced for each of the 5 glycemic indices to indicate the predictive performance of each CGM metric (Figures 1-5) in predicting if a participant met the ATTD clinical targets for the respective glycemic index. Area under the curve was estimated using the c-statistic (Table 4). Data from the primary phase (phase 1) of the JDRF trial was used to compute correlation coefficients and ROC curves.

All p-values reported were two-sided and all analysis will be performed using SAS version 9.4 (Cary, NC).

Results

Participant characteristics are displayed in Table 1. Mean age at baseline was 25 years old, 248 (55%) of participants were female, 425 (94%) were white, 332 (74%) had a bachelor's degree or higher, 367 (81%) used an insulin pump, and participants had been diagnosed with diabetes for an average of 14 (±12) years. During the primary phase of the study the median time spent below 54 mg/dL was 0.6% (IQR: 0.2%-2%), median time below 70 mg/dL was 4% (IQR: 1%-6%), median time in range was 61% (IQR: 50%-71%), median time above 180 mg/dL was 35% (IQR: 24%-46%), and median time above 250 mg/dL was 9% (IQR: 5%-17%). Summary statistics for CGM derived measures of glucose control and variability as well as HbA1c are shown in Table 2.

Table 1. Participant Demographic and Clinical Characteristics

	N = 451
Age at baseline (yrs) – Mean ± SD	25 ± 16
Female – N (%)	248 (55%)
Race – N (%)	
White	425 (94%)
Black	7 (2%)
Other	19 (4%)
Highest Education – N (%)	
Highschool or less	58 (13%)
Associates	61 (14%)
Bachelors	197 (44%)
Masters	100 (22%)
Doctorate/Professional	35 (8%)
Diabetes Duration (yrs) – Mean ± SD	14 ± 12
Pump Users - N (%)	367 (81%)
Treatment Group	232 (51%)

Table 2. Summary Statistics for Continuous Glucose Monitor Derived Metrics and HbA1c by Study Stage[1,2]

	Phase 1	Phase 2
HbA1c (%)	7.2 (6.8-7.7)	7.3 (6.8-7.8)
Time below 54 mg/dL (%)	0.6 (0.2-2)	0.6 (0.2-2)
Time below 70 mg/dL (%)	4 (1-6)	3 (2-6)
Time in Range (70-180 mg/dL) (%)	61 (50-71)	61 (51-71)
Time above 180 mg/dL (%)	35 (24-46)	34 (23-45)
Time above 250 mg/dL (%)	9 (5-17)	9 (4-16)
Pentagon Area	1081 (891-1401)	1066 (877-1326)
Personal Glycemic State	18 (13-22)	17 (12-21)
ADRR	40 (32-48)	39 (32-47)
GRADE	35 (32-39)	36 (32-39)
Q-Score	7.8 (5.6-10.5)	8.0 (5.6-10.3)
GMI (%)	7.2 (6.8-7.6)	7.2 (6.8-7.6)
J-Index	50 (40.6-63.6)	51 (39-63)
MAGE	117 (100-134)	115 (98-130)
GVP (%)	36 (29-51)	38 (30-52)
MODD	66 (56-77)	64 (54-74)
$CONGA_1$	29 (25-34)	29 (25-34)
$CONGA_2$	41 (35-48)	42 (36-48)
$CONGA_4$	51 (43-59)	51 43-59)

1. Shows median (interquartile range)
2. Summary statistics shown for hemoglobin A1c (HbA1c), the comprehensive glucose pentagon area (CGP), personal glycemic state (PGS), average daily risk range (ADRR), glycemic risk assessment diabetes equation (GRADE), Q-Score, glucose management indicator (GMI), J-index, mean amplitude of glycemic excursions (MAGE), mean of daily differences (MODD), continuous net glycemic action (CONGA) and time below 54 mg/dL, time below 70 mg/dL, time in range , time above 180 mg/dL and time above 250 mg/dL.

HbA1c showed week negative correlations with time below 54 mg/dL (R = -0.05) and time below 70 mg/dL (R = -0.21). HbA1c had a weaker correlation with time below 54 mg/dL than any CGM derived metrics, with the exception of the J-index (R = -0.01). ADRR had the strongest correlation with time below 54 mg/dL (0.60) and the second strongest correlation with time below 70 mg/dL (R = 0.45), with GRADE having the strongest correlation with time below 70 mg/dL. GVP, CONGA and CGP had moderate correlations with time below 54 mg/dL, while GMI had a moderate correlation with time below 70 mg/dL (Table 3).

HbA1c was moderately correlated with time in range (R = -0.62), however all other CGM derived metrics with the exception of GVP and $CONGA_1$ had stronger correlations. The Q-score

had the strongest correlation with time in range (R = -0.93), with J-index (R = -0.91), CGP (R = -0.88), PGS (R = -0.88), and GMI (R = -0.85) also being strongly correlated with time in range. HbA1c was also moderately correlated with time above 180 mg/dL (R = 0.68) and time above 250 mg/dL (R = 064). GMI had the strongest correlation with time above 180 mg/dL (R = 0.97), with J-index (R = 0.95) and GRADE (R = 0.95) also being highly correlated. J-index had the strongest correlation with time above 250 mg/dL (R = 0.97) with Q-score (R = 0.90), and GMI (R = 0.89) also being highly correlated.

HbA1c had the lowest area under the curve when predicting if a participant was meeting the clinical targets for time below 54 mg/dL (AUC = 0.51), time below 70 mg/dL (AUC = 0.57), time in range (AUC = 0.79), and time above 250 mg/dL (AUC = 0.80). The model with ADRR correctly predicted if a participant was meeting the clinical target for time below 54 mg/dL 84% of the time, and was more accurate than any other composite score. GRADE and ADRR were the best predictors of meeting the time below 70 mg/dL clinical target (GRADE AUC = 0.73, ADRR AUC = 0.71). The models with Q-score, J-index, and CGP all predicted meeting the clinical target for time in range correctly with 95% or greater accuracy, the Q-score and J-index had greater than 95% accuracy when predicting meeting the clinical target for time above 180 mg/dL, and the models with Q-score, J-index, CGP, and MODD all had greater than 95% accuracy when predicting meeting the time above 250 mg/dL target (Table 4).

Table 3. Spearman Partial Correlations between HbA1c, Composite Metrics of Glycemic Control Derived from Continuous Glucose Monitors and Time in Range, Time in Hypoglycemia, and Time in Hyperglycemia [1,2,3]

	$T_{<54}$			$T_{<70}$			T_{Range}			$T_{>180}$			$T_{>250}$		
	R	**P**	**Rank**	**R**	**P**	**Rank**	**R**	**P**	**Rank**	**R**	**P**	**Rank**	**R**	**P**	**Rank**
HbA1c	-0.05	0.3449	11	-0.21	<.0001	7	-0.62	<.0001	10	0.68	<.0001	6	0.64	<.0001	10
CGP	0.38	<.0001	4	0.25	<.0001	6	-0.88	<.0001	3	0.69	<.0001	5	0.83	<.0001	4
PGS	0.34	<.0001	5	0.13	0.0107	10	-0.88	<.0001	3	0.81	<.0001	3	0.84	<.0001	3
ADRR	0.60	<.0001	1	0.45	<.0001	2	-0.68	<.0001	8	0.48	<.0001	9	0.65	<.0001	9
GRADE	-0.29	<.0001	9	-0.52	<.0001	1	-0.79	<.0001	6	0.95	<.0001	2	0.82	<.0001	5
Q-Score	0.32	<.0001	7	0.15	0.0034	9	-0.93	<.0001	1	0.81	<.0001	3	0.90	<.0001	2
GMI (%)	-0.21	<.0001	10	-0.42	<.0001	3	-0.85	<.0001	4	0.97	<.0001	1	0.89	<.0001	3
J-Index	-0.01	0.8268	12	-0.19	0.0003	8	-0.91	<.0001	2	0.95	<.0001	2	0.97	<.0001	1
MAGE	0.33	<.0001	6	0.19	0.0002	8	-0.79	<.0001	6	0.68	<.0001	6	0.81	<.0001	6
GVP (%)	0.44	<.0001	2	0.26	<.0001	5	-0.50	<.0001	12	0.39	<.0001	10	0.49	<.0001	12
MODD	0.31	<.0001	8	0.21	<.0001	7	-0.80	<.0001	5	0.70	<.0001	4	0.83	<.0001	4
$CONGA_1$	0.40	<.0001	3	0.26	<.0001	5	-0.60	<.0001	11	0.48	<.0001	9	0.62	<.0001	11
$CONGA_2$	0.40	<.0001	3	0.27	<.0001	4	-0.66	<.0001	9	0.54	<.0001	8	0.70	<.0001	8
$CONGA_4$	0.38	<.0001	4	0.26	<.0001	5	-0.71	<.0001	7	0.59	<.0001	7	0.77	<.0001	7

1. Spearman partial correlations calculated using data from phase 1 of the JDRF clinical trial.
2. Correlation coefficients adjusted for age, sex, race, education, pump use, diabetes duration, and treatment group.
3. Correlations between hemoglobin A1c (HbA1c), the comprehensive glucose pentagon area (CGP), personal glycemic state (PGS), average daily risk range (ADRR), glycemic risk assessment diabetes equation (GRADE), Q-Score, glucose management indicator (GMI), J-index, mean amplitude of glycemic excursions (MAGE), mean of daily differences (MODD), continuous net glycemic action (CONGA) and time below 54 mg/dL ($T_{<54}$), time below 70 mg/dL ($T_{<70}$), time in range (T_{range}), time above 180 mg/dL ($T_{>180}$) and time above 250 mg/dL ($T_{>250}$).

Discussion

The associations between composite measures of glycemic control, measures glucose variability, HbA1c and hyperglycemia, hypoglycemia and time in range were examined using data from the JDRF randomized clinical trial to assess the efficacy of CGM. No composite scores were strongly correlated with hypoglycemia, suggesting a need for metrics to be more sensitive to changes in length of time and severity of hypoglycemia. ADRR, GVP, and CONGA were moderately correlated with time in severe hypoglycemia (<54 mg/dL), and ADRR, GRADE, and GMI were moderate correlated with time in hypoglycemia (< 70 mg/dL). GVP and CONGA are measures of glucose variability and were more sensitive to time below 54 mg/dL than most other metrics, suggesting that those spending more time <54 mg/dL have a high variability of glucose levels. Previous research suggested that hypoglycemia is associated with glycemic variability (Hachmann-Nelson, Bartholdy, Djurhoos, & Kvist, 2018). The average daily risk range was more correlated with time below 54 mg/dL than any other metric, likely because ADRR is composed of a hyperglycemic risk score and hypoglycemic risk score, and both scores are given equal weight when calculating the composite score. This may also explain why ADRR had weaker correlations with time in range and time in hyperglycemia, as many of those with a high risk score for hyperglycemia may have had lower risk scores of hypoglycemia, moving the overall score towards the average despite a high risk of hyperglycemia. GRADE was the strongest correlated metric with time below 70 mg/dL, with ADRR having the second strongest correlation. Both GRADE and ADRR are calculated by transforming each blood glucose measurement to reflect the risk of hypo/hyper glycemia, which

may have resulted in more weight being placed on hypoglycemic measurements compared to other composite scores.

Table 4. Area Under the ROC Curves for Predicting Clinical Targets for Glycemic Ranges Established by Advanced Technologies and Treatments for Diabetes Congress[1]

	$T_{<54}$	$T_{<70}$	T_{Range}	$T_{>180}$	$T_{>250}$
HbA1c	0.51	0.57	0.79	0.82	0.80
CGP	0.70	0.59	0.95	0.89	0.96
PGS	0.70	0.56	0.93	0.89	0.90
ADRR	0.84	0.71	0.88	0.77	0.86
GRADE	0.60	0.73	0.90	0.96	0.87
Q-Score	0.69	0.57	0.99	0.92	0.97
GMI	0.56	0.69	0.93	0.98	0.92
J-Index	0.54	0.58	0.97	0.99	0.98
GVP	0.76	0.62	0.80	0.77	0.81
MAGE	0.71	0.61	0.91	0.85	0.92
MODD	0.69	0.60	0.92	0.89	0.96
$CONGA_1$	0.74	0.63	0.86	0.80	0.87
$CONGA_2$	0.74	0.63	0.88	0.82	0.91
$CONGA_4$	0.72	0.63	0.88	0.82	0.93

1.Area under the receiver operating characteristics (ROC) curves to predicting if a participant was meeting the clinical target established by the Advanced Technologies and Treatments for Diabetes (ATTD). Area under the ROC curves for the following metrics are shown: Summary statistics shown for hemoglobin A1c (HbA1c), the comprehensive glucose pentagon area (CGP), personal glycemic state (PGS), average daily risk range (ADRR), glycemic risk assessment diabetes equation (GRADE), Q-Score, glucose management indicator (GMI), J-index, mean amplitude of glycemic excursions (MAGE), mean of daily differences (MODD), and continuous net glycemic action (CONGA)

Several metrics were more correlated with extreme ranges of glycemia (time < 54 mg/dL, time > 250 mg/dL) than with moderate ranges of glycemia (time < 70 mg/dL, time > 180 mg/dL) while the opposite was true with other metrics. GRADE and GMI had higher correlations with moderate ranges of glycemia. GRADE is calculated by taking the average of transformed glucose values while GMI is a function of mean glucose. Since individuals on average spend more time in moderate ranges of glycemia compared to severe ranges, time in moderate ranges will carry more weight when calculating composite scores based on the mean of all glucose measurements, which explains by GRADE and GMI are more sensitive to moderate ranges.

HbA1c also had higher correlations with moderate ranges of glycemia, which makes sense given that HbA1c is proportional to mean glucose.

Other metrics including CGP, PGS, ADRR, the Q-score and measures of glycemic variability were more correlated with time in extreme ranges of glycemia than moderate ranges. It is likely that those who spend more time in extreme ranges have less control over their glucose and are therefore more likely to experience both extreme hypoglycemia and hyperglycemia, and therefore have a higher glucose variability. The CGP, PGS, and Q-score each incorporated time in range into the calculation of their overall values, which may have resulted in higher correlations with the extreme ranges. An increase or a decrease with time in range may be more indicative of an increase or decrease in the extreme ranges than more moderate ranges of hypoglycemia and hyperglycemia.

ROC curves were used to assess each metrics ability to predict meeting the clinical targets for glycemic indices. HbA1c was a poor predictor of meeting hypoglycemia clinical targets, which is unsurprising given the low correlation with time in hypoglycemia shown in table 3. The model with HbA1c as a predictor made the correct prediction for meeting the time < 54 mg/dL target 51% of the time and made the correct prediction 57% of the time for meeting the time < 70 mg/dL target. While correlation between time in severe hypoglycemia and ADRR was moderate, ADRR correctly predicted meeting the clinical target 84% of the time, at least 10% more than any other metric. Trends in area under the curve were similar to trends in correlation coefficients when looking at the associations between composite scores and time in range and hyperglycemia. MODD and MAGE appeared to be strong predictors of time in range and hyperglycemia, despite having more moderate correlations with these metrics.

Most CGM derived composite scores were better predictors of both hyperglycemia and hypoglycemia compared to HbA1c. HbA1c was a poor predictor of time in hypoglycemia and was moderately correlated with time in range and time in hyperglycemia. Likewise, ROC curves showed HbA1c to be a poor predictor of meeting clinical targets for time in hypoglycemia, and was inferior to most CGM derived metrics when predicting if individuals met both hyperglycemia and hypoglycemia targets.

Prior research has shown that moderate correlations exist between HbA1c and time in range and between HbA1c and time in hyperglycemia (Beck et al., 2019). To date, no consensus has been reached as to the relationship between HbA1c and hypoglycemia. Recent research has suggested a J-shaped relationship, with higher risk of hypoglycemia occurring at extremely high or low values of A1c (Gimenez et al., 2018). However, other research as shown a negative relationship between HbA1c and hypoglycemia (Tsujino et al., 2016). Our study showed a week negative relationship between HbA1c and hypoglycemia. The use of CGM devices my alter the relationship between HbA1c and CGM and future research should evaluate the association between HbA1c and hypoglycemia in those not using CGM (Giminez et al., 2018).

No studies have examined the relationship between composite scores and time in range, time in hypoglycemia and time in hyperglycemia, and compared these correlations to correlations with HbA1c. To date no study has evaluated the ability of composite metrics or HbA1c to predict meeting ATTD clinical targets for the percentage of time in range, hypoglycemia and hyperglycemia. This study provides a comprehensive evaluation of a large number of CGM derived composite as measures of glycemic control and compares these measures with the current standard measure of glycemia control, HbA1c. Composite scores that reflect overall glycemic control in a single measure and that break down hypo and

hyperglycemia as well as other aspects of the glucose profile into smaller sub-scores are desirable, and further research should seek to develop and use such measures.

Limitations

This study was a secondary analysis of data from the JDRF clinical trial to assess the efficacy of CGM. This trial was conducted from 2007-2009, and CGM technology has changed significantly from that time, therefore this analysis should be repeated with more recent data. While we were able to compare CGM metrics based on their correlations with time in various ranges, we could not evaluate the associations between these metrics and common diabetes related complications such as nephropathy, neuropathy, retinopathy, and diabetic ketoacidosis. It has been established that HbA1c is strongly associated with these complications (Nathan et al., 2013), therefore in order to claim that CGM derived metrics are superior to HbA1c when evaluating patients with type 1 diabetes, a strong association between complications and said metrics needs to be established. To date no study collecting CGM data has lasted long enough to capture long term complications, however 7-point glucose profiles collected during the DCCT study may potentially be used as a surrogate for CGM data and used to compute composite scores and evaluate their associations with long term complications. Finally, CGM use may have distorted the relationship between HbA1c and indices of glycemia (Gimenez et al., 2018). Future research should use outcomes calculated from SMBG or other biochemical measures to compare HbA1 and CGM composite scores.

Conclusion

HbA1c was weakly correlated with time in hypoglycemia and should not be used to evaluate hypoglycemia in patients with type 1 diabetes. Better measurements than HbA1c are available to assess risk of hyperglycemia, including ADRR and GRADE. HbA1c had moderate

correlations with time in range and time in hyperglycemia, however metrics such as the Q-score, GMI, and the J-index had superior correlations with time in range and hyperglycemia. Composite scores derived from CGM data can provide a more accurate view of an individual's glucose profile than HbA1c. While we did not identify a single composite score that was highly correlated with time in range, time in hypoglycemia, and time in hyperglycemia simultaneously, CGP, GRADE, and GMI had higher correlations with time in all glucose ranges compared with HbA1c. The use of these composite scores is recommended when evaluating the glycemic control of individuals with type 1 diabetes.

Public Health Significance

Glycemic control is a challenge for individuals with type 1 diabetes, and it is important for health professionals to measure it as accurately as possible. It is also important when evaluating the efficacy of diabetes treatments in clinical trials to use primary outcomes that reflect overall glycemic control. This study demonstrates that several metrics including CGP, GMI, and GRADE were consistently more highly correlated with time in hypoglycemia and hyperglycemia than HbA1c. In the case of GRADE and CGP, these metrics can be broken up into sub-scales which reflect both hypoglycemia and hyperglycemia risk (Hill et al., 2007; Vigesrky et al., 2018). The use of these metrics would provide physicians with a more accurate assessment of glucose control when determining how best to treat their patients.

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