REVIEW

A Review of Continuous Glucose Monitoring-Based Composite Metrics for Glycemic Control

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Abstract

We performed a literature review of composite metrics for describing the quality of glycemic control, as measured by continuous glucose monitors (CGMs). Nine composite metrics that describe CGM data were identified. They are described in detail along with their advantages and disadvantages. The primary benefit to using composite metrics in clinical practice is to be able to quickly evaluate a patient's glycemic control in the form of a single number that accounts for multiple dimensions of glycemic control. Very little data exist about (1) how to select the optimal components of composite metrics for CGM; (2) how to best score individual components of composite metrics; and (3) how to correlate composite metric scores with empiric outcomes. Nevertheless, composite metrics are an attractive type of scoring system to present clinicians with a single number that accounts for many dimensions of their patients' glycemia. If a busy health care professional is looking for a single-number summary statistic to describe glucose levels monitored by a CGM, then a composite metric has many attractive features.

Keywords: Continuous glucose monitoring, Composite metrics, Composite index, Diabetes treatment, Glycemic control.

Introduction: What Is a Composite Metric?

A COMPOSITE METRIC is a value that is calculated by using a mathematical formula involving several components. Composite metrics are often calculated with several components that are assigned equal weighting; however, not all composite metrics for a subjective portrayal of a concept, such as the quality of a set of continuously monitored glucose concentrations in this review, use the same components nor are they all calculated with equal weightings of the same component.

Composite metrics have been used in various fields of medicine. The APGAR¹ score is used to evaluate a newborn infant's health, and the APACHE² score is used in critical care medicine to predict hospital mortality. In neurology, concussions can be measured using the King-Devick score³ effectively and accurately in adolescents. A composite impedance metric⁴ is used for distinguishing between benign

and malignant tumors to diagnose prostate cancer. A composite optical coherence tomography and magnetic resonance imaging score⁵ helps predict visual disabilities in patients with multiple sclerosis.

In the diabetes area, a well-established method of assessing glycemic control is the Hemoglobin-A1c (HbA1c), a laboratory value that reflects the risk of micro-⁶ and macrovascular⁷ complications. Although HbA1c can provide a rapid evaluation of glycemia over a course of 8–12 weeks, it has well described limitations.⁸ Compared to HbA1c, continuous glucose monitor (CGM) can provide a better assessment of the glycemic control, without the measuring of HbA1c. CGM classifies glucose levels into various dimensions over many days that can be expressed as mean glucose levels, time spent within optimal glucose ranges, time spent above acceptable levels, time spent below acceptable levels, numbers of episodes of glucose per unit of time that are either above or below defined cut-points, glycemic variability, and

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rates of change. These factors can be further subclassified according to time of day into overall (24 h), daytime, morning, afternoon, evening, and overnight glucose concentrations for most of the metrics. Just as many diners are comfortable with a global restaurant score that incorporates important features of the quality of a restaurant and they seek out sources of information and are more likely to patronize a restaurant when they can see an overall score in terms of stars or similar metrics (rather than seeking a set of components of quality that are individually described), many clinicians might be more inclined to prescribe continuous glucose monitoring if they would not have to always study each individual feature of a detailed report.

With the increased use of CGM, it can be useful to present the generated data in a simple efficient manner, so that HCPs (health care professionals) may interpret the information quickly and effectively to treat their patients. Composite metrics provide a simple way to qualitatively assess with number scores a patient's glycemic control by using CGM data. Presenting data in a digested format manner can allow HCPs to quickly distinguish between patients who do and do not require therapy adjustment. There is inadequate available data at this time to compare composite metrics against each other to decide which metric is best for which types of patients. It is difficult to select the "best" composite metric or optimal scaling references, because all of these metrics in the literature each use different components and some use different definitions for measuring the same component. There is also a lack of consensus as to the thresholds for these components. Integrating composite metrics into routine treatment of diabetes can be beneficial for patients and HCPs by simplifying care and ultimately making CGM even more attractive to both of these stakeholders who are seeking new insights and more personalized treatments for diabetes.

Methods

We performed a literature review of composite metrics to describe the quality of a set of continuous glucose monitoring data for defining glycemic control. Per PubMed, we used filters for the following two combinations of keywords: "continuous glucose monitoring + metric" and "composite metric + diabetes." We excluded metrics that were based on measures that were originally developed for blood glucose determinations before CGM became established in 2002, such as those metrics found in Schlichtkrull et al.⁹ and J Index.¹⁰ Our 2 searches revealed 140 and 78 articles, respectively. The search was performed on November 9, 2019. Articles found in these searches were then screened for relevance. Every article was reviewed and all of each relevant article's references were also checked for relevance to the topic of composite CGM metrics. Graphical methods for combining information from CGM systems were not reviewed.¹¹ Finally, every relevant article was entered into the Google Scholar database to search for articles that later cited any of our relevant articles. For any relevant article that was either uncovered through a review of reference or revealed on the Google Scholar database, we performed another pair of searches by reviewing all of its references for relevant articles and searching on Google Scholar for later articles citing that article. If a relevant article had no positive hits

through a reference search and no positive hits through a Google Scholar database search, then no further analysis of that article was performed. Figure 1 is a Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of article inclusion for this review. We limited our search to articles that pertained to the topic of determining overall glycemic control with CGM data.

Results

Total of 11 articles were found under our research method. Three articles discussed the same composite metric, which led us to merge these articles and cite all three articles under the Index of Glycemic Control section. In the end, nine unique metrics were found through our literature review, and each are discussed in individual sections in this article.

All articles focused on a single composite metric; they described how their respective composite metrics were derived and presented applications of these metrics on retrospective studies to demonstrate (1) how they would be used in a clinical setting and (2) how the metric could be proved to be reproducible. Eight of the nine composite metrics are described in detail below in order of publication date. One of the composite metrics, the Comprehensive Glucose Pentagon (CGP), is a newer version of the Glucose Pentagon. A list of the nine composite metrics and their components is presented in Table 1.

Average Risk Range

The premise of the average risk range (ARR) metric, which can be computed as average daily risk range (ADRR) or hourly risk range (HRR),^{12,13} is to combine two risk quantities, one strictly accounting for the risk of hypoglycemia and the other for the risk of hyperglycemia. The only difference between the ADRR and the HRR is in the time scale of data aggregation—a day or an hour—with the latter more appropriate for fine-tuning of CGM daily profiles. The notion of risk is embedded in the computation of these metrics as a gradual quadratic increase in the weight of each CGM reading when that reading deviates into hypo- or hyperglycemia from a predefined euglycemic central point. The mathematical formulas behind the computation of the ARR were established in 1997,¹⁴ adapted to CGM data in 2005,¹⁵ introduced in 2006,¹³ and reiterated in a more recent review in a section describing the theory of the Risk Analysis of Glucose Data.¹² The two components of the ARR are the low blood glucose index (LBGI) which increases with the frequency and extent of hypoglycemic excursions and by design ignores hyperglycemia, and the high blood glucose index (HBGI), which increases with the frequency and extent of hyperglycemic excursions and ignores hypoglycemia. The computation is balanced to account for the asymmetry of the glucose measurements scale, in a way that makes the ARR equally sensitive to both low- and high-glucose excursions.^{12,14} Both the LBGI and the HBGI include contributions from all values that are not exactly 112.5 mg/dL. At the same time, variability in a selected target range is numerically suppressed, which reduces data noise and allows extreme hypo- and hyperglycemic excursions to be emphasized.^{12,14} It has been shown that the LBGI is predictive of severe hypoglycemia,^{16,17} the HBGI is associated with HbA1c and with hyperglycemic excursions,¹⁸

FIG. 1. PRISMA flow diagram for article inclusion. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

and the ARR is a measure of overall glycemic variability (GV) that captures the risk of both hypo- and hyperglycemia as summarized by a review of studies using this metric in various settings.¹⁹ Today, the Risk Analysis construct is used in the design of artificial pancreas algorithms; that is, as a machine-readable (and not human-readable) composite representation of glycemic control.²⁰

Glycemic Risk Assessment Diabetes Equation

The glycemic risk assessment diabetes equation (GRADE) score,²¹ such as the ADRR, also summarizes the degree of risk associated by combining two risk quantities, one strictly accounting for the risk of hypoglycemia and the other for the risk of hyperglycemia. The risk increases as the score

TABLE 1. A SUMMARY TABLE OF CONTINUOUS GLUCOSE MONITOR-BASED COMPOSITE METRICS AND THEIR COMPONENTS

<i>Composite metric</i>	<i>Average risk range</i>	<i>Glycemic risk assessment diabetes equation</i>	<i>IGC</i>	<i>Hypoglycemia-A1c score</i>	<i>Q-score</i>	<i>Personal glycemic state</i>	<i>Hypo-triad</i>	<i>Original glucose pentagon</i>	<i>CGP</i>	<i>COGI</i>
Reference number	14	21	22-24	25	26	27	31	33	32	36
Year introduced	2006	2007	2009	2015	2015	2017	2018	2009	2018	2019
No. of components	2	3	2	2	5	4	3	5	5	3
Low blood glucose index	x									
High blood glucose index	x									
Hypoglycemia		x								
Euglycemia		x								
Hyperglycemia		x								
Hypoglycemia index		x	x							
Hyperglycemia index			x							
Change in HbA1c				X						
Rate and severity of severe hypoglycemic events				X						
Mean Glucose					x	x		x	x	
Time in hypoglycemia					x					x
Time in hyperglycemia					x			x		
Range of Glucose					x					
MODD					x					
TIR						x				x
GVP						x				
Frequency and severity of hypoglycemia						x				
Area under curve ($t < 70$ mg/dL)							x			
Mean time in hypoglycemia							x			
Frequency of hypoglycemia							x			
Area under curve ($t > 160$ mg/dL)								x		
SD								x		x
HbA1c								x		
%CV								x		
TooR									x	
Intensity of hypoglycemia									x	
Intensity of hyperglycemia									x	

Nine composite metrics are represented on this table. The IGC as originally proposed used 80 as a cutoff for hypoglycemia, but that this value is adjustable. CGP is a newer, reformulated version of the original Glucose Pentagon (which is the only metric that defines hyperglycemia as glucose readings >8.9 mmol/L or 160 mg/dL rather than >10 mmol/L or 180 mg/dL). Multiple values by various authors in various contexts have been used for the criteria for TIR, hypo- and hyperglycemia. The COGI is the only index that uses unequal weightings of its component metrics; all the other composite metrics use equal weightings. The individual metrics of a composite metric can be scaled nonlinearly, such as in the CGP, which can give extra weighting to an extreme value relative to a moderate value. However, except for the COGI, the weight of each individual metric, however scaled, is equal in the composite metrics presented in this article. TIR which means glucose readings in the range of 3.9–10 mmol/L or 70–180 mg/dL.

CGP, Comprehensive Glucose Pentagon; COGI, continuous glucose monitoring index; %CV, % coefficient of variation; GVP, glycemic variability percentage; HbA1c, hemoglobin-A1c; IGC, index of glycemic control; MODD, mean of daily differences; SD, standard deviation; TIR, time in range; TooR, time out of range.

deviates from an assigned nadir of 90 mg/dL by way of a log-log transformation. This metric, such as ADDR, provides a clinically meaningful measure of glycemic risk attributable to hypoglycemia and/or hyperglycemia, but with different weights to hyperglycemic and hypoglycemic values.

Index of Glycemic Control

The index of glycemic control (IGC) is the summation of (1) the hypoglycemia index and (2) hyperglycemia index, which are the weighted averages of their respective regions of glycemic status where more weight is given to severe hypo/hyperglycemic values.^{22–24} These components are able to show how far a CGM tracing has deviated from the target glucose levels. An advantage to using this as a composite metric is that the weightings of hypoglycemia, hyperglycemia, and the severe values are adjustable to give more weight to one component over the others. However, disadvantages to using IGC include the use of only hypoglycemia and hyperglycemia (but not other potential valuable metrics) as components. With this metric, the penalty for readings outside the lower limit of the target range increases rapidly as glucose falls from 70 mg/dL (or 3.9 mmol/L) to 60 mg/dL (or 3.3 mmol/L) to 50 mg/dL (or 2.8 mmol/L) to 40 (or 2.2 mmol/L) and in a non-linear way. On the contrary, the penalty for hyperglycemia increases roughly linearly as the glucose levels rise above the upper limit of the target range.

Hypoglycemia-A1c Score

The hypoglycemia-A1c score (HAS)²⁵ relies on (1) a change in A1c, (2) rate of severe hypoglycemic events, and (3) a change in the rate of severe hypoglycemic events.²⁵ Vigersky proposed this metric as a “think piece.” The overall score is based on subjective weightings assigned by the article’s author to the two components, rather than by a pre-defined weighting formula. Trends in data showed how decreasing, neutral, and increasing body weight during the period of time that a patient is wearing a CGM could affect the composite score. An advantage to using this composite metric is that it does not require large amounts of data, computation, or equations because the score is derived from clinical judgment. Conversely, the main disadvantage to using this composite metric is that the results are subjective. There is no assurance of reproducibility from one observer to the next when HAS is used as a metric for treating patients.

Q-score

The Q-score²⁶ uses (1) mean blood glucose (MBG), (2) time above range ($t_{G>8.9\text{mmol/L}}$ or 160mg/dL), (3) time below range ($t_{G<3.9\text{mmol/L}}$ or 70mg/dL), (4) range of blood glucose values to describe within day variability, and (5) mean of daily difference (MODD) to describe central tendency, hyperglycemia, hypoglycemia, and between day variability. These within-day scores are used to categorize the quality of one’s glucose control in a scoring range from poor (>12) to very good (<4). The ranges include good 4.0–5.9, satisfactory 6.0–8.4, and fair 8.5–11.9. Something important to note is that individuals’ Q-scores have been shown to increase with complexity of treatment, which means that the Q-score is able to identify subjects with poor metabolic control who require therapy optimization. Three independent physicians inte-

grated this composite metric into their practice to treat their patients; the data from two were completely concordant, while one had moderate concordance to the others. These subjective evaluations indicate that the Q-score could be applied into practice as results were consistent. Unlike any of the other seven composite metrics, the Q-score uses MODD to describe variability. An advantage to using this composite metric is that MODD could possibly provide a better insight to glycemic variability than other composite metrics, which use coefficient of variation (CV) or standard deviation (SD) to measure variability; however, there is no known evidence that MODD could perform better than SD or %CV as a metric for describing variability. An advantage of this metric is that it was validated through correlation with expert clinical judgment of three diabetes experts. A disadvantage to using this composite metric is that there is a small number of experts whose assessments were compared with Q-scores.

Personal Glycemic State

Another composite metric that has been developed is personal glycemic state (PGS)²⁷ with the components (1) time in range (TIR 3.9–10 mol/L or 70–180 mg/dL), (2) mean glucose, (3) glycemic variability percentage (GVP), and (4) number of episodes of hypoglycemia (<70 and <54 mg/dL). This number of episodes of hypoglycemia is itself a composite that incorporates the frequency of hypoglycemia, respectively, at these two different thresholds, the first of which reflects biochemical hypoglycemia and the second of which is often associated with neurocognitive impairment. PGS was designed to provide a simple measure to quickly identify problem areas of glycemic control, which could then lead to modification of therapy. This composite metric could also be used in conjunction with other tools; for example, like other composite metrics, it is intended to complement A1C not only in measuring one’s quality of glycemic control but also for assessing the effects of treatment modification. While PGS is a composite metric, it is numerically depicted (ranges: [excellent] <15, 15 ≤ PGS ≤20, 20 ≤ PGS ≤25, and [poor] >25) not as a standalone metric, but rather it is presented alongside its components so that a HCP can see which components must be further improved. This composite metric is unique compared to other metrics because of its inclusion of GVP rather than either CV or SD to measure glycemic variability. The results of GVP are expressed as percentages above the minimum line length with zero glycemic variability. GVP was chosen to be part of this composite over other metrics for glycemic variability because of how it might be easier to understand and use clinically. However, GVP can be a disadvantage to using PGS as a composite measure because it takes into account the frequency of glucose oscillations, making it partially a measure of frequency stability, rather than exclusively a measure of the magnitude of oscillations²⁸ beyond well-defined limits, which is what CV and SD measure.²⁹ Furthermore a change in the units for the time axis (seconds, minutes, hours, days, or unit time between glucose values) changes the importance of the effect of frequency. Another disadvantage to using this metric is that it does not include hyperglycemia as a component. A discriminating feature is PGS’ inclusion of severity of hypoglycemia as a component. A1C concentrations have been shown to be only weakly correlated with the percentage

of glucose values in the hypoglycemic range using CGM.³⁰ Inclusion of a severity of hypoglycemia component to the composite metric is an advantage of using this metric to assess glycemic control. This is because a measurement of the severity of hypoglycemia provides important insight into how much a patient's glycemic levels are in an acutely unsafe range.

The Hypo-Triad

The Hypo-triad³¹ uses three components in a three-dimensional space model. This metric is made up of two composite metrics of glycemic fluctuations that are each two-dimensional planes: intensity of hypoglycemia (IntHypo) and hypoglycemia risk volume (HypoRV). Intensity of hyperglycemia and IntHypo are defined as the equation $\sqrt{(\text{AUC}^2 + \text{time}^2)}$ where hyperglycemia is defined as glucose readings above 10 mmol/L or 180 mg/dL and hypoglycemia is defined as glucose readings under 3.9 mmol/L or 70 mg/dL. The three unique components of this metric are (1) hypoglycemic area under curve ($\text{AUC}_{\text{G}<3.9\text{mmol/L or }70\text{mg/dL}}$), (2) time in hypoglycemia ($<3.9\text{ mmol/L or }70\text{ mg/dL}$), and (3) frequency of hypoglycemic episodes ($3.9\text{ mmol/L} < 70\text{ mg/dL}$) per day and comprise the axes of the three-dimensional space model. IntHypo is calculated as the vector between AUC and time in hypoglycemia, which helps measure the severity of a hypoglycemic episode that a patient may experience. Because IntHypo is used to calculate HypoRV, the final composite is three-dimensional since HypoRV is the product of the IntHypo vector and the rate of hypoglycemia per day. Essentially, HypoRV is a measure of the probability that a patient will experience a hypoglycemic event. It is believed that IntHypo provides information about the immediate clinical impact of hypoglycemia, while HypoRV represents a patient's overall experience of hypoglycemia. What makes this composite metric advantageous is that it uses AUC as a component because it represents an integrated measure of hypoglycemic glucose values over a time period; only the original Glucose Pentagon has used AUC as a component. The Hypo-triad, thus, has a component to account for severity because AUC is able to distinguish periods of mild hypoglycemia from periods of severe hypoglycemia, although it is not clear that there is any real distinction between TBR and $\text{AUC} < 3.9\text{ mmol/L or }70\text{ mg/dL}$. A disadvantage of using the Hypo-triad is that it does not include any components that describe hyperglycemia, which is an important factor for many patients with poor glycemic control.

Glucose Pentagon and CGP

The CGP³² was adapted from the original model of the Glucose Pentagon by Thomas et al.³³ The original glucose pentagon used the axes (1) MBG, (2) hyperglycemic $\text{AUC}_{\text{G}>8.9\text{mmol/L or }160\text{mg/dL}}$, (3) time in hyperglycemia ($t_{\text{G}>8.9\text{mmol/L or }160\text{mg/dL}}$), (4) SD, and (5) HbA1c.³³ CGP uses the axes (1) %CV, (2) Time out of Range (TooR, glucose not 3.9–10 mol/L or 70–180 mg/dL), (3) intensity of hyperglycemia ($\text{IntHyper}_{\text{G}\geq 10\text{mmol/L or }180\text{mg/dL}}$), (4) $\text{IntHypo}_{\text{G}\leq 3.9\text{mmol/L or }70\text{mg/dL}}$, and (5) mean glucose in the CGP.³² The scaling of the axes for CGP for mean glucose and glycemic variability were also taken from the original Glucose Pentagon model. For IntHypo, IntHyper, and TooR, the axes were adapted from Kovatchev.¹² Glycemic variability,

as measured by %CV, is included in this composite metric because it has been hypothesized to be associated with microvascular complications in diabetes.^{32,34} %CV was chosen over SD to describe glycemic variability to accommodate nonnormal distribution of glucose values and because CV is independent of mean glucose.³² The area of the resulting pentagon is the component score for the measurements involved. A glucose pentagon for a healthy person without diabetes would be defined as having an area equal to 1; the area of the pentagon increases as a patient's overall glycemic control worsens. The area of a set of CGM-derived data enables that set to be compared to another individual's or a group's data set in terms of glycemic control. The ratio of the affected patient's or patient population's area compared to a healthy person's pentagon area is postulated to represent a relative risk of a combination of hypoglycemia and long-term complications on a scale of 1 to 5. This risk is referred to by the developers of this metric as the prognostic glycemic risk (PGR). The developers of this composite metric went on to arbitrarily assign subjective descriptions of risk to the PGR as follows: for $\text{PGR} \leq 2.0$, the risk for diabetes short- and/or long-term complications is very low; for $2.0 < \text{PGR} \leq 3.0$, the risk is low; for $3.0 < \text{PGR} \leq 4.0$, the risk is moderate; for $4.0 < \text{PGR} \leq 4.5$, the risk is high; and for $\text{PGR} > 4.5$, the risk is extremely high.

The large array of components provides an HCP with much information to accurately assess the source of poor metabolic control if the resulting pentagon has a large area (i.e., if the score is poor). The advantage to including IntHyper and IntHypo in this composite metric is that both provide duration and severity of hyperglycemic and hypoglycemic episodes. However, a disadvantage to using CGP is that the CGP uses the Hypo Intensity and Hyper Intensity metrics. These metrics are entirely nonstandard and were not available before the introduction of the CGP. They are a bit mathematically complex, using the quadratic average or quadratic sum of two of the components. Most people do not visualize quadratic sums very well.

In a study conducted in Singapore, patients with three classes of diabetes (first: type 2 on oral drugs, second: type 2 on insulin, and third: type 1) HbA1c levels were not significantly different between the three groups, however the PGR was higher in class 2 than type 1 ($P < 0.05$ class 1 vs. class 3) and higher in class 3 than class 2 ($P < 0.05$ class 2 vs. class 1). This study indicated that similar HbA1c levels between groups of patients could be associated with significantly different glycemic profiles.³⁵ The developers of this metric considered using a log transformation of the data, but decided that this approach would make the metric difficult to understand.

Continuous Glucose Monitoring Index

Similar to the Hypo-triad, another composite metric known as continuous glucose monitoring index (COGI)³⁶ also uses three components. The COGI uses (1) TIR (3.9–10 mmol/L or 70–180 mg/dL), (2) time in hypoglycemia ($\text{TBR} < 3.9\text{ mmol/L or }70\text{ mg/dL}$), and (3) SD which represent, respectively, time spent in a target range (between 3.9 and 10 mM or 70–180 mg/dL) glucose, hypoglycemia, and glycemic variability; These aspects of glucose control were felt to be most important for type 1 diabetes patients, and this

composite metric is only intended to evaluate patients with type 1 diabetes. COGI also differs from the other seven composite metrics because this metric is calculated with the composite metric's components, each having different weights in the calculations. These weightings were determined by the expert opinions of the developers of the metric. TIR has 50%, TBR has 35%, and SD has 15% weighting. Even though COGI does not include mean glucose as a component, it is reasoned that TIR and SD are sufficient as components because of their high correlations with mean glucose.^{36,37} The authors included a statement that this metric could also be used with CV instead of SD for expressing glycemic variability. COGI is expressed as an index ranging between 0 and 100. A potential limitation to using COGI is how it weighs its components. Time in hypoglycemia carries more weight than SD to account for the importance of avoiding hypoglycemia because it remains one of the biggest risks to safely achieving near normal glucose control. The relative weightings are, nevertheless, arbitrary. Finally, this composite metric has yet to be applied to type 2 diabetes patients in any published articles. An advantage to using COGI is that since this composite metric uses only three components, it provides a focused view on three components felt by many clinicians to be the three most important determinants of assessing glycemic control. A disadvantage of this metric is that its definition of hypoglycemia (duration of readings below 3.9 mmol/L or 70 mg/dL) does not account for severity of hypoglycemia. This metric's definition of hypoglycemia can be problematic because an intervention that can significantly decrease the incidence of severe symptomatic hypoglycemia does not necessarily decrease the percentage of time spent below a threshold-defined level of hypoglycemia.³⁸

Discussion

Currently, the Ambulatory Glucose Profile (AGP)³⁹ is the most widely used method to visualize one's glycemic control in a detailed presentation. It utilizes many graphs and charts to provide HCPs and patients with a large amount of important information in a compact space. However, some HCPs who do not have the time or skill to analyze a CGM profile might not be able to easily process all the important information that an AGP provides. Another approach to analyzing a large amount of data from a CGM tracing is to base the assessment on a calculation of 14 metrics recently recommended by an international consensus panel as important dimensions of glycemia to consider when assessing glycemic control.³⁹ Several of these can be further divided into subset dimensions by the range of times of day that the data were collected. Here again, some HCPs might not be able to easily process all the important information that this set of 14 metrics provides.

For some patients, HCPs might wish to see a CGM composite metric, which summarizes into a single score the rich types of data that are generated by a CGM. While a composite metric cannot replace any of the individual components used for describing glycemia, and it certainly cannot replace a detailed data presentation, it may still have many advantages. A composite metric can allow for a simplified rapid analysis of glycemic data from a CGM. A composite metric is not intended to guide treatment, but is intended to be a screening tool, for identifying at-risk patients with abnormal values of the composite metric. HCPs can then focus on the detailed

CGM reports of these individuals, making the necessary adjustments in their medication regimen. Currently, HbA1c is the main screening tool that is used to evaluate glycemic control. HbA1c has been called the ultimate composite measure as it does, in part, reflect times above, within and below range, and it is associated with some measures of GV. However, many conditions are associated with falsely elevated or falsely lowered HbA1c values.⁴⁰ Furthermore, HbA1c values differ among patients from various ethnic groups/races.⁴¹ Finally, patients have individual glycation rates and red cell survivals that affect the relationship of mean glucose to HbA1c.^{42,43} As HbA1c represents an estimate of the mean glucose value, it does not provide granular information about glucose variability, TIR, or duration and severity of hypoglycemia and hyperglycemia, which are all important parameters of glycemic control. A composite metric can capture a complete picture better than the HbA1c can by overcoming the above limitations, assuming that these components will be included and appropriately weighted. A composite metric can include a visual representation in addition to a numerical score, which is the case with the Hypo-triad and CGP composite metrics. Comparable with using HbA1c, primary care physicians as well as endocrinologists can use composite metrics for evaluating glycemic control and might choose to refer patients to diabetologists only in cases of abnormal composite metric values. A composite metric can also be beneficial to diabetologists. Considering that many of them evaluate patients with diabetes in less than 15–20 min in a typical clinic visit, a composite metric can provide a rapid assessment of glycemic control, allowing diabetes HCPs to focus on other areas that may require more attention such as recommending diabetes education, a healthy lifestyle, a healthy diet, and proper use of technology. Finally, even a patient might use a composite metric as a tool to track their overall glycemic control on a routine basis to understand whether they are making progress.

To our knowledge, this is the first article to summarize currently published composite CGM scores. All composite metrics that we reviewed are intended to allow for rapid assessment of a CGM wearer's glycemic control. They are capable of delivering information about a patient's glucose control over the time period that the device was worn, but there are little data available about their value in predicting long-term complications or response to therapy. Recently, there was a cross-sectional study published in *Diabetes Care* from China about the link between TIR and retinopathy.⁴⁴ Perhaps there is an opportunity to assess the performance of some of the composite measures to see whether there is the link with complications and whether adding additional information increases the predictability of complications compared to TIR alone.

The specific components and ratios of the components for each composite metric have been arbitrarily selected based on expert opinion, but not on evidence linked to outcomes data. As described in Table 2, which presents advantages and disadvantages of using composite metrics for analyzing CGM data, there is a lack of validation of these measures because there is no gold standard to compare any of the proposed-to-date composite metrics against each other for making a diagnosis, determining the best form of treatment, or predicting a complication. Various composite metrics might be validated through analysis of CGM data in those

TABLE 2. ADVANTAGES AND DISADVANTAGES OF USING COMPOSITE METRICS FOR ANALYZING CONTINUOUS GLUCOSE MONITOR DATA

<i>Features of composite metrics</i>	<i>Advantages</i>	<i>Disadvantages</i>
How composite metrics are used in medicine	Composite metrics have been successfully used in other fields of medicine and outside of medicine	For each component of a composite metric that is to be scored on a range of quality, these ranges are arbitrarily assigned. There is no agreement on the cutoffs for scoring noncontinuous discrete metrics that are components of a composite metric. For example, hypoglycemia or hyperglycemia can be defined at various cutoff levels for these states and these are common components for composite metrics.
Selection of composite metrics	Compared to AGP or the long list of various CGM parameters/components that have been proposed to define good glycemic control, a simple composite metric may be sufficient to support a conclusion that a patient is doing well. If the patient is doing poorly, then each of the component metrics can be studied to provide focused therapy intended to improve glycemic control.	There is currently no consensus on the optimal metric for assessing glycemic variability. The International Consensus suggests using CV rather than SD or GVP.
Benefits of using composite metrics	Compared to HbA1c, a composite metric may provide a better assessment of glycemic control, by also considering important parameters of glycemia, such as glucose variability, TIR, severity and duration of hypoglycemia. These are metrics that are not fully accounted for when only HbA1c, reflecting mean glucose, is used.	So far, no composite metric has been tested against another to address which metric is the best for assessing quality of glycemic control in long-term prospective outcome studies.
Clinical applications	The majority of patients with diabetes are managed by primary care physicians. A composite metric may help these professionals to identify patients that have acceptable or inappropriate glycemic control, directing them to focus mainly on the latter group.	There is some overlap in components used between composite metrics but there is no consensus on which components are necessary to consider when treating patients. There is also no agreement on how a set of multiple component metrics should be weighted within a composite metric.
Reasons for using composite metrics	Considering that many physicians must evaluate patients with diabetes in less 15–20 min in a typical clinic visit, a composite metric can provide a rapid assessment of glycemic control, allowing these professionals to focus on other areas (such as education, a healthy lifestyle, a healthy diet, and proper use of technology).	There are limited clinical data with objective outcomes assessing the minimum safe percentage of time spent in the target range (also known as TIR) ^{23,38} although an expert consensus panel recently recommended at least 70% of the time patients should be time in a range of glucose concentrations 70–180 mg/dL. ³⁸
How CGM composite metrics are linked to the use of CGM	CGM is increasingly being prescribed by diabetes HCPs and covered by insurers.	Calculation of the described composite metrics requires the use of CGM, which some patients with diabetes may not be able to afford or need to use (for example patients treated with some oral antidiabetic medications)
How CGM component metrics are linked to long-term outcomes	Cross-sectional data suggest that TIR, measured with CGM, which is a component of recent composite metrics, is inversely associated with the prevalence of diabetic retinopathy ⁴⁴ and carotid intima media thickness ⁴⁵	Composite metrics have not been tested for their relationship to predicting long-term complications. HbA1c remains the best validated prognostic marker of long-term diabetes complications.

AGP, Ambulatory Glucose Profile; CGM, continuous glucose monitor; HCPs, health care professionals.

studies collecting serial CGM tracings for long-term post-approval studies mandated by the FDA for new diabetes drugs. TIR, TooR, and glycemic variability are frequently selected components for published composite metrics and are important dimensions for understanding a patient's glycemia;

however, not all composite metrics use all of them. The international consensus panel recommended a list of components to be included when differentiating between severe and mild hypoglycemia, but none of these composite metrics aside from PGS makes this distinction.³⁹

Conclusion

A composite metric for continuous glucose monitoring is useful for quickly assessing a patient's quality of glycemic control. A composite metric to summarize the features of a set of many days of continuous glucose tracings can present a HCP with a single number to quickly gauge how well their patient is doing without a potentially overwhelmingly large amount of information or numbers. If a patient has a score indicating poor performance, then the clinician can examine the individual components of the composite metric to see whether a particular component of the metric scored minimally and this area can then become a focus of treatment.

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Disclaimer

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References

1. Apgar V: A proposal for a new method of evaluation of the newborn infant. *Curr Res Anesth Analg* 1953;32:260–267.
2. Knaus WA, Zimmerman JE, Wagner DP, et al.: APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. *Crit Care Med* 1981; 9:591–597.
3. Galetta KM, Liu M, Leong DF, et al.: The King-Devick test of rapid number naming for concussion detection: meta-analysis and systematic review of the literature. *Concussion* 2016;1:CNC8.
4. Khan S, Mahara A, Hyams ES, et al.: Prostate cancer detection using composite impedance metric. *IEEE Trans Med Imaging* 2016;35:2513–2523.
5. Poretto V, Petracca M, Saiote C, et al.: A composite measure to explore visual disability in primary progressive multiple sclerosis. *Mult Scler J Exp Transl Clin* 2017;3: 2055217317709620.
6. Diabetes Control and Complications Trial Research Group, Nathan DM, et al.: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986.
7. 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;352:837–853.
8. Campbell L, Pepper T, Shipman K: HbA1c: a review of non-glycaemic variables. *J Clin Pathol* 2019;72:12–19.
9. Schlichtkrull J, Munck O, Jersild M: The M-valve, an index of blood-sugar control in diabetics. *Acta Med Scand* 1965; 177:95–102.
10. Wojcicki JM: “J”-index. A new proposition of the assessment of current glucose control in diabetic patients. *Horm Metab Res* 1995;27:41–42.
11. Rodbard D: Evaluating quality of glycemic control: graphical displays of hypo- and hyperglycemia, time in target range, and mean glucose. *J Diabetes Sci Technol* 2015;9:56–62.
12. Kovatchev BP: Metrics for glycaemic control—from HbA1c to continuous glucose monitoring. *Nat Rev Endocrinol* 2017;13:425–436.
13. Kovatchev BP, Otto E, Cox D, et al.: Evaluation of a new measure of blood glucose variability in diabetes. *Diabetes Care* 2006;29:2433–2438.
14. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Clarke W: Symmetrization of the blood glucose measurement scale and its applications. *Diabetes Care* 1997;20:1655–1658.
15. Kovatchev BP, Clarke WL, Breton M, et al.: Quantifying temporal glucose variability in diabetes via continuous glucose monitoring: mathematical methods and clinical application. *Diabetes Technol Ther* 2005;7:849–862.
16. Kovatchev BP, Cox DJ, Gonder-Frederick LA, et al.: Assessment of risk for severe hypoglycemia among adults with IDDM: validation of the low blood glucose index. *Diabetes Care* 1998;21:1870–1875.
17. Cox DJ, Gonder-Frederick L, Ritterband L, et al.: Prediction of severe hypoglycemia. *Diabetes Care* 2007;30:1370–1373.
18. Clarke W, Kovatchev B: Statistical tools to analyze continuous glucose monitor data. *Diabetes Technol Ther* 2009; 11(Suppl 1):S45–S54.
19. Patton SR, Clements MA: Average daily risk range as a measure for clinical research and routine care. *J Diabetes Sci Technol* 2013;7:1370–1375.
20. Doyle FJ, 3rd, Huyett LM, Lee JB, et al.: Closed-loop artificial pancreas systems: engineering the algorithms. *Diabetes Care* 2014;37:1191–1197.
21. Hill NR, Hindmarsh PC, Stevens RJ, et al.: A method for assessing quality of control from glucose profiles. *Diabet Med* 2007;24:753–758.
22. Rodbard D: Interpretation of continuous glucose monitoring data: glycemic variability and quality of glycemic control. *Diabetes Technol Ther* 2009;11(Suppl 1):S55–S67.
23. Rodbard D, Bailey T, Jovanovic L, et al.: Improved quality of glycemic control and reduced glycemic variability with use of continuous glucose monitoring. *Diabetes Technol Ther* 2009;11:717–723.
24. Rodbard D: Metrics to evaluate quality of glycemic control: comparison of time in target, hypoglycemic, and hyperglycemic ranges with “Risk Indices”. *Diabetes Technol Ther* 2018;20:325–334.
25. Vigersky RA: Escaping the hemoglobin A1c-centric world in evaluating diabetes mellitus interventions. *J Diabetes Sci Technol* 2015;9:1148–1151.
26. Augstein P, Heinke P, Vogt L, et al.: Q-Score: development of a new metric for continuous glucose monitoring that enables stratification of antihyperglycaemic therapies. *BMC Endocr Disord* 2015;15:22.

27. Hirsch IB, Balo AK, Sayer K, et al.: A simple composite metric for the assessment of glycemic status from continuous glucose monitoring data: implications for clinical practice and the artificial pancreas. *Diabetes Technol Ther* 2017;19(Suppl 3):S38–S48.
28. Intelligent Management, Inc.: Variation. <https://www.intelligentmanagement.ws/learningcentre/what-is-a-systemic-organization/variation> (accessed December 13, 2019).
29. Measuring Usability LLC: Fundamentals of Statistics 1: Basic Concepts: The Standard Deviation and Coefficient of Variation. <https://www.usablestats.com/lessons/sdev> (accessed December 13, 2019).
30. Hirsch IB, Welsh JB, Calhoun P, et al.: Associations between HbA1c and continuous glucose monitoring-derived glycaemic variables. *Diabet Med* 2019;36:1637–1642.
31. Thomas A, Shin J, Jiang B, et al.: The development of new composite metrics for the comprehensive analytic and visual assessment of hypoglycemia using the hypo-triad. *J Diabetes Sci Technol* 2018;12:69–75.
32. Vigersky RA, Shin J, Jiang B, et al.: The comprehensive glucose pentagon: a glucose-centric composite metric for assessing glycemic control in persons with diabetes. *J Diabetes Sci Technol* 2018;12:114–123.
33. Thomas A, Schonauer M, Achermann F, et al.: The “glucose pentagon”: assessing glycemic control of patients with diabetes mellitus by a model integrating different parameters from glucose profiles. *Diabetes Technol Ther* 2009;11:399–409.
34. Hirsch IB: Glycemic variability and diabetes complications: does it matter? Of course it does! *Diabetes Care* 2015;38:1610–1614.
35. Rama Chandran S, Vigersky RA, Thomas A, et al.: Role of composite glycemic indices: a comparison of the comprehensive glucose pentagon across diabetes types and HbA1c levels. *Diabetes Technol Ther* 2020;22:103–111.
36. Leelarathna L, Thabit H, Wilinska ME, et al.: Evaluating glucose control with a novel composite continuous glucose monitoring index. *J Diabetes Sci Technol* 2019. [Epub ahead of print]; DOI: 10.1177/1932296819838525.
37. Rodbard D: Clinical interpretation of indices of quality of glycemic control and glycemic variability. *Postgrad Med* 2011;123:107–118.
38. Rickels MR, Peleckis AJ, Dalton-Bakes C, et al.: Continuous glucose monitoring for hypoglycemia avoidance and glucose counterregulation in long-standing type 1 diabetes. *J Clin Endocrinol Metab* 2018;103:105–114.
39. Danne T, Nimri R, Battelino T, et al.: International consensus on use of continuous glucose monitoring. *Diabetes Care* 2017;40:1631–1640.
40. Radin MS: Pitfalls in hemoglobin A1c measurement: when results may be misleading. *J Gen Intern Med* 2014;29:388–394.
41. Wright LA, Hirsch IB: Metrics beyond hemoglobin A1C in diabetes management: time in range, hypoglycemia, and other parameters. *Diabetes Technol Ther* 2017;19(Suppl 2): S16–S26.
42. Nathan DM, Kuenen J, Borg R, et al. Translating the A1C assay into estimated average glucose values. *Diabetes Care* 2008;31:1473–1478.
43. Malka R, Nathan DM, Higgins JM: Mechanistic modeling of hemoglobin glycation and red blood cell kinetics enables personalized diabetes monitoring. *Sci Transl Med* 2016;8: 359ra130.
44. Lu J, Ma X, Zhou J, et al.: Association of time in range, as assessed by continuous glucose monitoring, with diabetic retinopathy in type 2 diabetes. *Diabetes Care* 2018;41: 2370–2376.
45. Lu J, Ma X, Shen Y, et al.: Time in range is associated with carotid intima-media thickness in type 2 diabetes. *Diabetes Technol Ther* 2020;22:72–78.

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