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The Use of Standardized Reporting and Time-in-Range in the Management of Diabetes: A Consensus Report

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Abstract

Introduction: The exhaustion of healthcare resources due to the rising prevalence in Saudi Arabia mandates the search for each method that can help in better control of diabetes. **Methods:** The gathered task force gathered to develop an explicit, evidence-based consensus for the use of time-in-range targets as guidance for better glycemic control while using continuous glucose monitoring (CGM). This article has the recommendations of this expert panel. **Results:** HbA1c and self-monitoring blood glucose (SMBG) are not enough to detect blood glucose (BG) fluctuations on a daily basis. The incorporation of technology like FreeStyle Libre with its applications like Libre View is now used in many institutes in Saudi Arabia. This system is comprehensive and has all the standardized metrics needed. However, training and support are always needed. Barriers and challenges include the awareness & experience of the technology, the time barrier, the patients' barriers, the technical barriers, and of course, the availability barrier. All the barriers and challenges should be dealt with by designing new training programs. **Conclusion:** The expert

panel recommended using CGMs technology in people with type 1 diabetes (T1DM) children and adults, type 2 diabetes (T2DM) on multiple insulin injections, gestational diabetes (GDM) who need further glycemic control, and those at high risk for hypoglycemia. In addition, we recommend using them for a short period for those who require intensive BG control or during acute illness or stress. In addition, Ambulatory Glucose Profile (AGP) could be used as an educational tool for any individuals with DM to study the impact of certain elements of lifestyle modifications on their immediate BG level.

Keywords

Diabetes, Time in Range, Glycemic Control, HbA1c

1. Introduction

Worldwide, by the year 2045, diabetes mellitus (DM) prevalence is expected to be 9.9%, with a total number of 629 Million [1]. The Kingdom of Saudi Arabia (KSA) has a rising prevalence of DM [2], with the consequent exhaustion of healthcare resources.

In 2019, the American Diabetes Association (ADA) coined and published its first recommendations for the time-in-range (TIR) targets to guide those who help in the management of DM as well as people with DM achieve better glycemic control by the utilization of the continuous glucose monitoring (CGM) [3]. The consensus panel included researchers from all geographic regions to ensure that the recommendations can be generalizable [4].

A panel of experts in DM was gathered to generate a clear, evidence-based consensus for the use of TIR targets as guidance for better glycemic control while using CGM. This manuscript presents the recommendations of this task force.

2. Available Metrics for Blood Glucose Monitoring

Fasting blood glucose (FBG) level, postprandial blood glucose (PPBG) level, and random blood glucose (RBG) level—metrics for blood glucose (BG) monitoring—were used once for the diagnosis and management of DM. However, they give only a snapshot of the glycemic status at a certain point in time. Glycated hemoglobin (HbA1c) and fructosamine were also introduced as metrics for glycemic control over a duration ranging from two weeks to three months. The introduction of self-monitoring blood glucose (SMBG) helps in glycemic control daily; however, to reflect the actual status, it should be carried out at least seven times per day, which is sometimes not practical. All those lead to the evolution of continuous blood glucose monitoring systems (CGMs), particularly in those people who are in intensive insulin therapy. Consequently, new metrics have been developed to reveal new insights into the short-term glucose dynamics; this is the topic of this consensus [5] [6].

2.1. Glycated Hemoglobin (HbA1c) Is Not Enough Metric for Glycemic Control on a Daily Basis

Elevated HbA1c is a significant contributor to complications in people with type 1 DM (T1DM), as confirmed by the DM Control and Complications Trial (DCCT). In addition, the UK Prospective Diabetes Study (UKPDS) confirmed how the control of BG affects health outcomes in type 2 DM (T2DM) [7] [8].

However, HbA1c has its limitations. First, it does not show the glycemic level and variability daily, as it just shows an average level of BG for the last three months.

Second, HbA1c is inaccurate in people with anemia, hemoglobinopathies, and pregnancy [9] [10] [11] [12]. In addition, it does not reveal the rapid changes in BG levels daily; thus, adjustment of therapy is not easy. Moreover, there is a racial difference in the accuracy of HbA1c because of different glycation rates [9]. Therefore, even though HbA1c has been evidenced valuable measure and validated as a risk factor for DM complications, it seems not helpful for glycemic control on a personal level as it reflects only a piece of the severity of hyperglycemia and glycemic variability are contributing to the pathogenesis of complications [13] [14].

2.2. Self-Monitoring Blood Glucose (SMBG) Also Has Its Limitations as a Metric for Glycemic Control

SMBG has been associated with better management in T1DM and T2DM. Nevertheless, it requires a finger-stick and it only gives a snapshot for one point in time; therefore, it does not show the trend or the rate of change of BG levels. Thus, using it alone may result in improper treatment decisions. Moreover, it often fails to detect hypoglycemia, either nocturnal or asymptomatic [15]-[22].

3. The Advent of Continuous Blood Glucose Monitoring Systems (CGMs)

The search for new methods for BG monitoring was continuous to address the limitations in HbA1c and SMBG, leading to the development of real-time CGM (rtCGM) and flash glucose monitoring (FGM). The former tracks the glucose level uniformly, providing real-time measurements, while the latter, at the time of checking, shows continuous glucose measurements retrospectively. Both types facilitate monitoring of the time spent in the target glycemic range; TIR.

Nevertheless, only rtCGM can warn users if their BG level is trending toward hypoglycemia or hyperglycemia, while FGM requires scanning of the sensor to reveal these trends, where newer generations of FGM are available with optional alarm functionality. Plentiful studies have demonstrated that the use of CGM improves both glycemic control and quality of life in different populations with T1DM or T2DM. In addition, one meta-analysis has shown that the frequency and persistence of its utilization of rtCGM are directly correlated to its benefit [9] [23]. Moreover, a meta-analysis has shown that the use of Flash glucose monitoring was associated with a clinically significant reduction in

HbA1c [24].

A critical note about CGMs is validating their performance, whereas FGM is factory-calibrated, indicating that no validation against SMBG is required. The most common metric used to assess CGMs performance is the mean absolute relative difference (MARD), which is the mean of the absolute errors between all CGMs values and the reference values. The lower the MARD is, the better the performance is [9]. However, the methodology for calculating MARD has not yet been standardized, so this would be misleading [25].

3.1. Continuous Blood Glucose Monitoring Systems in Saudi Arabia

In KSA, insulin pump therapy and CGMs are now available and increasing as a modality for better management of DM and as an educational tool. The new user-friendly generations of CGMs encouraged people with DM to use this technology. The initiation of reimbursement of these tools by the national health bodies and insurance organizations paved the way in front of the healthcare professional to explore the recent technologies for better glycemic control and its subsequent improvements in the quality of life of their patients. All these are reflected in reducing the cost of illness and the burden of DM. CGMs are available in Saudi Arabia with all its four categories: rtCGM like the Dexcom; FGM like the FreeStyle Libre; blinded (professional) CGM like the Guardian; and the unblinded CGM. Although CGMs have become the gold standard in managing patients who are in intensive insulin therapy, some physicians are reluctant to utilize them, most probably due to the lack of experience and knowledge with this technology.

3.2. The Clinical Targets for CGMs Data Interpretation

In 2019, the international panel of diabetes experts demonstrated ten metrics with their target range in the CGM data interpretation with a consensus on the TIR to complement HbA1c. These metrics include the number of days CGMs has worn (recommended 14 days); the percentage of time CGMs is active (recommend 70% of data from 14 days); mean BG; glucose management indicator (GMI); glycemic variability (% CV); time-above-range (TAR) with two levels; time-in-range (TIR); and time-below-range (TBR) in two levels. In addition, the expert panel set the accepted target in each metric for T1DM, T2DM, and older/high-risk T1DM or T2DM, and for pregnant women with T1DM, T2DM, or gestational diabetes (GDM) [3].

The new term GMI replaced the term estimated A1C. It is based on the CGM-derived mean BG in the previous 14 days [14]. In addition, different research studies showed the correlation between HbA1c and the TIR. One was conducted upon 545 patients with T1DM and the other upon 1137 patients with T1DM and T2DM [26] [27]. TIR was validated as an outcome measure for DM complications like retinopathy and microalbuminuria [28].

3.3. Integrating Continuous Glucose Monitoring Systems into Clinical Practice

CGMs provide current and future BG data and display them in numerical and graphical ways, along with glucose trends. Retrospective analysis of CGMs historical data can help in carbohydrate counting and lifestyle modifications. Moreover, some CGMs have an alert feature, which is crucial for those with frequent hypoglycemia. In addition, the data-sharing ability and trend arrows can help in better glycemic control. Each type of CGMs has its advantages and disadvantages. The accuracy, the need for calibration, the easy applicability, and the cost are among the critical factors when choosing one of them.

4. CGMs Metrics

4.1. Time-in-Range

In general, the term TIR refers to the total time spent in a target BG range (70 - 180 mg/dL) or the more strict range (70 - 140 mg/dL) in some conditions. Of course, it adds a valuable piece of information about the current level of glycemic control at a specific time. That also has led to new terms like times below range (TBR) and times above range (TAR), which gave a better quantification of the level of BG control. TIRs can help people with DM watching the improvement or deterioration in the amount of clinically significant hyperglycemia or hypoglycemia over time [9] [29].

4.2. Hypoglycemia

In people with DM, particularly T1DM, hypoglycemia is a common complication of treatment and is a significant barrier to glycemic control. In adults with T2DM on insulin or sulfonylureas, severe hypoglycemia, defined as needing assistance, is more frequent when HbA1c is at the lowest or highest levels. Quantification of the risk for hypoglycemia can be carried out using the low BG index (LBGI). However, LBGI, when based on CGM data, tends to underestimate the risk to some extent [29] [30] [31] [32]. Grading hypoglycemic events is essential in managing DM, specifically when the CGM levels indicate BG levels < 54 mg/dL for ≥two hours (**Table 1** & **Figure 1**) [9].

4.3. Glycemic Variability

Another important CGM metric is glycemic variability (CV). A CV < 36% means stable BG levels, and CV ≥ 36% means unstable levels [30]. The relationship between CV to DM complications, cognitive function, and quality of life has been studied and established. Therefore, it has been accepted as an important and valuable marker for glycemic control [31] [32] [33] [34]. It gives a better insight into the dynamicity of the BG levels and their fluctuations. It is a waveform process that has an amplitude, frequency, and duration. It contributes to the risks of hyperglycemia and hypoglycemia. The higher the CV, the higher is the association to mortality in the intensive care setting [35]-[41].

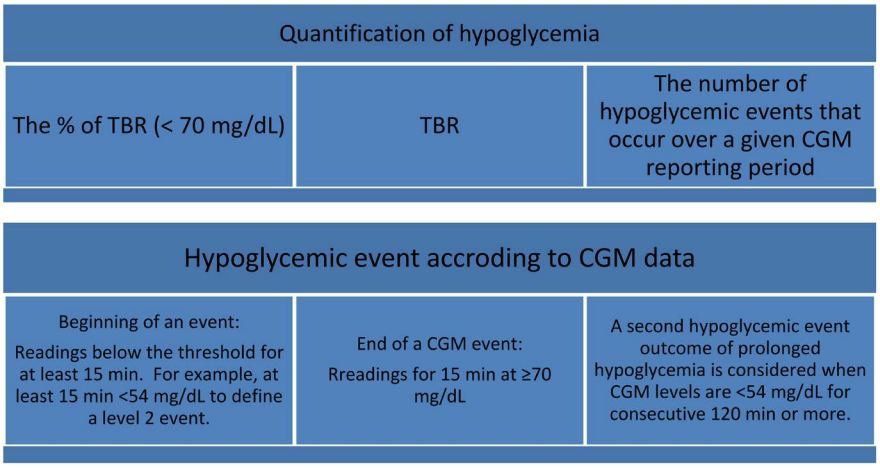

Figure 1. Quantification of hypoglycemia.

Table 1. Categorization of hypoglycemia.

Level 1	Level 2	Level 3
BG value (70 - 54 mg/dL), with or without symptoms.	BG value < 54 mg/dL, with or without symptoms.	Severe hypoglycemia, denotes cognitive impairment, is not defined by a specific BG value.
Minimization of the time spent in this range will reduce the risk of developing more clinically significant hypoglycemia.	Clinically significant hypoglycemia, requires immediate attention.	Requires external assistance for recovery.

5. The Need for a Glucogram Similar to an Electrocardiogram

Using standardizing reporting is beneficial in the clinical decision-making in DM management. Several reporting tools, such as the standardized Ambulatory Glucose Profile (AGP) report (**Figure 2**), have been developed using at least 14-consecutive-days CGM data with 70% of readings [42] [43] [44]. Several expert panels previously adopted the AGP and recommended it as a standard tool for picturing CGM data [9] [45].

Moreover, integrating these metrics into the electronic records of people with DM is of utmost importance as they can facilitate communication with patients and help them self-manage their DM [46].

Different types of graphs help figure out the exact situation of BG control and BG distribution in one day or in a certain period in time (**Figure 3(a)**). These reports can be printed, certain areas of hypo or hyperglycemia can be marked and discussed with patients efficiently in relation to their daily routine (**Figure 3(b)**). In addition, the graphs can be daily, each day in a line graph (**Figure 3(c)**). In addition, another graph can show a summary and give how much time of the 14 days the device was active (**Figure 2**).

The four key metrics that require attention are data sufficiency (a minimum of two weeks of CGM use); the percentage of time (or minutes) on TIR, TAR & TBR;

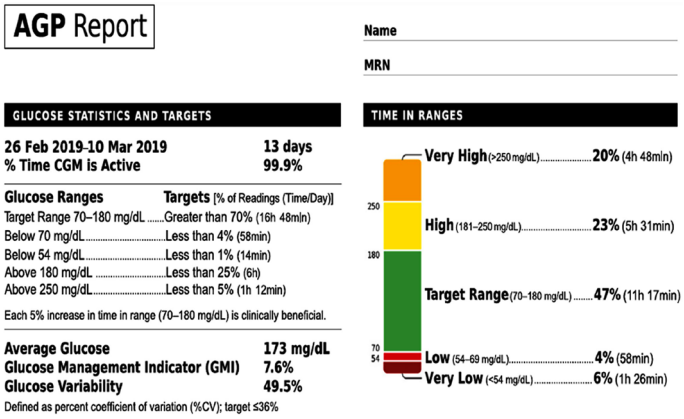

Figure 2. Ambulatory Glucose Profile (AGP) Report-Metrics and glucose pattern summary. For illustrative purposes, the outputs from the FreeStyle Libre Health Management System software (Abbott Laboratories). The Ambulatory Glucose Profile (AGP). ([a]2021 International Diabetes Center at Park Nicollet, Minneapolis, MN. AGPreport.org).

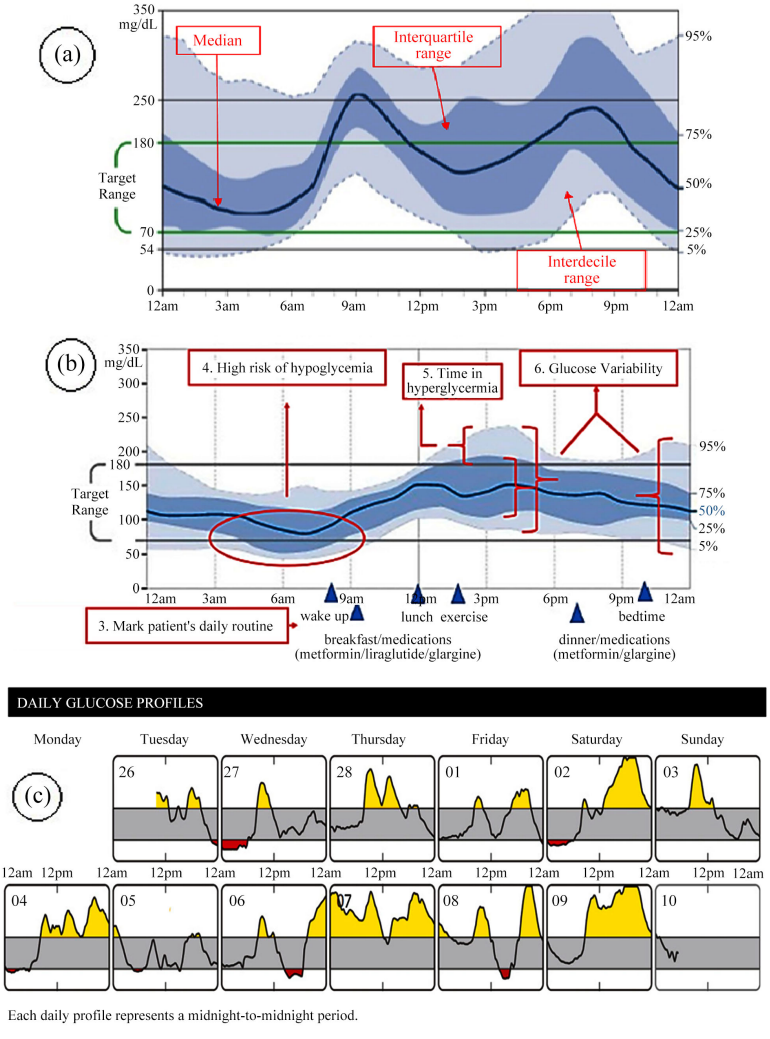

Figure 3. Ambulatory Glucose Profile: (a) glucose distribution as if happening over a period of 24 hours; (b) Areas to target for management; (c) glucose distribution in different days. For illustrative purposes, the outputs from the FreeStyle Libre Health Management System software (Abbott Laboratories). The Ambulatory Glucose Profile (AGP). ([a]2021 International Diabetes Center at Park Nicollet, Minneapolis, MN. AGPreport.org).

CV, which indicates the level of glycemic variability over the period reported; glucose management indicator (GMI) which replaced the term estimated HbA1c. The patients using CGMs need to check their BG by fingerprick whenever there is low blood sugar, rapidly changing BG level if symptoms do not match BG reading if sensor glucose does not match BG, and confirmatory check pre-prandial. However, newer algorithms of improved accuracy would require a confirmatory fingerstick in case of symptoms not matching the readings. Training for the patients is essential for using the AGP and managing their BG accordingly. One important note mentioned is that despite no calibration is needed, still, finger-stick glucose checks are needed.

6. Conclusions and Recommendations

Statement 1: If we are to improve our healthcare programs in line with international evidence and technology, we need to redesign programs, re-organize and redirect our resources, and focus on our needs and goals. In diabetes care, we need to adopt new helpful technologies in an integrated, planned, shared, and structured model of care in line with the significant reform objectives of our health system.

Statement 2: HbA1c and SMBG are not enough to detect BG fluctuations daily.

Statement 3: Daily use of CGM provides the ability to obtain immediate feedback on the current level, and the trend of glucose provided by CGMs allows people with DM to act in response instantaneously and appropriately according to these data.

Statement 4: In clinical practice, metrics like TIR, TBR, TAR, GMI, and CV are valuable clinical targets that complement the laboratory HbA1c. They are an integral component of day-to-day DM management.

Statement 5: We recommend using CGMs technology in people with T1DM children and adults, T2DM on multiple insulin injections, GDM who need further glycemic control, those at high risk for hypoglycemia. In addition, we recommend using them for a short period for those who require intensive BG control or during acute illness or stress. In addition, AGP could be used as an educational tool for any individuals with DM to study the impact of some aspects of lifestyle modifications on their immediate BG level.

Statement 6: The incorporation of CGMs technology like FreeStyle Libre with its applications like Libre View is now used in many institutes in Saudi Arabia. This system is comprehensive and has all standardized metrics needed. However, training and support are always needed. In addition, two complementary ways are needed; one is the clinical evidence of its benefits, and the second is its impact on the budget (is it cost-saving?).

Statement 7: Barriers and challenges include the awareness & experience of the technology, the time-barrier, the patients' barriers, the technical barriers, and of course, the availability barrier. All the barriers and challenges should be dealt with by designing new training programs.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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