ORIGINAL ARTICLE

Intermittent Use of Continuous Glucose Monitoring: A New Paradigm in Treatment of Type 2 Diabetes

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Abstract

Objectives: To suggest how continuous glucose monitoring (CGM) may be used intermittently in individuals with type 2 diabetes (T2D).

Materials and methods: The use of CGM is largely in those with type 1 diabetes (T1D), in whom it makes sense to use CGM continuously as CGM provides a valuable tool to not only adjust their insulin doses but also to match it with their diet, physical activity, and other lifestyle modifications. In the case of T2D, however, especially for those not on insulin, the use of CGM may not be needed on a continuous basis. The use of CGM on an intermittent basis is rarely discussed in the literature. This article tries to provide clinical situations where CGM can be used intermittently.

Results: Intermittent use of CGM defined as the "use of CGM once in 2 or 3 months or a fixed frequency," and may be useful in several situations in those with T2D. We suggest the following indications for the intermittent use of CGM in T2D—newly diagnosed patients where treatment is being started, uncontrolled diabetes where treatment is being altered, starting intensive lifestyle modification, during infections, during preoperative control, in children and adolescents with T2D, as a motivational tool to improve behavioral modification, after metabolic surgery, and in patients on steroids, apart from other indications.

Conclusion: Intermittent use of CGM in T2D can be useful in special situations and can also be cost saving particularly in resource-constrained regions of the world.

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Introduction

Adoption of CGM in the treatment of patients with diabetes has been increasing globally as it addresses many limitations inherent to glycated hemoglobin (HbA1c) testing and self-monitoring of blood glucose (SMBG).[1] However, the vast majority of CGM studies to date have been done in persons with T1D,[2,3] and studies on CGM in T2D are limited.[4–10] Even in these studies in T2D, the use of CGM has been mostly restricted to T2D patients on insulin, and its use in those not on insulin is rarely discussed.

There are several potential barriers to patient acceptance that impede the propagation of CGM on a wider scale. User burden associated with the currently existing systems, high cost, reimbursement issues, pain, allergy, and unfamiliarity with the system were identified as reasons among patients for not using CGM in developed countries.[11] Given these barriers, using CGM on a temporary or intermittent basis increases the benefits and possibilities of its use in T2D patients. Indeed, intermittent use of CGMs allows its allocation to suitable patient groups and indications, especially in limited-resource settings.[12] Intermittent use of CGM could provide economic flexibility, rather than not using it at all. However, there is a need for clarity on the frequency of the intermittent use of CGM which undoubtedly has to be individualized for T2D patients depending upon their stage of the disease and multiple other factors like the presence of comorbidities and complications of diabetes. In this review, we discuss the use of the intermittent use of CGM and its benefits and suggest ways to more effectively use CGM intermittently.

Use of CGM in T2D

Continuous glucose monitoring (CGM) has been shown to produce a significant reduction in HbA1c levels in T2D patients.[4] One study reported the utility of CGM use in T2D patients in revealing glycemic fluctuations. which could otherwise go undetected in routine SMBG.[11] Use of CGM has helped clinicians and patients to make appropriate treatment changes.

Continuous glucose monitoring (CGM) can be a great tool to ensure adherence to lifestyle and behavioral modifications. Retrospective data which includes trends, ambulatory glucose profile, and time in range (TIR) facilitate better exercise adherence and reduced caloric/carbohydrate intake in patients with T2D.[13–15] There are some studies that have looked at the cost-effectiveness of CGM in T2D.[16]

What is the Intermittent Use of CGM?

Intermittent use of CGM may be defined as "the use of CGM, once in 2 or 3 months or a fixed frequency in T2D." According to a recent review, "intermittent use of CGM systems is any planned and agreed use that is intended not to be continuous or all-the-time use but for predefined periods of time or situations."[12] In a real-world setting, adherence to CGM remains suboptimal irrespective of technological advancements, patient education, and support programs.[17] Depending upon the financial resources and personal choices,

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some patients may choose intermittent use of CGM as an educational and/or motivational tool, rather than a permanent or continuous diabetes management strategy. Therefore, clinicians should explore the potential of intermittent use of CGM as an option for particular patient groups and situations from this angle.

The guidelines of the Endocrine Society[18] recommend the intermittent use of CGM for short-term retrospective analysis in the following groups of patients:

- Pediatric patients with nocturnal hypoglycemia, dawn phenomenon, and postprandial hyperglycemia.
- Patients with hypoglycemia unawareness.
- Patients experimenting with important changes to their diabetes regimen.[19]
- Adult patients with T2D (not on prandial insulin) with HbA1c > 7% and who are willing and able to use the device.

Intermittent CGM can be used for specific events or situations such as pregnancy and hypoglycemia or hyperglycemia during certain life events.[20] Healthcare personnel could utilize CGM judiciously at periodic intervals in order to assess and adapt the therapy provided.[21]

Clinical Evidence of the Efficacy of Intermittent Use of CGM

Intermittent short-term use of real-time CGM (rtCGM) as clinically indicated has been shown to produce greater improvement in A1c in T2D patients compared to non-CGM users.[22,23] Ehrhardt et al.[24] randomized subjects to rtCGM in an intermittent manner (2 weeks on, 1 week off) over 12 weeks compared to SMBG four times per day. It was observed that HbA1c reduction occurred even without treatment intensification or increased incidence of hypoglycemia, which underscores the advantages of rtCGM in T2D in a lifestyle intervention. Yoo et al.[25] demonstrated that the rtCGM use (3 days at a time for 3 months) can induce better glycemic outcomes (compared to SMBG) by helping to bring about modifications in diet and exercise in patients with poorly controlled T2D. Kesavadev et al.[26] utilized CGM intermittently to analyze its effect on glycemic control in T2D patients, on a wide range of treatment regimens and based on these, consensus guidelines have also been developed in some countries like India.[27] Simonson et al.[28] showed that the use of a professional CGM in primary care used along with a doctor or registered nurse was effective in lowering A1c, increasing TIR, and reducing hypoglycemia.

Possible Indications for Intermittent Usage of CGM in T2D Patients

We suggest that clinicians could explore using CGM intermittently in the following situations in T2DM.[29] These are summarized in Table 1 and described in detail below.

Newly Diagnosed Patients where Treatment is being started

Wherever a newly diagnosed patient is started on treatment (especially if diabetes is severe at the onset with glucolipotoxicity and either short-term insulin or a combination of oral drugs is used), it is useful to initiate intermittent CGM to see the response to therapy and to avoid hypoglycemia.

Case Study

A 19-year-old obese boy presented with symptoms of polyuria, polydipsia, and weight loss of 3 kg. Both his parents had T2D. His weight was 92.4 kg, height was 178 cm, and body mass index was 29.2 kg/m^2. Fasting plasma glucose was 297 mg/dL (16.5 mmol/L), postprandial plasma glucose was 412 mg/dL (22.8 mmol/L), and HbA1c was 12.6% (114.2 mmol/mol). There was no ketosis. He had marked acanthosis nigricans. His waist circumference was 97 cm and he had dyslipidemia with elevated serum triglycerides (300 mg/dL) and a low high-density lipoprotein (32 mg/dL). C-peptide assay showed reduced, but detectable pancreatic β-cell reserve (fasting—0.8 pmol/mL, stimulated—1.4 pmol/mL). In view of the glucolipotoxicity, a CGM was initiated which showed the following (Fig. 1).

As can be seen, the TIR was 0% and all of the readings above range [Time above range (TAR) = 100%]. He was started on a long-acting basal insulin analog at bedtime (glargine—12 units) along with a combination of a dipeptidyl peptidase-4 inhibitor (sitagliptin) and metformin. The sugars started responding well by the 4th day and by the end of the 2nd week, the sugars were under fairly good control. The insulin was continued in a reduced dose for another 2 weeks during which time the TIR was 98% and the TAR was 0% (Fig. 2). There was no significant hypoglycemia. At the end of 4 weeks, the insulin was withdrawn. Later, sitagliptin was also withdrawn and he was stabilized with just metformin. After 3 months, his fasting plasma glucose had decreased to 92 mg/dL, postprandial plasma glucose to 134 mg/dL, and HbA1c to 6.4%. His fasting C-peptide improved to 1.8 pmol/mL and stimulated C-peptide to 3.4 pmol/mL. The CGM was withdrawn at this stage.

The use of intermittent CGM, in this case, was helpful to see the response to the therapy and to note whether there were any hypoglycemic reactions during the initial phase of aggressive treatment with insulin plus oral agents.

Table 1: Suggested indications for intermittent use of CGM

1. Newly diagnosed patients where treatment is being started
2. Uncontrolled diabetes where treatment is being altered
3. Starting intensive life style modification
4. Infections
5. Perioperative control
6. Gestational diabetes mellitus and diabetes complicating pregnancy
7. Children and adolescents with T2D
8. As a motivational tool to improve behavioral modification
9. After metabolic surgery
10. Patients on steroids (e.g., during COVID–19 and other pandemics)

Uncontrolled Diabetes where Treatment is being Altered

Intermittent use of CGM can be efficiently used to track the glucose response after changes in therapy regimen and can support patients and physicians to decide whether the insulin adjustments were appropriate. In addition, patients have more glucose data to guide them in adjusting their insulin dosing at mealtime.[9,14] Intermittent use of CGM can also be suggested for patients with T2D who are currently on oral antidiabetic drugs or insulin to see whether their TIR is within recommended guidelines.[30]

Starting Intensive Lifestyle Modification

Yoo et al.[25] showed that intermittent use (3 days of rtCGM every month for 12 weeks) generated a significant decrease in calorie consumption, an increase in physical activity, an improvement of weight, and a 1% decrease in HbA1c in poorly controlled patients with T2D. A community-based study in India used retrospective CGM with two sessions over 3 months in 181 T2D patients. The study observed a 0.6% reduction in HbA1c and noted that 67.6% of participants made dietary changes and 48.6% made exercise modifications accordingly.[31] Vigersky et al.[23] conducted a trial of 100 T2D patients intermittently using CGM (2 weeks on, 1 week off) over 12 weeks and compared the results to patients using

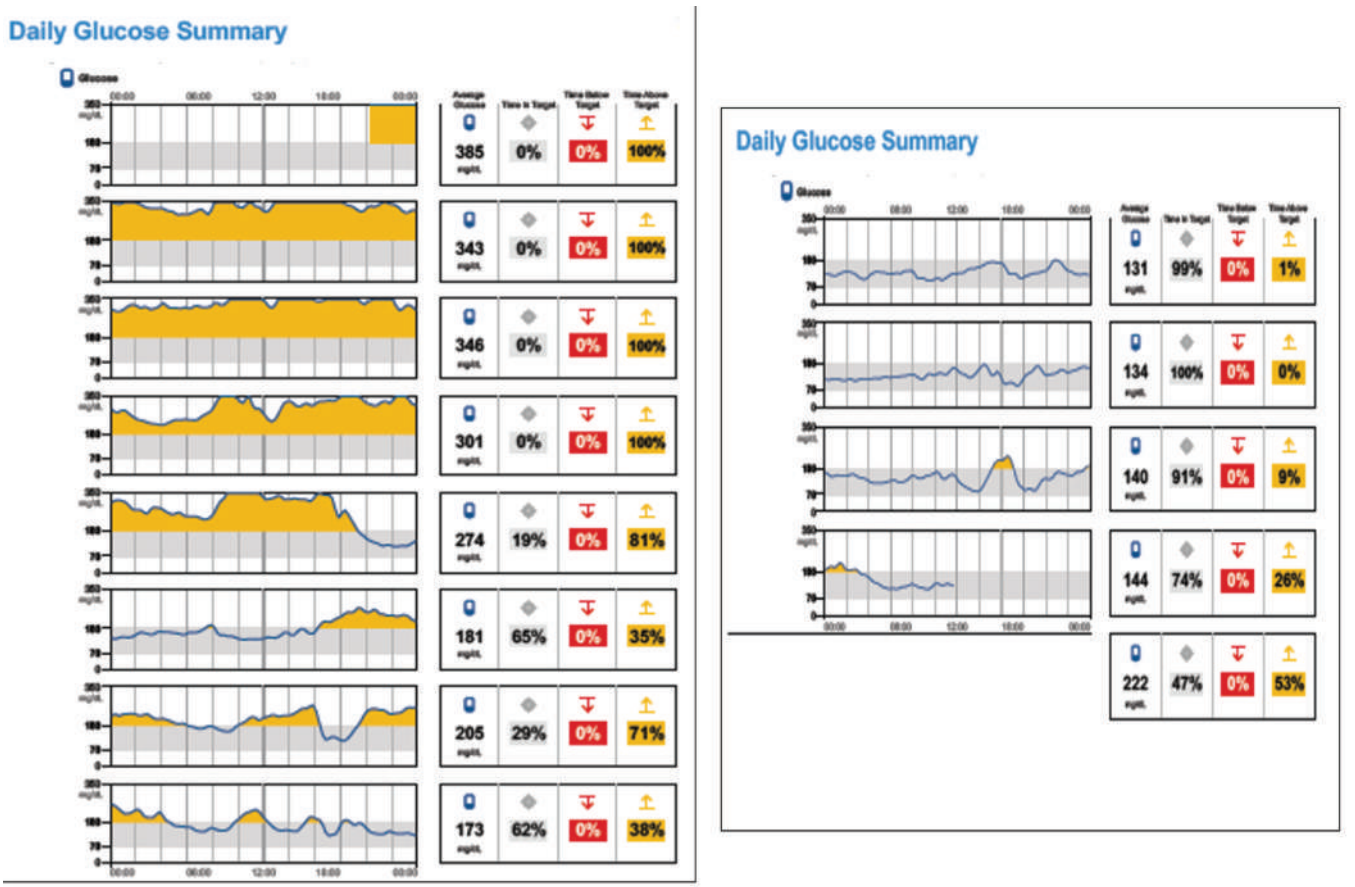

Fig. 1: CGM graphs of a newly diagnosed T2D patient during first 2 weeks of treatment

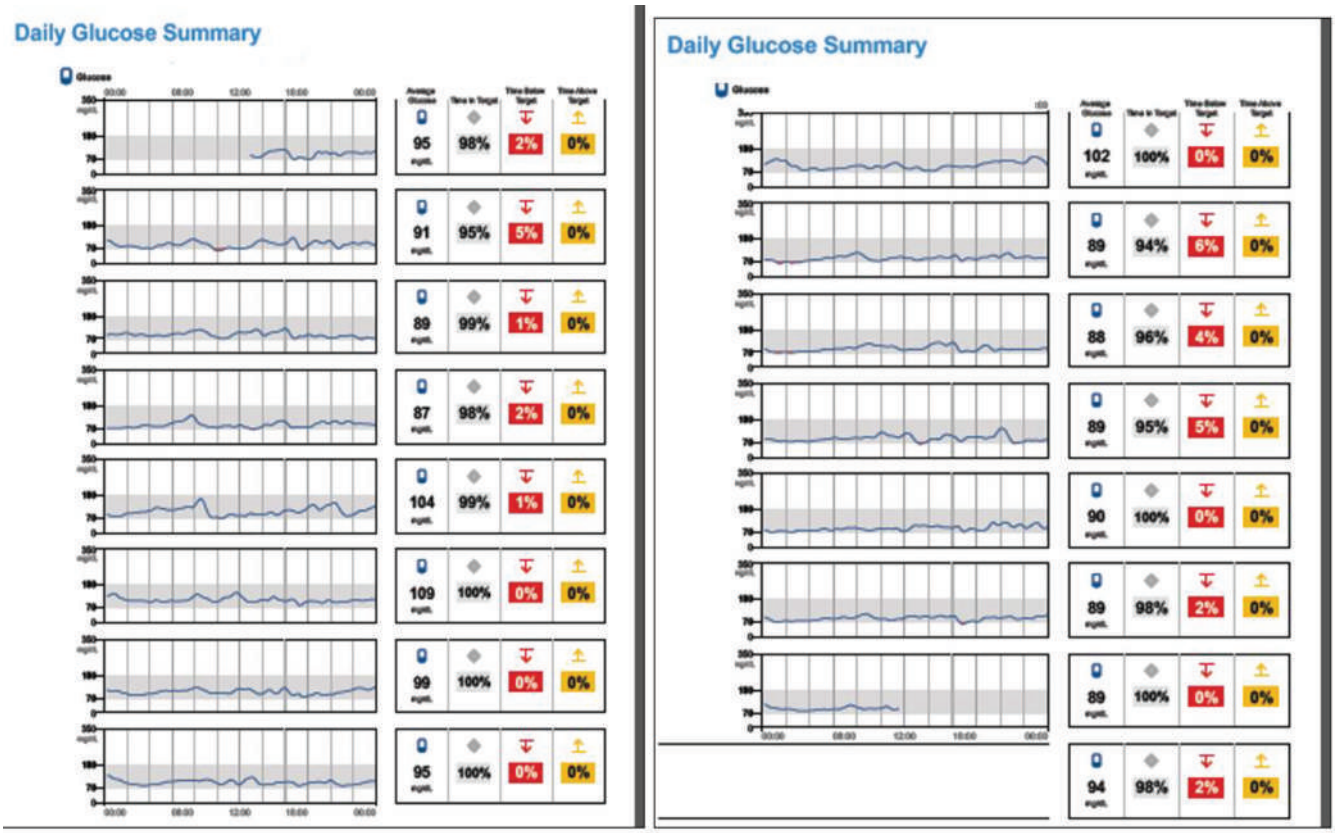

Fig. 2: CGM graphs for next 2 weeks after starting treatment

SMBG four times per day. They reported that HbA1c reduction occurred in the absence of medication intensification or increased hypoglycemia, and this indicates that one of the benefits of intermittent use of rtCGM in T2D is behavior and lifestyle modification. There are anecdotal instances of severe hypos occurring after a sudden increase in physical activity. These can be avoided by using intermittent CGM.

Infections

In the presence of infections, glucose levels tend to fluctuate widely. Also, insulin may be given for a short time to cover this period. Intermittent CGM use is ideal in this situation.

Perioperative Control

Perioperative hyperglycemia is considered to be an independent marker of poor surgical outcomes. Strict glucose control is beneficial for accelerating wound healing, reducing infection rates, reducing the number of days of hospital stay, and reducing postoperative mortality.[32] Maintaining glucose control in perioperative patients often is a great challenge for physicians. Here, intermittent use of CGM before and after surgery can be an excellent tool to monitor glucose levels closely and this helps to improve patient outcomes.

Gestational Diabetes Mellitus (GDM) and Diabetes complicating Pregnancy

There are several studies that have shown the usefulness of CGM in GDM and diabetes-complicating pregnancy.[33–38] The intermittent use of CGM in pregnant women with pregestational diabetes or GDM has been shown to improve pregnancy outcomes. CGM has provided relevant perspectives about neonatal glucose metabolism and there is an increasing interest in its use, especially in preterm infants where glucose management is difficult.[39] Intermittent CGM application can reduce the number of blood tests required and improve long-term outcomes in neonates.[40–42] A systematic review has compiled all studies on the use of CGM in pregnancy.[43]

Children and Adolescents with T2D

In children where frequent finger pricks can be difficult, intermittent CGM offers an excellent tool to detect nocturnal hypos or unexpected peaks of blood glucose.

As a Motivational Tool to improve Behavioral Modification

Physical activity and meals exert a great influence on glycemic variability and are often difficult to manage, but intermittent use of CGM enhances diabetes knowledge and awareness about glycemic fluctuation and is useful in the education and motivation of patients with T2D.[44] Kesavadev et al.[26] have demonstrated that intermittent use of CGM produces actionable data that helps and motivates patients for diabetes self-care practices, leading to improvement in glycemic control. Fonda et al.[45] revealed that intermittent use of CGM may be suitable for motivating or helping avoid burnout in T2D patients.

After Metabolic Surgery

After metabolic (bariatric) surgery, glucose levels can suddenly drop and postprandial hypoglycemia is a major complication after gastric bypass surgery and bariatric surgery.[46,47] Intermittent use of CGM can be effectively applied to diagnose this condition and to adjust diet and therapy postoperatively. This application also helps in the prediction of diabetes remission.[48,49]

Patients on Steroids (e.g., during COVID–19 and Other Pandemics)

Intermittent CGM can produce superior outcomes for patients on steroids by enabling appropriate therapy adjustment. This is particularly relevant during these times of COVID–19 when steroids are given for a few days to weeks. CGM can be used to adjust insulin doses during these brief periods of very severe hypoglycemia especially during some times of the day when the steroids push up the sugar levels.

Suggested Timing of Intermittent CGM use in the Outpatient Clinic

Evaluation of glycemic control in a patient with T2D requires the judicious and integrated use of all available tools such as HbA1c, SMBG readings, lab blood tests, and CGM at the most appropriate times, as each of these provides information on different aspects of the patient's glycemic profile. Most diabetes clinics in developing countries assess patients' glycemic control utilizing a combination of HbA1c and lab blood glucose tests, with only a few patients performing SMBG on a regular basis. The need of the hour, therefore, is to integrate intermittent CGM into the existing assessment paradigm so that the "blind spots" of the conventional tests can be removed.

Proposed Strategies for Intermittent CGM Use

We propose that three strategies can be utilized for integrating intermittent CGM into the routine diabetes clinic assessment (Fig. 3).

- Strategy 1: The patient can be initiated on CGM after he/she has reported for a routine clinic visit and has had his/her HbA1c (and blood glucose) estimated. The clinician would have made alterations to the therapeutic regimen based on these results and the CGM (usually read after a week or 15 days) will help to assess the adequacy of these alterations.
- Strategy 2: Patients can initiate the CGM 15 days in advance of the clinic visit so that the clinician has a clear idea about the patient's glycemic excursions along with the HbA1c result. This will help in adjusting the dose of antidiabetic drugs that is tailored to the patient's glycemic profile. This is an excellent example of precision diabetes monitoring.
- Strategy 3: The patient can be initiated on CGM 1 week (i.e., 7 days) prior to the clinic

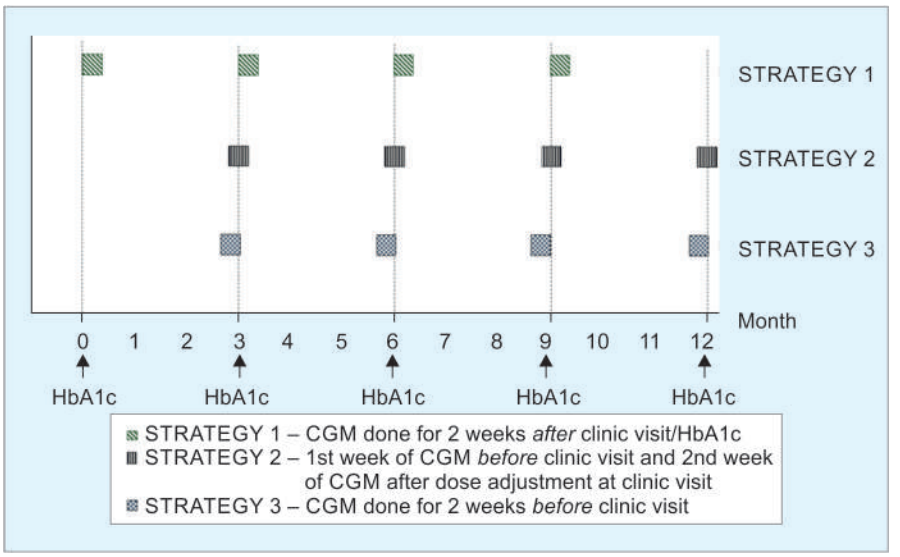

Fig. 3: Proposed strategies for intermittent use of CGM—diagrammatic representation

Table 2: Frequency of CGM use in T2D at two diabetes centers in India over a 3-year period

Frequency of sensor use	*Chennai (DMDSC) n (%)*	*Ahmedabad (Diacare) n (%)*
Total no. of sensors used	18,321	1,864
Once	17,060 (93.1%)	1,576 (84.5%)
Twice	1,051 (5.7%)	206 (11.1%)
Thrice	159 (0.9%)	60 (3.2%)
Four or more times	51 (0.3%)	22 (1.2%)

visit and continued on the same for 1 week (7 days) after therapy has been modified based on the lab results. This will enable the clinician as well as the patient to directly visualize the improvements in glycemic control due to the alterations in therapy by directly comparing it with the profile obtained in the 1st week of recording.

Barriers to the Use of CGM

An early discontinuation rate of 27% and a nonadherence rate of 13.9–31.1% were observed within 12 months of CGM initiation. Therefore, it is essential to identify the factors that influence nonadherence and early discontinuation to improve treatment adherence and reduce healthcare resource waste. Tanenbaum et al.[50] identified the cost of supplies, accuracy issues, user burden of the device, pain, and nonuser-friendliness as the top reasons for patients to discontinue CGM use. Another interesting study observed that 75% of youth who stopped using hybrid closed-loop systems also suspended the use of CGM due to poor CGM accuracy, failed sensor calibrations, and sensor errors.[51] Such repercussions underscore the need for assessing individual barriers to CGM use. Intermittent use of CGM can address many of these barriers, especially the cost issues as it is associated with significant cost savings as compared to continuous use. If the patient is initiated on intermittent CGM quarterly, he/she is required to purchase only four sensors per year, as compared to 26 (if the CGM needs to be continued without a break for the entire year) and this translates to 75% reduction in the cost of use.

Challenges to Implementation of Intermittent Use of CGM

As already discussed, the large-scale implementation of CGM technology especially for continuous use continues to be a major challenge. Very few physicians have developed or implemented a systematic approach to interpret CGM data, although comprehensive guidelines have been published for the same.[30] There is also a lack of training support for the physicians and the patients on the appropriate use of CGM. Although intermittent CGM is definitely less expensive than continuous CGM, it is still not within the reach of many people if they have to pay "out of pocket." Lack of reimbursement options, patient support programs, the cost of insulin, and other medicines might impede the widespread adoption of CGM which could be perceived to be "nonessential" when one has limited resources. Most importantly, there are no established clinical guidelines to define the intermittent use of CGM and these are urgently needed. Rodbard[52] has elegantly reviewed the success, challenges, and opportunities of CGM use. We would argue that in situations where continuous use of CGM remains a challenge, at least its intermittent use could be considered.

Table 2 summarizes the real-life experience at two centers in India, that is, at Chennai and Ahmedabad, which shows the frequency of use of CGM sensors in T2D patients. The similarity of the use at the two centers is striking with 93.1% of T2D at Chennai and 84.5% of T2D at Ahmedabad using CGM only once and a smaller number of individuals using it more frequently over a 3-year period.

In summary, intermittent use of CGM could be a new paradigm in the therapy of T2D and certainly, it would make it more affordable, especially in developing countries. Obviously, randomized clinical trials are needed to prove both the short-term and long-term efficacy of this method of monitoring diabetes control as well as its cost-effectiveness.

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