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MEETING REPORT

Recommendations for Standardizing Glucose Reporting and Analysis to Optimize Clinical Decision Making in Diabetes: The Ambulatory Glucose Profile (AGP)

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Abstract

Underutilization of glucose data and lack of easy and standardized glucose data collection, analysis, visualization, and guided clinical decision making are key contributors to poor glycemic control among individuals with type 1 diabetes. An expert panel of diabetes specialists, facilitated by the International Diabetes Center and sponsored by the Helmsley Charitable Trust, met in 2012 to discuss recommendations for standardization of analysis and presentation of glucose monitoring data, with the initial focus on data derived from CGM systems. The panel members were introduced to a universal software report, the Ambulatory Glucose Profile (AGP), and asked to provide feedback on its content and functionality, both as a research tool and in clinical settings. This paper provides a summary of the topics and issues discussed during the meeting and presents recommendations from the expert panel regarding the need to standardize glucose profile summary metrics and the value of a uniform glucose report to aid clinicians, researchers, and patients.

Introduction

An expert panel of diabetes specialists met in Tampa, FL, March 28–29, 2012, to discuss the utility of continuous glucose monitoring (CGM) in clinical practice and research applications. A representative from the U.S. Food and Drug Administration (FDA), Health Level Seven International, and a type 1 diabetes (T1D) patient advocate were also in attendance. The 2-day meeting was hosted and facilitated by the International Diabetes Center (IDC), Minneapolis, MN,

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and funded by the Helmsley Charitable Trust. The purpose of the meeting was to develop recommendations for standardization of analysis and presentation of glucose monitoring data, with the initial focus on data derived from CGM systems. The panel acknowledged that self-monitoring of blood glucose (SMBG) was currently the predominate mode of glucose monitoring in diabetes and that additional conferences were needed to address the issues particularly relevant to reporting and analysis of SMBG data, even though there is considerable overlap between SMBG and CGM standardization.

As a starting point for standardization discussions the panel members were introduced to a universal software report, the Ambulatory Glucose Profile (AGP), created by Mazze et al.[1] and further developed by the IDC,[2] and asked to provide feedback on its content and functionality, both as a research tool and in clinical settings. This article provides a summary of the topics and issues discussed during the meeting and presents recommendations from the expert panel regarding the value of a uniform glucose report to clinicians, researchers, and patients. Directly following the expert panel discussions, a brief summary of the preceding discussion and recommendations was presented to representatives of medical device companies involved in glucose monitoring for reaction and feedback.

Critical Issues Impacting Diabetes Management

Several issues potentially impacting the effectiveness of diabetes management were presented to the group to provide context for the meeting and outline the rationale for standardization of glucose data reporting. Many of the barriers to optimal glycemic control discussed below apply to both T1D and type 2 diabetes (T2D), particularly T2D patients treated with insulin, but time constraints at the meeting and space constraints here only allow for a focus on T1D. The following is a summary of the issues discussed at the expert panel.

Suboptimal glycemic control in T1D

Despite advances in insulin preparations, insulin delivery devices, and glucose monitoring technology, glycemic control in most T1D patients is suboptimal. Recently published data[3] from the T1D Exchange Clinical Registry (T1D Ex), which maintains health records on over 26,000 participants with T1D from 68 clinics throughout the United States, reveals that the average glycated hemoglobin (HbA1c) among younger patients (≤25 years) ranges from 8.3% to 8.7%; average HbA1c among older patients is only somewhat better, at approximately 7.7%. It is interesting that among the adult and pediatric age group participants in the T1D Ex, improved glycemic control (lower HbA1c levels) was associated with CGM use and more frequent SMBG, insulin pump use, white race, higher household income, higher participant or parent education, and private insurance. Although the data from these 68 clinics, expert in the management of T1D, may not be completely representative of the entire U.S. population of individuals with T1D, they clearly identify some important associations between epidemiologic characteristics or approaches to management with metabolic and clinical outcomes, thus suggesting areas for further investigation.[3,4]

Suboptimal glycemic control is often the result of poor adherence to prescribed insulin regimens; however, studies have shown that many T1D patients are reluctant to follow and/or adjust their insulin regimens as needed.[5–7] T1D Ex data confirm that missing insulin doses, avoiding insulin at the start of the meal, and not working to refine insulin-to-carbohydrate ratios at each meal are also associated with a higher HbA1c level.[8] Poor adherence to insulin therapy may also be due to fear of hypoglycemia.[9] Patients quickly learn that severe hypoglycemia is potentially dangerous, physically punishing, and a source of possible social embarrassment.[10] Cryer[11] has established that hypoglycemia is the limiting factor in optimizing glycemic control in both T1D and T2D. A recent study by Anderbro et al.[12] identified frequency of severe hypoglycemia as the most significant factor associated with fear of low glucose levels in adults with T1D. Strategies and technologies that can improve clinician and patient understanding of glucose patterns and facilitate therapy intensification while reducing the frequency and fear of hypoglycemia may, in turn, improve overall glycemic control in diabetes.

Limitations of HbA1c as the sole measure of glycemic control

HbA1c is the glycemic marker most linked to the complications of diabetes and remains a key component of diabetes management but is not without controversy.[13] Although an elevated HbA1c level was clearly the major factor identified as the cause of diabetic retinopathy in the Diabetes Control and Complications Trial, HbA1c still accounted for only about 11% of the variation in risk between intensive and standard glycemic control patients.[14] A clear limitation of this measure of average glucose control or glucose exposure over 2–3 months is the inability of the HbA1c level to characterize diurnal glucose patterns, which are critical to understand for safe, effective, and timely insulin adjustment and informed clinical decision making. Patients with similar HbA1c values can have markedly dissimilar patterns of glucose excursions and rates of hypoglycemia throughout the day and overnight.

Including the amount or severity of hypoglycemia in any measure of overall glucose control is particularly relevant in light of growing evidence that links severe hypoglycemia to excessive morbidity and mortality.[15–18] In addition, persistent glucose excursions are associated with increased oxidative stress and the generation of potentially harmful reactive oxygen species.[19] Although glucose variability has not been shown in a randomized controlled trial to directly result in diabetes complications, there are strong associations between glucose variability and increased carotid intima media thickening and the risk of microvascular complications.[20,21] Determining the effects of acute and long-term glucose variability on diabetes complications will require additional studies in both inpatient and outpatient settings.[22]

The fact that increased glycemic variability (GV) is a strong predictor of hypoglycemia[23,24] and is also correlated with poor glycemic control[25] is probably the most compelling reason to identify and to work to minimize GV today. GV, independent from other measures of glycemic control, is predictive of patient satisfaction with an intensive insulin regimen.[26] This is worth noting as healthcare teams strive to achieve the triple aim of improved quality and patient experience at a reasonable cost.[27] Although data from SMBG can reveal gross patterns of GV, its episodic nature often overlooks significant glucose excursions.[28] There are numerous

case reports of significant and potentially dangerous hypoglycemia, particularly overnight, or hyperglycemic excursions after meals that are missed with SMBG but are evident with CGM. Evaluating the additional data and glucose patterns that CGM provides can enable a meaningful change in lifestyle or drug therapy.

Many feel it is time to establish a definition of optimal glycemic control that includes HbA1c being at target (personalized for each individual, but somewhere around 7% for many adults) without any severe hypoglycemia and only a minimal number of very low or dangerously low glucose values.[29] CGM reported in a standardized way along with an HbA1c value would foster a precise definition of this composite goal. Using a standardized composite goal, the medical community could establish with more confidence whether or not a particular insulin formulation, new technology for insulin delivery, or an innovative patient-centered approach to care was an important factor in helping individuals with diabetes reach optimal glycemic control. At this time, minimizing glucose variability is a treatment goal that if achieved can help one reach an acceptable HbA1c level without excessive hypoglycemia. If GV is shown in randomized trials to be an independent causative factor in diabetes complications and if the definition of variability is standardized, it could be added to the optimal glucose control composite target. Additionally, if CGM becomes the standard research and clinical tool to evaluate and manage glycemic control, a logical glycemic goal would be to maximize "time in target range," also known as "time in range" (TIR).[30,31] To make the TIR more broadly acceptable as a research end point or clinical measure, it would need to be qualified with the addition of some measure that quantifies the amount and severity of accompanying hypoglycemia. Further studies will need to be conducted to define in a variety of patient groups, from pediatrics to the frail elderly, what is an acceptable and achievable TIR and the accompanying acceptable level of hypoglycemia.

Although this discussion focuses on glycemic control, it is important to note that other composite targets for good diabetes management are being explored (HbA1c + hypoglycemia + weight gain[32,33] or HbA1c + low-density lipoprotein + blood pressure[34] or HbA1c + low-density lipoprotein + blood pressure + acetylsalicylic acid if high-risk cardiovascular disease + no tobacco use[35,36]). These composites emphasize the importance of taking a multifactorial approach to reducing diabetes complications, in particular, cardiovascular disease.[37]

Underutilization of CGM

CGM can provide immediate (real-time) feedback on current glucose levels and trends (direction and rate of change), as well as retrospective data that can reveal patterns of glycemic control over specified time periods and glucose metrics that can be compared from visit to visit or for research analysis. CGM devices measure glucose levels in interstitial fluid in 1- or 5-min increments (depending on the system used) on a continuous basis. Use of CGM has recently been demonstrated to be associated with improved glycemic control in both children and adults in the T1D Ex.[38] Additionally, studies have shown CGM use to be effective in improving HbA1c levels and reducing the risk of hypoglycemia in subjects with poorly controlled T1D and T2D,[39–43] even in patients already using insulin pump therapy.[44] A recent meta-analysis showed that using real-time CGM compared with SMBG reduced the HbA1c level and reduced hypoglycemia.[45] A second meta-analysis showed that using CGM with insulin pump therapy compared with SMBG and multiple daily insulin injections resulted in a lower HbA1c level with no increase in hypoglycemia.[46] Trials have also demonstrated that CGM is beneficial for T1D patients who have already achieved excellent control[47] and that safe and efficacious CGM use in children and adults can be sustained over time.[48–51] Despite the benefits of CGM, adoption of this technology in clinical practice has been very slow. Only 3% of young patients (≤25 years) in the T1D Ex use CGM for their diabetes management; CGM use among older T1D patients (26–49 years) is slightly higher, at 14%.[3]

Although underutilization of CGM is often attributed to limited reimbursement and patients' and parents' perceptions regarding the complexity and inconvenience of CGM use, clinician reluctance is also a key issue. This may be due to clinicians' lack of experience/expertise in determining the most appropriate candidates for CGM or in interpreting CGM data. There are also time constraints and the potential disruption of workflow associated with CGM initiation, downloading, and interpretation in clinical practices. Lack of a relatively simple or (at least) straightforward and intuitive statistical and graphic visualization of the glucose data via download software is a major contributor to clinicians' uncertainty and reluctance to incorporate CGM into their practices. In addition, people with diabetes who were very strong advocates in the 1980s for the use of SMBG have been less vocal regarding their desire to use CGM. This is, in part, because patients have not been actively engaged in viewing data displays and understanding how the glucose data and patterns might guide them to optimize insulin delivery or lifestyle choices. Despite the fact that CGM provides a means of better characterizing glucose control and may improve the management many patients with diabetes, there remains a desire on the part of patients, providers, and researchers to see continued progress on making the technology more accurate and more convenient.

Lack of standardization of glucose reporting

Currently there are three commercial CGM device manufacturers: DexCom (San Diego, CA), Medtronic (Northridge, CA), and Abbott Diabetes Care (Alameda, CA) (but currently available in Europe). Each of these manufacturers provides software to download and analyze the CGM data and generate a report or series of reports. Although there are some similarities among the various software programs, there is no standardization regarding which statistics are reported or how the data are presented graphically, nor is there common terminology for the various analyses presented. Moreover, the sheer diversity and number of reporting options create such a daunting "learning curve" that many clinicians never invest the time necessary to even start using CGM technology, let alone attempt to become proficient in its use. More focus on patient-friendly presentations of the data would also be of great benefit.

Common definitions and metrics are needed in order to assess patient status, make more informed clinical decisions, and evaluate the performance of clinicians (e.g., Has the

percentage of time patients are in good glycemic control improved? Are patients in good control with fewer low, very low and dangerously low glucose readings?). Standardization of clinical terms and metrics allows a more accurate assessment of individual patients and comparisons of progress from visit to visit. Patient populations, diabetes medications, new technology, and systems of care can more effectively be assessed, thus facilitating efficient clinical decision making and appropriate design of clinic process and flow. Standardization also has the potential to make patient care and clinical research more efficient from a reimbursement and regulatory standpoint.

Summary

In light of recent data, it is clear that most children and adults with T1D are not in optimal glycemic control. Although the around-the-clock demanding nature of this disease explains much of the difficulty in achieving good glycemic control, there are factors that can be improved, such as facilitating adherence to principles of effective insulin delivery and minimizing the occurrence and thus fear of dangerous hypoglycemia. Other factors such as use of HbA1c as the primary or often sole measurement of glucose control and underutilization of glucose data by clinicians and patients also contribute to the problem.

Given the demonstrated benefits of CGM in managing glycemia and reducing hypoglycemia, which can potentially lead to greater patient adherence and improved clinical outcomes, it is imperative that healthcare providers, clinical researchers, industry, regulators, and payers work together to find ways to expand *appropriate* adoption of CGM use in clinical practice. An important first step in this effort is to standardize the reporting and analysis of CGM data and create a universal template in which data are presented in a predictable, easy-to-view format, yet allowing users to customize settings (e.g., glucose target range) for each patient and to perform more in-depth analyses of the data as desired. Standardized reporting and analysis of CGM data would help clinicians develop expertise in CGM use, enhance quality of care through enhanced pattern recognition, improve practice efficiencies with minimal disruption of workflow, and engage patients, thereby reinforcing consistent use of CGM technology.

Standardization of Glucose Reporting, Analysis, and Clinical Decision Making

The second part of the meeting focused on a discussion of the relevant metrics and defaults that require standardization for initial review and analysis of CGM data. The key metrics/defaults identified by the group were as follows: target range; glucose exposure; GV; hypoglycemia; and hyperglycemia. After considerable open discussion, panel members provided their input on each metric/default via an electronic audience response system, allowing us to tabulate their opinions. The following is a summary of the panel's responses and justification for metrics selected for the simplified clinical AGP report and the expanded research AGP report.

Target range

Most panel members (56%) selected 70–180 mg/dL as the default target range. Although not an ideal or normal glucose range, it represents a target range commonly used in clinical practice and one that promotes realistic and safe expectations. It has been shown with SMBG data, and to a certain extent with CGM data, that if 50% of the readings are in this range, the HbA1c will usually be around 7%.[52] Some of the panel voted for 70–140 mg/dL to get a sense of how close to ideal control the patient had come but agreed this could be saved for an expanded or research view.

The notion of TIR was thought to be an important concept that needs to be standardized for clinical care, research, and regulatory purposes.[53] TIR can be expressed as "% of readings" in range (primary AGP output) and "hours per day" in range (secondary AGP output). Both of these are easy for patients to understand and can be followed over time for signs of improvement. The time above and below the target range should also be prominently displayed, and it is important to agree on a series of divisions of the ranges below and above the target that convey the severity of hypoglycemia and hyperglycemia experienced by the patient. TIR is a logical clinical management and clinical research outcome metric that would be more meaningful or reliable if also combined with the degree or severity of hypoglycemia and hyperglycemia.

Glucose exposure

Overall, more than three-quarters (82%) of the panel members were neutral or considered a glucose exposure metric to be of little value for clinical management. Nevertheless, when evaluating options for reporting glucose exposure (area under the curve [AUC] for 24 h; AUC normalized hourly; excess AUC for 24 h; mean glucoses of all readings; median glucose of all readings), 82% of panel members chose mean glucose of all readings as the metric to which clinicians and patients can most easily relate. Although mean/median glucose of all readings was not considered critical to clinical decision making, most (59%) participants indicated that mean glucose exposure for specific time periods (e.g., overnight, fasting, 2–4 h postprandial) could be helpful in evaluating the effects of food, exercise, or insulin. Because the HbA1c value is not always available when the CGM report is being reviewed, it seems appropriate to include the estimated HbA1c level[54] based on the average glucose. Finally, it was agreed that having the actual AUC glucose exposure data can be a helpful clinical research metric.

Glycemic Variability

The majority (69%) of panel members indicated that SD was the metric most commonly used and understood for assessing and reporting GV. In a 2010 review titled "Glucose Variability; Does It Matter?," the team lead by DeVries concluded that SD was the easiest and best validated measure for quantifying variability from CGM.[22] Rodbard[55] greatly expanded the dialogue on SD, concluding it is a reasonable measure because most other measures being considered are related in a linear manner to SD. He explained that in addition to total SD, which most investigators and automated programs calculate, there are actually at least eight different components of SD that all have potential research or clinical merit, including some fairly commonly recognized as intraday SD (SD within-day) and inter-day SD (SD between-days). Many authors have pointed out that if the distribution of glucose data collected from CGM were Gaussian, distributed normally around the mean, then SD would be a very reliable

clinical and research measure of GV. However, nearly all agreed real-world patient CGM data come in a variety of shapes and are invariably skewed. Some very novel and important methods of nonlinear transformation of the glucose scale to achieve a nearly symmetrical or Gaussian distribution have allowed Kovatchev et al.[56,57] to define indexes of risk for low and high glucose.

The panel acknowledged that there are many ways to analyze or transform glucose data to measure one component or another of GV, including SD, coefficient of variation (CV), interquartile range (IQR), mean amplitude of glucose excursion (MAGE), M-value, mean of daily difference (MODD), continuous overall net glycemic action (CONGA), and others; however, the panel focused on three: SD, CV, and IQR. SD was selected for ease of use, familiarity, and correlation with other factors despite the drawback of most real-world data not being normally distributed. Another perceived drawback for SD and some other measures of GV is their dependence on measures of mean glucose level or HbA1c. Percentage coefficient of variance or CV (% CV), derived from SD (100×SD/mean of observations), was also selected by the panel as one component of GV to follow. This measure was recently proposed by Rodbard[58] as the best parameter to use to characterize GV because it is relatively more constant than other measures irrespective of mean glucose or HbA1c level, which we know can vary in T1D. Although this makes CV a good marker to follow for research purposes, CV is not easily displayed in a visual fashion, so it is less helpful as part of the CGM clinical view. The third GV factor the panel considered worthy of including was IQR, the only commonly recognized method of expressing GV that is not dependent on the assumption of normal distribution; it simply takes the difference between the 75th and 25th percentiles of glucose values, and that 50% of glucose values is called the IQR. IQR has long been considered to be the most logical and visually understandable way to express GV using SMBG,[1,55] and it has been shown to have equal clinical utility in analyzing and visualizing CGM data.[2] If CGM data are collected for an adequate amount of time (discussed later in this article) and the data are displayed as a modal day, then IQR provides a reliable (not influenced by non-Gaussian distribution) aggregate measure of GV, and it allows one to easily visualize the time of day or relationship to a meal or medication that there is high GV, which may need clinical attention. Increasing numbers of studies are showing that high GV must be addressed if one is to improve the overall mean glucose or HbA1c level and that one must work to reduce a high GV in order to minimize the risk of hypoglycemia.[23–25] Although a value for SD or CV might also indicate a problem with excessive GV (once the community agrees on the definition of excessive), there is the additional potential clinical benefit of being able to visualize GV hour by hour throughout the day as reliably portrayed by the IQR.

Most (64%) panel members saw little or no value in reporting glycemic stability (rate of change in glucose measured from the median curve [mg/dL/h]); 29% were neutral on this metric and thought because it was a different measure than classic GV it could be further explored in a research view as desired.

Hypoglycemia

The discussion of hypoglycemia focused on two main issues: cut points for hypoglycemia and the definition of severe hypoglycemia. The majority (88%) of panel members selected <70 mg/dL as the criterion for "reportable hypoglycemia." This value agrees with what most clinicians use in practice and publications as well as what the FDA used in their recent guidance regarding the conduct and evaluation of artificial pancreas clinical trials where the degree of hypoglycemia will be a major consideration.[31] This is similar to the 2005 American Diabetes Association (ADA) Workgroup report[59] on hypoglycemia (which used ≤70 mg/dL as the definition of hypoglycemia) and consistent with the 2013 ADA standards of medical care,[60] which state in the summary of glycemic recommendations that the preprandial capillary plasma glucose goals are 70–130 mg/dL (with room for individualization), so logically below this would represent hypoglycemia. The panel thought there needed to be some additional gradation or separation of hypoglycemia into buckets or categories so that the patient, clinician, researcher, or regulatory agency can better quantify the severity of hypoglycemia. The majority (53%) of participants were satisfied with <55 mg/dL as the criterion for more significant hypoglycemia. Further correspondence after the panel led to the splitting of both hypoglycemia and hyperglycemia into three categories of severity. For hypoglycemia, it is <70 mg/dL (3.9 mmol/L), <60 mg/dL (3.3 mmol/L), and <50 mg/dL (2.8 mmol/L), corresponding to the glucose being considered low, very low, or dangerously low, respectively (Fig. 1). These three levels of severity of hypoglycemia are also the ones frequently referenced as being worthy of note in the final FDA artificial pancreas guidance, which is one of the first FDA documents to acknowledge the use of CGM as an outcome marker.[31] There is also a clinical category of severe hypoglycemia (e.g., requiring assistance from another person). The panel acknowledged that this definition of severe hypoglycemia was almost universally accepted but (79% of the panel) thought there needed to be another subcategory of severe hypoglycemia, which they suggested be called "major severe hypoglycemia" (requiring medical personnel intervention in the home or an emergency center, hospitalization, seizure, coma, or death). This seemed necessary because quantifying severe hypoglycemia can be difficult given that the term "requiring assistance" is subjective, hard to collect from claims data or electronic medical records, and often not appropriate in pediatrics where hypoglycemia of any severity often requires assistance. It was also thought that administering glucagon by lay individuals should qualify as major severe hypoglycemia, but, again, this is somewhat subjective and can also be hard to capture reliably.

In addition to the percentage of glucose values below these thresholds, hypoglycemia would be quantified by the time in each range of hypoglycemia and the number of episodes (defined as at least 10 consecutive min below the criteria) of each range of hypoglycemia per day, as discussed earlier (target range).

Finally, the panel acknowledged there are other important categories or classifications of hypoglycemic events such as the ADA Workgroup on Hypoglycemia report[59] discussed earlier. This report classifies a hypoglycemic event as "severe" (requiring assistance), "documented symptomatic" (symptoms and glucose ≤70 mg/dL), "asymptomatic hypoglycemia" (no typical symptoms but glucose ≤70 mg/dL), "probable symptomatic hypoglycemia" (typical symptoms but no glucose available), and "relative hypoglycemia" (typical symptoms but glucose >70 mg/dL). These classifications

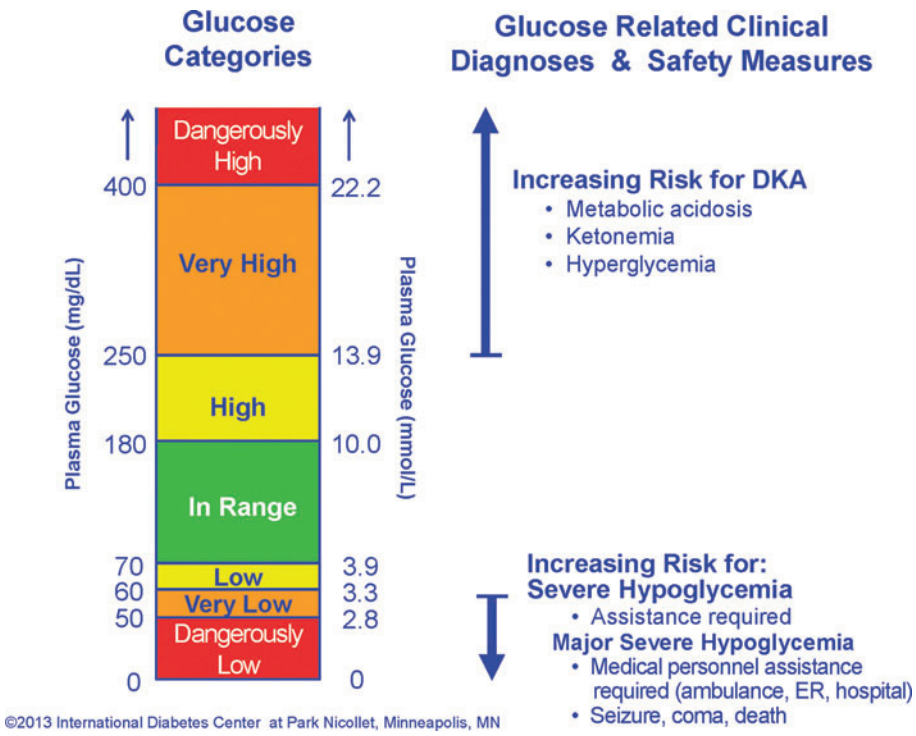

FIG. 1. Glucose target ranges and categories. DKA, diabetic ketoacidosis; ER, emergency room.

are helpful and are considered the standard approach to classification of hypoglycemia if CGM is not being used; however, if continuous glucose data are used in clinical practice or clinical trials, the classification system proposed here with documenting severe and major hypoglycemic events, along with percentage of readings and time spent with and number of episodes of glucose readings <70 mg/dL, <60 mg/dL, and <50 mg/dL, may allow the medical community to more clearly define safe glycemic control and be able to effectively compare treatments and strategies for reducing hypoglycemia. The ADA, FDA, and European Medicines Agency, along with other organizations, will need to continue to work to define what constitutes a meaningful reduction in hypoglycemia in the era of increasingly more accurate and frequently utilization of CGM, but that work must start with standard definitions of hypoglycemia.

Hyperglycemia

Panel members again thought there should be several levels of severity of hyperglycemia above the upper range of the treatment target of 180 mg/dL that have some relevance to clinical practice. Many thought significant hyperglycemia should be >250 mg/dL (43%), and 25% thought it should be even higher, such as >300 or 400 mg/dL. Again, trying to be consistent in quantifying the severity of hyperglycemia into three levels, we propose >180 mg/dL (10.0 mmol/L), >250 mg/dL (13.9 mmol/L), and >400 mg/dL (22.2 mmol/L), corresponding to the glucose being consider high, very high, or dangerously high, respectively (Fig. 1). As with hypoglycemia there is a clinically based category of severe hyperglycemia, called diabetic ketoacidosis, that is a clinical diagnosis only in part related to hyperglycemia but also including acidosis and ketosis. Although the criteria for hyperglycemia severity are arbitrary, they do represent values that are commonly used in clinical practice to signal an advancing degree of concern, and many clinical or nursing guidelines are associated with these numbers to increase aggressiveness of clinical management (e.g., increase fluid intake, give an additional or increased insulin correction dose, change insulin infusion set if using a pump, or check urine or capillary ketones) or initiate more frequent phone, electronic, or in-person contact.

Proposed AGP "Dashboard"

The IDC has developed a data-analysis software program (captūr AGP™) that statistically and visually represents glycemic exposure, GV, glycemic stability, and TIR over a period of time using downloaded CGM or SMBG data.[2] The visual report allows clinicians, educators, and patients to identify glucose patterns and areas of highest clinical concern so that lifestyle and pharmacologic therapy can be appropriately adjusted.

Panel members were asked to evaluate a preliminary draft of the AGP and provide input regarding its content, statistical default settings, graphic elements, and overall functionality. The primary focus was a "simplified" single-page document to be used in clinical practice or in communicating with a patient. Some thought was give to expanded parameters for use in clinical trials or more detailed clinical analysis. This first version was to focus on glucose data only, whereas later versions can incorporate other insulin pump, lifestyle, and pharmacologic information. Figure 2 presents the most recent version of the proposed AGP developed by the IDC, which incorporates input from the panel. Figure 3 shows an AGP from an individual without diabetes and is representative of a normal

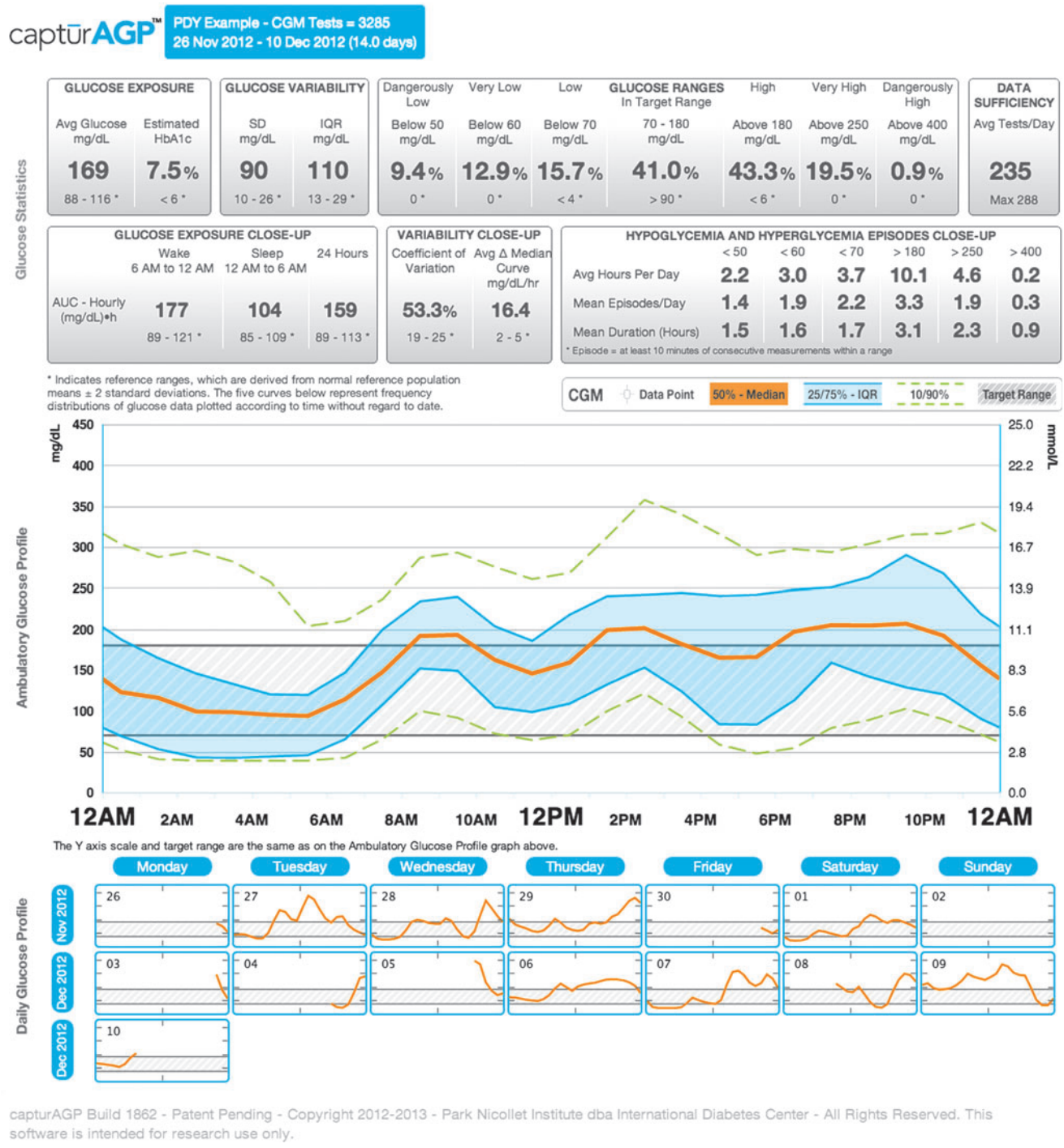

FIG. 2. Ambulatory glucose profile (AGP) "Dashboard"—diabetes. Clinical view is provided in row 1 of glucose statistics. Research view is provided in rows 1 and 2 of glucose statistics. AUC, area under the curve; Avg, average; CGM, continuous glucose monitoring; HbA1c, glycated hemoglobin; IQR, interquartile range.

reference population.[2] This comparison, although not the expected outcome for most patients, serves as a helpful reference tool for clinicians and patients to graphically see how tightly regulated the glucose is in individuals without diabetes.

The AGP "Dashboard" serves as the default page of the software program and is designed to present the most relevant statistical and graphical information that would allow clinicians to quickly assess patients' glycemic status and make meaningful, clinical decisions, in most cases, while the patient is also viewing the "Dashboard" and providing helpful insights and feedback.

As shown in Figure 2, the AGP "Dashboard" presents a summary of the patients' glucose data in three parts: (1) Statistical Summary; (2) Visual Display; and (3) Daily Views. For a comprehensive prospective glucose analysis, it is recommended that patients collect approximately 14 days of CGM data. In a series of analyses of CGM data in T1D and T2D, 14 days of CGM data gave a very accurate, relatively

FIG. 3. Ambulatory glucose profile (AGP) "Dashboard"—normal. Clinical view is provided in row 1 of glucose statistics. Research view is provided in rows 1 and 2 of glucose statistics. AUC, area under the curve; Avg, average; CGM, continuous glucose monitoring; HbA1c, glycated hemoglobin; IQR, interquartile range.

stable reflection of the key glucose metrics discussed previously, and the modal day displays of glucose medians, peaks, troughs, and variability were highly reflective of what the display would look like after 30 days of CGM use in most patients.[61] Although fewer days of CGM data can be analyzed, approximately 14 days, displayed as an AGP, gives the patient and clinician an acceptable degree of confidence to make clinical decisions in most cases without having to normalize or transform the data into other tables, graphics, or indices to assist with management. From 7 to 10 days of CGM data may provide enough data for reasonable clinical decision making if 14 days of data are not

available or according to the clinician's judgment. Additional indices or composite measures may be helpful for research and may be used to meet the needs of certain patients.

Part 1: "Statistical Summary"

The "Statistical Summary" presents groupings of data components (Fig. 2). The box at the top of the "Dashboard" presents the patient name, date range, and total number of CGM tests. If a CGM device is used that measures glucose at 5-min increments, the maximum number of tests would be 288 per day, 2,017 over 7 days, and 4,032 over 14 days. Patients often achieve approximately 70–80% of the 14-day goal, or 2,822–3,225 tests.[62]

In the first row of data, the "Glucose Exposure" box presents the average glucose and estimated HbA1c levels based on collected data. The "Glucose Variability" box presents the SD (total SD) and IQR of the collected data. Within the "Glucose Ranges," collected data are presented as a percentage of values "In Target Range" (default, 70–180 mg/dL) bounded by low ("Low" [< 70 mg/dL], "Very Low" [< 60 mg/dL], and "Dangerously Low" [< 50 mg/dL]) and high ("High" [> 180 mg/dL], "Very High" [> 250 mg/dL], and "Dangerously High" [> 400 mg/dL]) ranges.

The "Data Sufficiency" box provides guidance to clinicians regarding whether the amount of data is sufficient in reflecting patients' actual glucose status. The "Average Tests/Day" is automatically generated depending on which device is downloaded. The maximum is 288/day if glucose is measured at 5-min increments, or 144/day if measured at 10-min increments. This information allows clinicians to verify the glucose sampling frequency of patients' devices and provides a quick check to see if the patient captured most of the possible tests per day.

Only the first row of the "Statistical Summary" shows up as the default or "Dashboard" clinical view of AGP. With a click, one can expand to a second row of statistical variables (the research view of AGP) that include" Glucose Exposure Close-up," "Variability Close-up," and "Hypoglycemia and Hyperglycemia Episodes Close-up."

The "Glucose Exposure Close-up" displays the hourly average (mean of the hourly averages or AUC for three segments: "Wake" (daytime; 6 a.m. to midnight); "Sleep" (nocturnal; midnight to 6 a.m.); and "24 h." There is growing consensus among clinicians and trial investigators that if the "Wake" and "Sleep" times are not known or documented, these are reasonable default times with the intention of making the default nocturnal time narrow so it has high probability of reflecting the sleep, nocturnal, or basal time segment.

The "Variability Close-up" presents the CV as a percentage ($SD/N \times 100$), which is often used for tracking change in overall glycemic variability in research studies. Stability of glucose is defined as mean hourly change from the median curve ([mg/dL] × h). This reflects the average stability represented as the change in glucose per hour measured along the median glucose curve over the day. Individuals with diabetes can have fluctuations in glucose with a high or low degree of variability or consistency. Although the clinical significance of glucose fluctuations is not known, significant glucose fluctuations do not occur in individuals with normal glucose metabolism.

The "Hypoglycemia and Hyperglycemia Episodes Close-up" addresses the considerable clinical and research interest in how much time patients spend in the target range or above or below the target. Because the more time patients spend in the extremes of low or high glucose is known to be detrimental, it can be helpful to record this information in several ways. Although the target range panels (in the first row or default "Dashboard" view) express this as the percentage of CGM reading in each range, this panel gives three additional measures: "Average Hours Per Day," "Mean Episodes/Day," and "Mean Duration (Hours)." "Average Hours per Day" presents the percentage of values in each range of below target, in target, and above target. "Mean Episodes/Day" presents the mean of episodes in each range. An episode is defined as at least 10 min of consecutive measurements within a given range (or three consecutive readings if glucose is measured at 5-min increments). Once the readings are below or above a target and last for three readings (10 min), the episode continues until reading moves into a new target zone. Over time the research community needs to determine if the number of episodes or the cumulative time spent in hypoglycemia or hyperglycemia is most impactful on quality of life or risk of complications.

Note that below each data component or panel in the "Statistical Summary" section is a reference range derived from a normal reference population (mean ± 2 SD).[2] Although patients with diabetes (particularly T1D) are not expected to achieve completely normal glucose values, this gives a frame of reference. Acceptable or desirable values for various subsets of T1D patients (toddlers, adolescents, adults, elderly, those with hypoglycemic unawareness, etc.) can be established over time. Right now those caring for toddlers (< 6 years old), children (<13 years old), and adolescents (13–20 years old) can change target ranges as desired and look at the derived HbA1c (based on CGM data) to see if these patients are reaching the ADA[60] or International Society for Pediatric and Adolescent Diabetes[63] suggested age-specific targets.

Part 2: "Visual Display"

The "Visual Display" presents a modal day (also called standard day or average day) in which all collected data over multiple days are collapsed and plotted according to time (without regard to date) as if they occurred over 24 h, starting and ending at midnight. Smoothed curves representing the median (50^{th}), 25^{th} and 75^{th} (IQR), and 10^{th} and 90^{th} frequency percentiles define the 24-h AGP. At a glance one can observe the time(s) of day when the glucose value is most consistently low or high and when the most variability is occurring (the width of the 25^{th}–75^{th} percentile [50% of reading] or 10^{th}–90^{th} frequency [80% of readings]) that needs to be addressed. This is an exercise clinicians can do together with patients in a matter of minutes. For instance, without dependence on numbers, formulas, or derived indices, clinicians and patients can quickly become skilled at identifying the risk of hypoglycemia. For example, if the 10^{th} percentile curve crosses 70 mg/dL or lower, there is moderate risk of hypoglycemia at that time because consistently 10% of the values fall in this range. However, if the 25^{th} percentile curve crosses into hypoglycemia, this implies a marked risk because more than 25% of the glucose values fall in the hypoglycemic range, and consequently this should be addressed before additional

therapy is instituted to treat accompanying hyperglycemia as is often seen with significant GV.

The target range is noted, and the default view is 70–180 mg/dL to match the default statistics; however, this is interactive and can easily be changed by the clinician, as needed. Also, with one click each individual glucose reading that makes up the AGP can be overlaid on the glucose curves.

Part 3: "Daily View"

The "Daily View" is presented as a calendar of thumbnail AGPs (target range and median line) of the 24-h pattern for each day that is included in the overall profile. This allows for comparison of patterns on specific days (e.g., weekend vs. weekday) and permits a deeper discussion with the patient regarding special circumstances that may be responsible for extremes or fluctuations in glucose readings. Clicking a thumbnail will enlarge it to a full-size 1-day AGP with corresponding glucose metrics for that day. A modified daily view as well as a concise modal day AGP view that captures pump download data that are important to healthcare professionals (basal rates, insulin:carbohydrate ratio, correction doses, carbohydrate intake, etc.) as they refine pump therapy is in development. Over time, standardized glucose reporting and analysis using tools like AGP must be extended for T1D and T2D patients using multiple daily injections of insulin.

Moving forward

The current iteration of the AGP "Dashboard" (the first row of glucose statistics) provides a basic starting point that allows clinicians and patients to begin to more effectively visualize and utilize glucose data as a key component in addition to the HbA1c value to drive lifestyle and therapy decisions in the management of diabetes. The clinician can click and reveal the second row of glucose statistics if desired. Piloting is underway to quickly incorporate the AGP "Dashboard" into an electronic medical record so that it is easy to compare with the next AGP after a therapy adjustment or at a subsequent visit or electronic communication. Key to the successful implementation of AGP or other ways of analyzing and viewing CGM data is an enhanced workflow that seamlessly and rapidly acquires the glucose data from any device at a clinic visit or over the Internet cloud network. Additional functionality, such as inclusion of data relevant to insulin or other diabetes medication administration, nutrition (timing and carbohydrate content), and physical activity, is being explored. Currently, these data can be added by the clinician on the AGP modal day graphic at a clinic visit. This can assist in clear communications and help come to a jointly agreed-upon action plan with the patient. Workflow usability studies and patient and provider preference or satisfaction evaluations are being designed using the AGP "Dashboard."

Industry Issues and Consideration

Representatives from the diabetes device industry (SMBG, CGM, insulin pump systems, and data management) attended the final report-out and summary portion of the meeting to discuss their reaction and possible concerns regarding the AGP "Dashboard" and reporting standardization. Although some representatives expressed concern that standardization could potentially stifle innovation, others stated that the AGP "Dashboard" approach, in fact, encourages more innovation because it creates an entry for clinicians to immediately begin interacting with CGM data, thus allowing manufacturers to focus on more sophisticated data analysis features and capabilities (e.g., "secondary visualizations"). Many participants (panel members and industry representatives) thought that the AGP "Dashboard" approach was analogous to the electrocardiogram, noting that although several manufacturers produce electrocardiogram systems, visualization of the data is standardized. Although all the issues regarding integration of insulin pump data and proprietary software have yet to be resolved, there was general consensus among industry representatives that there would be value to including a standard report such as the AGP "Dashboard" in their product features so there would be a consistent approach to presenting glucose data for patients and diabetes care providers. It was agreed to continue discussions and to collaborate in some manner with the IDC/Helmsley Trust/Expert Panel and others to move the standardization of glucose data collection, display, and interpretation forward.

Conclusions

Despite advances in insulin preparations, insulin delivery devices, and glucose monitoring technology, glycemic control in many T1D patients remains suboptimal. Use of the HbA1c value as a primary (or sole) measure of glycemic status, underutilization of SMBG and CGM data, and lack of easy and standardized glucose data collection, analysis, visualization, and guided clinical decision making are, clearly, key contributors to poor glycemic control within this population.

Working with the Helmsley Charitable Trust, expert collaborators, industry, and regulatory officials, the IDC will continue to develop, test, and assist with implementation of the AGP "Dashboard" as the standard reporting system for CGM and, ultimately, data from SMBG. Through standardization of clinical terms and key metrics, with glucose data visualized in an easily interpreted format, the AGP "Dashboard" has the opportunity to benefit clinicians, patients, payers, and regulators through improved patient care, better understanding and utilization of glucose data in clinical practice, and greater ability to evaluate and improve clinical performance. Standardized reporting also has potential to benefit clinical research by enabling investigators and regulators to agree on standardized benchmarks that define improvement in glycemic control and a reduction in hypoglycemia, hyperglycemia, and glucose variability. This will allow for new drugs, new devices, and new team-based approaches to diabetes management to be evaluated more effectively.

Standardizing glucose reporting and analysis, with tools such as AGP, may be one step toward optimizing clinical decision making in diabetes. Although CGM has been shown to be valuable in several clinical settings, continued research is needed to define which individuals with T1D or T2D will benefit most from either real-time use of CGM or retrospective analysis of intermittent use of CGM.

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Companies Represented at Report-Out

Abbott Diabetes Care, Animus Corporation, Bayer HealthCare LLC, BD Medical-Diabetes Care, Close Concerns, Inc., DexCom, Diasend, LifeScan Inc., Medtronic Diabetes, Park Nicollet Foundation, RocheDiagnostics, Sanofi US, and SweetSpotDiabetes.

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Advisory Board/Consultant/Research Support: Abbott Diabetes Care, Amylin, Bayer, Becton Dickinson, Boehringer Ingelheim, Intuity, Calibra, DexCom, Eli Lilly, Halozyme, Helmsley Trust, Hygieia, Johnson & Johnson, Medtronic, Merck, NIH, Novo Nordisk, ResMed, Roche, Sanofi, and Takeda.

His employer, non-profit Park Nicollet Institute, contracts for his services and no personal income goes to Dr. Bergenstal. He has inherited Merck stock. He has been a volunteer for ADA and JDRF.

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None to report

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