Journal of Diabetes and Its Complications xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Role of continuous glucose monitoring for type 2 in diabetes management and research

Robert Vigersky [a,*], Maneesh Shrivastav [b,1]

[a] 950 F St., NW, Suite 500, Washington, DC 20004, U.S.A.
[b] Medtronic Plc, Non-Intensive Diabetes Therapies, 3033 Campus Drive, Minneapolis, MN 55441

ARTICLE INFO

Article history:
Received 21 September 2016
Accepted 9 October 2016
Available online xxxx

Keywords:
Continuous glucose monitoring
Diabetes management
Type 2 diabetes mellitus
Glycemic control
Hypoglycemia

SUMMARY

The advent of continuous glucose monitoring (CGM) is a significant stride forward in our ability to better understand the glycemic status of our patients. Current clinical practice employs two forms of CGM: professional (retrospective or "masked") and personal (real-time) to evaluate and/or monitor glycemic control. Most studies using professional and personal CGM have been done in those with type 1 diabetes (T1D). However, this technology is agnostic to the type of diabetes and can also be used in those with type 2 diabetes (T2D). The value of professional CGM in T2D for physicians, patients, and researchers is derived from its ability to: (1) to discover previously unknown hyper- and hypoglycemia (silent and symptomatic); (2) measure glycemic control directly rather than through the surrogate metric of hemoglobin A1C (HbA1C) permitting the observation of a wide variety of metrics that include glycemic variability, the percent of time within, below and above target glucose levels, the severity of hypo- and hyperglycemia throughout the day and night; (3) provide actionable information for healthcare providers derived by the CGM report; (4) better manage patients on hemodialysis; and (5) effectively and efficiently analyze glycemic effects of new interventions whether they be pharmaceuticals (duration of action, pharmacodynamics, safety, and efficacy), devices, or psycho-educational. Personal CGM has also been successfully used in a small number of studies as a behavior modification tool in those with T2D. This comprehensive review describes the differences between professional and personal CGM and the evidence for the use of each form of CGM in T2D. Finally, the opinions of key professional societies on the use of CGM in T2D are presented.

1. Introduction

Among the major advances in the field of diabetes has been the development of accurate methods of self-monitoring of blood glucose (BG). The Diabetes Control and Complications Trial which began recruiting in 1983 was the first large clinical trial to use self-monitoring of blood glucose (SMBG) with either a reflectance meter or visual observation of the color changes of a glucose-oxidase embedded strip (Diabetes Control and Complications Trial Research Group, 1993). Although primitive by today's standards, these BG measurements permitted intensive insulin administration. The next advance in glucose measurement technology occurred in 1987 when a biosensor system was developed employing artificial electron acceptors (i.e., electron mediators or redox dyes) instead of oxygen (Clarke & Foster, 2012). The resultant current was read amperometrically, permitting the development of smaller and more accurate BG meters. Subsequent improvements in this technology afforded faster results in devices that require less blood.

Essentially the same glucose-oxidase methodology developed for BG meters has been adapted for use in most continuous glucose monitoring (CGM) systems. The first of these CGM systems using a glucose-oxidase sensor for venous blood was contained in an artificial pancreas system over 40 years ago (Albisser et al., 1974). Devices using other methodologies such as microdialysis (Dehennis, Mortellaro, & Ioacara, 2015; Schierenbeck, Owall, Franco-Cereceda, & Liska, 2013; Valgimigli, Lucarelli, Scuffi, Morandi, & Sposato, 2010) and fluorescence (Dehennis et al., 2015) have been developed for both subcutaneous and intravenous use but neither is currently commercially available. The advantage of CGM over SMBG by fingerstick is that CGM displays interstitial glucose readings every 5 min. As a result, CGM can show the effects of diet, exercise, medications, sleep, and stress on glucose levels and makes a "vital sign." With 288 glucose measurements a day, CGM has enabled investigators to develop new metrics of glycemic control that were not feasible with BG monitoring alone. This enhanced our understanding of how diabetes interventions affect glycemic control beyond the surrogate metric for mean glucose, hemoglobin A1C (HbA1C). These include the percent time-in-range, in hypo- and hyperglycemic ranges, the intensity of

Conflict of interest: Both authors are full time employees of Medtronic Diabetes.

* Corresponding author: Tel.: +1 202 442 3653, +1 202 394 5395 (Mobile).
E-mail addresses: robert.a.vigersky@medtronic.com (R. Vigersky), maneesh@ieee.org (M. Shrivastav).
[1] Tel.: +1 763 526 3509.

http://dx.doi.org/10.1016/j.jdiacomp.2016.10.007
1056-8727/

the hypo- and hyperglycemic excursion (area-under-the-curve), and glycemic variability (e.g., standard deviation [SD], Mean Amplitude of Glucose Excursion [MAGE], continuous overlapping net glycemic action [CONGA], and mean of daily differences [MODD]) within and between days. The value of these glucose measurements was demonstrated by the FDA accepting for labeling purposes the area-under-the-curve of nocturnal low sensor glucose values as the primary outcome metric in the in-home trial evaluating the threshold suspend insulin pump (Bergenstal et al., 2013).

2. Use cases of CGM

The two major use cases for CGM are professional (retrospective or diagnostic) CGM in which the patient does not see the display in real-time and personal (real-time) in which the patient can observe the changes and also be alerted to values that cross a preset or predicted high or low glucose threshold (Table 1). These use cases apply to patients with both type 1 diabetes (T1D) and type 2 diabetes (T2D) with or without insulin therapy in those with T2D. A new approach to glucose monitoring called "flash" glucose monitoring (FGM) has been recently introduced into the market in several countries outside the United States. FGM records data every 15 min, only displays data when a monitor is swiped over the sensor or when returned to the healthcare provider's office, and has no alerts or alarms. The uses of CGM described below may or may not have been consistent with the approved labeling of the device depending on the jurisdiction. Some of the studies may have been done off-label but with the approval of an Investigational Review Board. Before using use a CGM device clinically, the label should be carefully reviewed by the healthcare provider.

2.1. Professional (masked or diagnostic) CGM

Professional CGM is often referred to as a Holter monitor for glucose measurements since it is primarily used 1–6 times a year as a diagnostic tool (Chase et al., 2001; Ludvigsson & Samuelsson, 2007). In this use case, the patient is masked or unaware of the glucose values in real-time and there are no alarms for hyper- or hypoglycemia. The advantage of such an approach is that it limits the possibility that patients will modify their diet and/or exercise behavior and/or medication adherence in response to real-time data which can occur within a few days of real-time CGM use (Fonda et al., 2013). This, then, provides a test that is closer to the "real-world." This permits the healthcare provider to make appropriate therapy changes (if they are required) whose effects are more likely to be sustained than a temporary behavior change. The sensor is inserted into the patient in the provider's office or in a laboratory setting by a trained member of the healthcare team and the patient is instructed to calibrate the sensor two or more times a day using a BG meter. Patients also maintain a food and activity diary to provide behavioral information that enhances the interpretation of the data. Upon return of the device to the provider's office, the data are uploaded, a series of comprehensive reports is generated, and the data are then analyzed in conjunction with the patient-generated diary. The healthcare team can then have a detailed and educational conversation with the patient about glycemic patterns and the effects of their behavior on those patterns. The healthcare provider can then determine if medication changes are needed.

Table 1
Differences in professional and personal CGM.

	Professional	Personal
Owned by healthcare provider	X	
Owned by patient		X
Intermittent Use	X	
Continuous Use		X
Masked	X	
Real-time		X
Alerts/Alarms		X[a]

[a] While FGM can be used in personal form, it does not provide alerts and alarms in its real-time use due to design limitations.

2.2. Personal (real-time) CGM and flash glucose monitoring (FGM)

Personal or real-time (RT) CGM and FGM are generally used by those who are on regimens that include basal and prandial insulin requiring long-term monitoring. The sensor is placed by the patient him/herself every 6–14 days. Glucose values are graphically displayed and updated every 5–15 min along with the trending information on a separate device, on an insulin pump with which it is integrated, or by swiping a handheld receiver (FGM). In CGM but not FGM, there are high- and low-glucose alarms that provide important, actionable information for patients who use these devices. Alarm "fatigue" is a real problem for those using CGM in the personal configuration depending on how the alarms are set-up. This, in part, may explain why overall only 9% of the 17,000 patients (children, 6%; adolescents, 4%; young adults, 6%; adults, 21%) with T1D that are registered in the T1D Exchange currently are using RT-CGM (Wong et al., 2014). Finally, because clinically relevant decision support tools for both interpreting RT-CGM data and providing actionable advice about the data are currently not currently available, reviewing CGM data remains time consuming and largely subjective for both the patient and healthcare provider.

3. Evidence for use of professional CGM in patients with type 2 diabetes

Professional and real-time CGM has been used primarily in patients with T1D and most of the evidence for its benefit is in that group (Floyd, Liebl). However, there has been growing evidence that those with T2D may benefit from the use of this technology by CGM's ability to uncover previously unknown hypoglycemia particularly in those with hypoglycemic unawareness and/or during sleep as well as unrecognized hyperglycemia particularly post-prandially. The evidence for use of professional and personal CGM in those with T2D is presented in the sections below.

3.1. Discovery previously unrecognized hypoglycemia or hyperglycemia

Hypoglycemia is one of the major barriers to more intensive management in patients with both T1D and T2D. There have been several CGM studies using professional CGM that were specifically designed to document the presence of hypoglycemia in adults with T2D diabetes (Gehlaut, Dogbey, Schwartz, Marling, & Shubrook, 2015; Kim et al., 2014; Munshi et al., 2011; Tanenberg et al., 2004). In the largest and most recent of these studies, Gehlaut et al. (2015) observed that almost half of the patients had mild or severe hypoglycemia and 75% of those episodes were asymptomatic. The CGM examination provided actionable information in that there was treatment modification in 64% of patients. No follow-up results of that treatment modification have been reported to date. Kim et al. used a propensity-matched design in which 65 patients with T2D were matched to 301 controls (15). Twenty-four (37%) of the 65 patients (15 on orals and 9 on insulin) had hypoglycemia during the 3-day CGM study. These observations were actionable as shown by the therapy changes that were made — the dose of the oral medications was reduced in 14 of the 15 and a DPP-4 inhibitor added in 10 of the 15. Seven of the 9 patients on insulin therapy had changes in their regimen. Similarly, Munshi et al. (2011) found asymptomatic hypoglycemia in 93% of 40 patients with T2D (18 on orals or orals plus insulin) whose mean age was 75 years and who had a baseline HbA1C of 9.3%. This is consistent with the subsequent findings by

Please cite this article as: Vigersky, R., & Shrivastav, M., Role of continuous glucose monitoring for type 2 in diabetes management and research, *Journal of Diabetes and Its Complications* (2016), http://dx.doi.org/10.1016/j.jdiacomp.2016.10.007