Continuous Glucose Monitoring (CGM) Systems

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INTRODUCTION

Continuous Glucose Monitoring (CGM) systems display the glucose level, the direction and magnitude of change of glucose levels, and can be used as a tool to predict impending glucose excursions (hypo- and hyperglycemia), and to assess glycaemic variability. In addition, reliable alarm signals of low or high glucose values warn the patient to take action. All this is being executed on a near-continuous basis, throughout the day, and this for several days, thereby facilitating pattern recognition, and helping the patient (and physician) to optimize therapy and improve metabolic control.[1]

Hyperglycemia, hypoglycemia, and glycemic variability have been associated with increased morbidity, mortality, length of stay, and cost in a variety of critical care and non–critical care patient populations in the hospital.[2]

Despite advances in insulin preparations, insulin delivery devices, and glucose monitoring technology, glycemic control in most T1DM patients is suboptimal. Published data from the T1D Exchange Clinical Registry (T1D Ex), which maintains health records on over 26,000 participants with T1DM from 68 clinics throughout the United States, reveals that the average glycated hemoglobin (HbA1c) among younger patients ranges from 8.3% to 8.7% (≤25 years); average HbA1c among older patients is only somewhat better at approximately 7.7%.[3] The fact that increased glycemic variability (GV) is a strong predictor of hypoglycemia and is also correlated with poor glycemic control is probably the most compelling reason to identify and to work to minimize GV today. Glycemic variability, independent from other measures of glycemic control, is predictive of patient satisfaction with an intensive insulin regimen

THE EVOLUTION OF CGMS

Diabetes technology has progressed remarkably over the past 50 years-a progress that includes the development of markers for diabetes control, sophisticated monitoring techniques, mathematical models, assessment procedures, and control algorithms. Continuous glucose monitoring (CGM) was introduced in 1999 and has evolved from means for retroactive review of blood glucose profiles to versatile reliable devices, which monitor the course of glucose fluctuations in real time and provide interactive feedback to the patient.[4] Depending on whether the CGM device penetrates/breaks the skin and/or the sample is measured extracorporeally, these devices can be categorized as totally invasive, minimally invasive,

and noninvasive. In addition, CGM devices are further classified according to the transduction mechanisms used for glucose sensing (i.e., electrochemical, optical, and piezoelectric). CGM highlights different contributions of fasting and postprandial glucose values at different HbA1c levels in contrast to SMBG measurements, and can be used as a tool to assess the effect of a meal on postprandial glycemia. CGM can detect high postprandial glucose levels more reliably than SMBG. Indeed, the optimal timing of postprandial glucose measurement varies according to the composition of each meal, and single postprandial measurements can miss the highest peak values, which are only detectable with CGM[1]Many attempts to develop commercial devices for real-time noninvasive glucose measurements, such as those based on near infrared spectra, have been unsuccessful due to interference from other blood metabolites, inter- and intrapatient differences in tissue characteristics, and miniaturization of technology. Furthermore, either the poor accuracy or the short lifetimes of these devices have limited the amount of information on the alarm components of these devices. The GlucoWatch was the first commercial device that monitored glucose noninvasively and in real-time. Cygnus received the CE mark in 1999 and FDA clearance for the GlucoWatch in 2001, with an updated model approved in 2002. This device made use of reverse iontophoresis, a process by which an electric current brings interstitial glucose to the surface of the skin and then measures the amount of glucose via an electrochemical sensor. Although its noninvasive glucose monitoring was conceptually appealing, the GlucoWatch was plagued with high false alarm rates, an excessive warm up period of 2-3 hours, inability to operate under temperature changes and increased perspiration level, and the tendency to cause skin irritation in some patients. The GlucoWatch was discontinued on July 31, 2007.

High sensor accuracy and alarm sensitivity has propelled the use of CGMs to warn of glycemic excursions. CGMs make use of small enzymatic sensors inserted beneath the skin to measure interstitial glucose. An oxidation-reduction reaction produces a measureable current that is calibrated with a blood glucose measurement. The first commercial CGM, the MiniMed (Medtronic, Northridge, CA), was approved by the FDA in 1999, but alarms did not appear on commercial devices until the mid-2000s with the introduction of the Guardian (Medtronic, Northridge, CA) and the STS™ (DexCom, San Diego, CA) CGMs.[5]

THE CURRENT GAP- LACK OF STANDARDIZATION OF GLUCOSE REPORTING

At present, there are three commercial CGM device manufacturers: DexCom, Medtronic, and Abbott with a software to download and analyze the CGM data and generate a report or series of reports. Despite similarities between 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. This represents a challenging "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. The sheer diversity and the options for the number of reporting have to be uniform and minimised. 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

Some issues to be addressed include,

1. Has the percentage of time patients are in good glycemic control improved?

2. Are patients in good control with fewer low, very low, and dangerously low glucose readings?

3. Standardization is a must as the clinical terms and metrics allows a more accurate assessment of individual patients and comparisons of progress from visit to visit.

Although CGM is called continuous, CGM devices actually sample interstitial fluid glucose intermittently, with a testing frequency ranging from every few seconds to several minutes between measurements. The measurements are averaged and presented as a single reading every few minutes to quarter hour. Software within the CGM devices can combine current levels with previous results to predict a future trend and direction of glucose change. CGM can thus display not only a single glucose result, but also the direction of glucose change (up, down, or stable), as well as the magnitude of change (the difference between glucose concentration per time interval). Because CGM presents current levels of glycemia along with trend information, this technology offers the potential to predict hypoglycemic events before they occur and describe patterns of glucose variability that may not be detectable from utilizing SMBG devices that intermittently sample blood only a few times per day.[2]

Glycemic variability (GV) - swings in blood glucose level, takes into account the intraday glycemic excursions including episodes of hyper and hypoglycemia. The postprandial hyperglycaemic excursions also contribute to GV. [3] Glucose variability has been identified as a predictor of hypoglycemia and has been found to be related to intensive care unit mortality. Other putative relations are between glucose variability and oxidative stress, as well as microvascular and macrovascular complications

of diabetes. With regard to prediction of hypoglycemia, glucose variability has been shown predictive of severe hypoglycaemia in type 1diabetes and of non severe hypoglycaemia in type 2diabetes. With the development of the CGMS, a number of indicators, including the standard deviation of blood glucose (SD) and the mean amplitude of glucose excursion (MAGE), have been proposed to estimate glycemic variability. CGMS is now widely used to estimate glycemic variability in studies of diabetes and prediabetes.[6,7]

UTILITY OF CGMS IN HOSPITALISED PATIENTS

A hospital CGMS will be routinely used by clinicians if it

(1) decreases the amount of caregiver time and effort required for glucose monitoring and BG control, (2) is easy to set-up, calibrate, and use in a variety of hospital environments, (3) produces real-time glucose measurements with accuracy and reliability sufficient for dosing insulin (4) has a low incidence of false alarms for hyper and hypoglycaemia, (5) has a low incidence of device-related adverse events and no risk for a serious adverse event, and (6) has a cost/benefit ratio that justifies adding a new point-of-care technology for the critical care and general floors of the hospital

CGM devices are also categorised as 1) real time RT CGM (Personal CGM) and 2) Retrospective CGM (Professional CGM)

Professional CGM equipment (also sometimes referred to as retrospective CGM) is owned by the health care professional, clinic, or hospital, and is generally used for masked data collection. Patients remain unaware of monitoring results until they are downloaded and analyzed by the health care professional; this allows for an unbiased assessment of patients' glucose control. Professional CGM is used in patients with type 1 diabetes mellitus (DM) or type 2 DM who are not at their hemoglobin A1c (HbA1c) target, who have recurrent hypoglycemia or hypoglycemia unawareness, or who are pregnant. Patients are typically asked to attend an office visit, receive instruction, wear a sensor for 3 to 7 days, keep a food and activity logbook, and then return to the office for interpretation. Professional CGM does not have alerts to indicate hyperglycemia or hypoglycemia. Patients are recommended to use professional CGM on an episodic basis. Since professional CGM requires minimal training and setup time, it may be easier for patients to use than personal CGM.[8]

Professional CGM devices includes Medtronic's Ipro 2, Abbott's Freestyle Libre Pro (Figure 1)

In contrast, a personal CGM device is owned by the patient. With personal CGM, glucose values are visible continuously; this allows for immediate therapeutic adjustments on the basis of "real-time" glucose results (personal CGM is also referred to as real-time CGM). Personal CGM is typically used by patients with type 1 DM who are not at their HbA1c target level and (a) have the ability to use and understand the information supplied; (b) have hypoglycemia or hypoglycemic unawareness; and/or (c) are pregnant. In addition, any patient who

could benefit from the continuous feedback of glucose readings and/ or the hyperglycemia and hypoglycemia alarms in available personal CGM devices (such as patients with type 1 DM with HbA1c levels less than 7.0%) are potentially good candidates for this technology. Some personal CGM devices also have alarms that indicate a rapid rate of glucose change using trend markers or arrows, and some have "predictive alarms," which calculate whether high or low glucose thresholds will be crossed, depending on rate of change and current glucose level (ie, they predict a low or high glucose level). The setup requirements for personal CGM are more intensive than for professional CGM and include programming customized glucose targets and alarm thresholds.[9,10]

Personal CGM devices include Guardian® REAL-Time CGMS, Dexcom G4TM PLATINUM (DG4P), Dexcom Seven Plus , Abbott's FreeStyle Navigator® and Freestyle Navigator II , Abbott's Flash glucose monitors (Figure 2).

New product category that rests somewhere between blood glucose meters and continuous glucose monitors (CGMs) - Flash glucose monitors

The disposable, water-resistant round sensor is the size of a silver dollar and the width of a finger, similar to a traditional CGM sensor. It can be worn up to 14 days on the back of the upper arm. No finger prick calibration is needed, since that functionality is all embedded into the core technology. Glucose readings can be taken as many times per day as needed or desired, with only a painless one-second scan. Results are transmitted to the receiver via wireless radio frequency tech. Scanning can take place while the sensor is under clothing, making testing more discreet and convenient. Each scan displays a real-time glucose result, a historical trend and the direction the glucose is heading. The reader holds up to 90 days of data, providing a historical snapshot of glucose levels over time. The FreeStyleLibre System software enables the data to be presented in a user-friendly, visual chart for both healthcare professionals and patients, driving a more productive discussion around treatment and any necessary modification.[11]

The ambulatory glucose profile (AGP) provides a mean value across the day. All of the values from multiple days are shown on a single time scale from midnight to midnight. The average for each period is shown along with a standard deviation.

Professional version of the flash glucose monitor has been launched recently in India.

A round sensor—slightly larger than a Rs 10 coin. The physician can apply the water-resistant and disposable sensor on the back of the upper arm of a patient. The sensor is held in place with a self-adhesive pad and remains for 14 days, requiring no patient interaction with the sensor or finger-prick calibration. The system continuously measures glucose in interstitial fluid through a small filament that is inserted just under the skin. It records glucose levels every few minutes, capturing up to 1,340 glucose readings over the period, giving the treating physician comprehensive data for a complete glucose profile of their patient. After 14 days, the physician uses a reader to scan the sensor and download the glucose results stored in the sensor. However, scanning and downloading of data can be done intermittently by the physician every few days as and when required. Scanning can also be done while the sensor is under clothing.
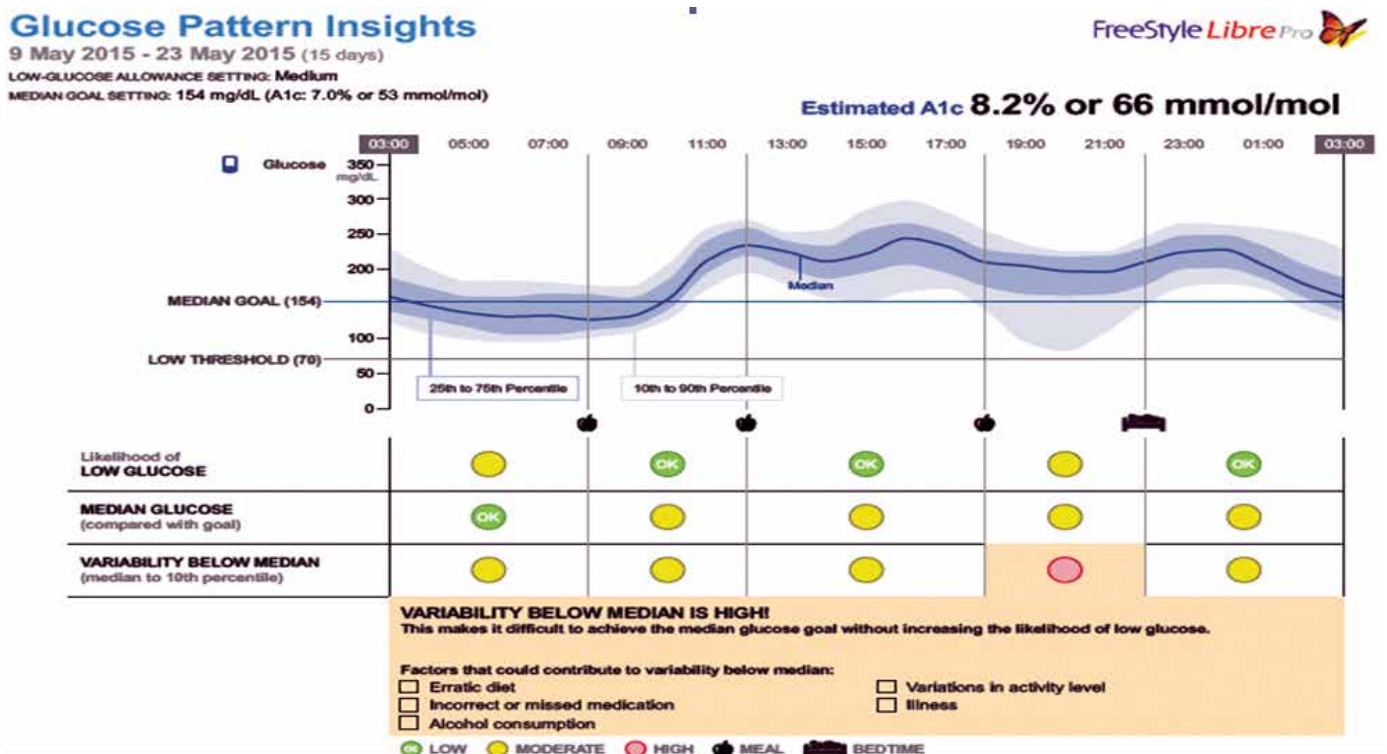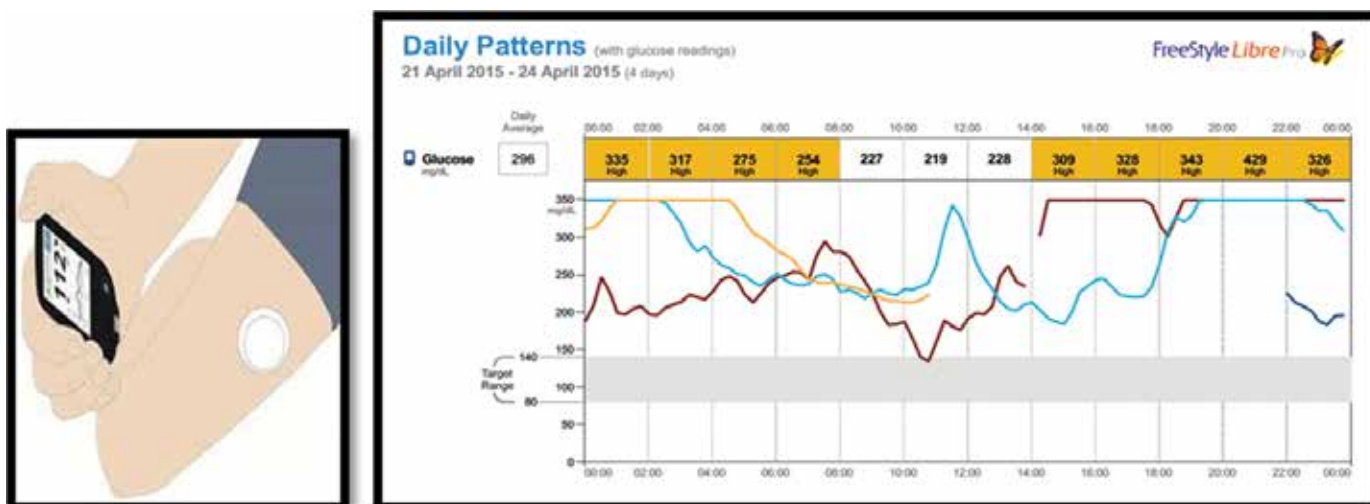

Fig. 1: Free Style Libre Pro

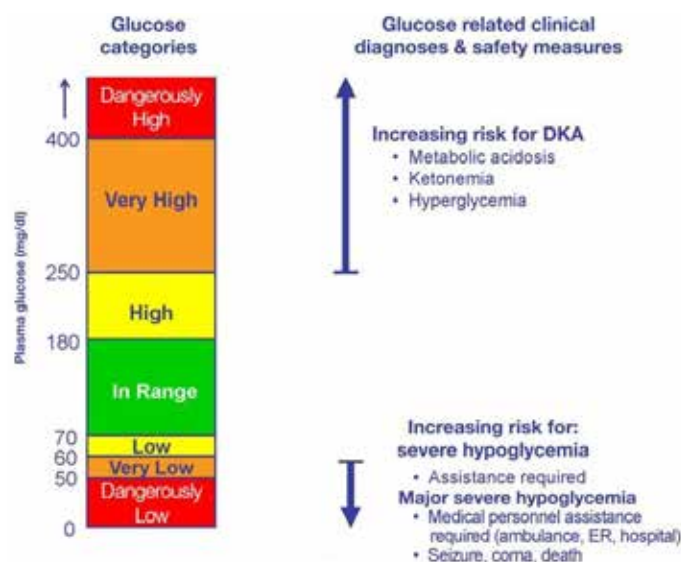**Fig. 2: Freestyle libre Pro- Flash glucose monitor**

Fig. 3: Glucose Categories & Related Clinical Diagnosis

GLUCOSE TARGET RANGES AND CATEGORIES

An appropriate patient selection, in order to choose those able to run the tool and motivated to use it, is necessary. Two approaches have been compared: patient-led and physician-driven prescription. Both modes of using CGM provide similar long-term metabolic improvement. However, physician-driven prescription is probably more cost-effective. The last key question is the education of patients by an experienced team. It can help them to translate the large amount of data from the monitor into effective self-management for optimalizing the CGM experience. However, elaboration of a validated algorithm is necessary to take full advantage of this device (Figure 3).

The patients best suited for CGMS include,[12,13]

1. The best suited - All T1DM, poor metabolic control, especially those treated with continuous subcutaneous insulin infusion (CSII), and compliant patients with HbA(1c) levels <7%.

2. Less best suited - patients aged 8-18 years because they are reluctant to wear the sensors or those with new-onset T1DM

3. Deserving patients but with less evidence- patients aged <8 years, women during pregnancy, and those with HbA(1c) >10% and/or severe hypoglycaemia

Are all type 1 diabetes (T1DM) patients potential candidates for continuous glucose monitoring (CGM)? Clearly, some patients improve their metabolic control with this tool, such as adults with poor metabolic control, especially those treated with continuous subcutaneous insulin infusion (CSII), and compliant patients with HbA(1c) levels <7%. There are also less good candidates for CGM, such as patients aged 8-18 years because they are reluctant to wear the sensors or those with new-onset T1DM. Other patient groups have not yet been evaluated, such as patients aged <8 years, women during pregnancy, and those with HbA(1c) >10% and/or severe hypoglycaemia. Beyond the indications, the mode of use of CGM is crucial. An appropriate patient selection, in order to choose those able to run the tool and motivated to use it, is necessary. How to prescribe the sensors is also an important question. Two approaches have been compared: patient-led and physician-driven prescription. Both modes of using CGM provide similar long-term metabolic improvement. However, physician-driven prescription is probably more cost-effective. The last key question is the education of patients by an experienced team. It can help them to translate the large amount of data from the monitor into effective self-management for optimizing the CGM experience. However, elaboration of a validated algorithm is necessary to take full advantage of this device.

SUMMARY

Automation and standardization of the glucose measurement process have the potential to significantly improve BG control, clinical outcome, safety and cost.

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 health care providers, clinical researchers, industry,

regulators, and payers work together to find ways to expand appropriate adoption of CGM use in clinical practice. 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. While CGM has been shown to be valuable in several clinical settings, continued research is needed to define which individuals with T1DM or T2DM will benefit most from either real-time use of CGM or retrospective analysis of intermittent use of CGM

It is anticipated that CGM devices will utilize constant feedback of analytical information from a glucose sensor to activate an insulin delivery pump, thereby ultimately realizing the concept of an artificial pancreas. The use of these technologies could be extended to current clinical care of type 2 diabetic patients especially for motivating them to accept earlier insulin treatments in case of 'oral antidiabetic drug secondary failure', and further for choosing the most appropriate insulin regimen.

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