ORIGINAL ARTICLE

Use of Retrospective Continuous Glucose Monitoring for Optimizing Management of Type 2 Diabetes in India

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Abstract

Background: Retrospective continuous glucose monitoring (CGM) studies may provide healthcare professionals (HCPs) with better understanding of glycemic patterns in patients with type 2 diabetes (T2D) and thereby support patient education and appropriate therapeutic interventions.

Methods: Adults with T2D and A1C values between 8% and 10% were eligible for this 3-month study. Patients were scheduled for 5 visits that included baseline and a month-2 retrospective CGM study (iPro2, Medtronic) followed by data review and therapy modifications. A1C values were determined at baseline and at study end.

Questionnaires were completed at each visit. HCP questionnaires assessed perception of the utility of studies; patient questionnaires assessed understanding of the importance of compliance with HCP recommendations. Indices of glycemic variability and control were calculated from CGM data retrospectively.

Results: A total of 181 subjects enrolled and 148 completed the study (81.8%). There were no serious adverse device effects. Most subjects (91.2%) had >1 therapy change after review of the first iPro2 test. Mean A1C decreased from 8.6% at baseline to 8.0% at month 3 ($p<0.001$). Questionnaire results from patients and HCPs indicated that both groups viewed the iPro2 studies and results as acceptable and useful. CGM-based glycemic variability metrics were similar in the two iPro2 tests.

Conclusion: *i*Pro2 studies provided HCPs with insights and opportunities for initiating changes to treatment regimens and to diet and exercise behaviors, and provided patients with improved knowledge of the importance of therapy compliance. Favorable reductions in A1C suggest that iPro2 tests can facilitate optimal management of T2D.

Editorial Viewpoint

- This study highlights theme of iPro2 system for continuous glucose monitoring (CGM) and its application in making therapeutic changes.
- Having results of CGM may help better counting of diabetes by more appropriate changes in regimens.
- However, if CGM is feasable in developing country like India remains to be seen considering factors like cost and compliance.

Introduction

Type 2 diabetes (T2D) is highly prevalent in India, with over 62 million people diagnosed with diabetes and 11 million with prediabetes.[1] The disease is often poorly controlled, and there are many people for whom the diagnosis has not been confirmed.[2] Even among patients known to have T2D, many

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Fig. 1: Components of the iPro2 System. Panel A shows the iPro2 recorder attached to a subcutaneous glucose sensor (the small filament protruding from the bottom right). Panel B shows the iPro2 Smart Dock (top) and the iPro2 recorder (bottom). Panel C shows data being uploaded to a remote server from the iPro2 via the Smart Dock. Panel D shows 3 report formats available from an iPro2 study - the Daily Overlay, Overlay by Meal, and Daily Summary

are unaware of the extent of their own blood glucose fluctuations and therefore, of the potential benefits from therapy modification or intensification.[3]

Continuous glucose monitoring (CGM) is a straightforward method of providing patients and clinicians with data regarding glucose levels. CGM data can be provided in real time, or collected unobtrusively in a recording device that is worn for several days. Data can then be retrospectively downloaded and reviewed in an office setting, where it is typically used to motivate and educate patients and guide decisions regarding therapy modifications.

Figure 1 shows the iPro2 system for collection and retrospective analysis of CGM data, which includes the waterproof recording unit and subcutaneous glucose sensor (Figure 1A), the docking station for retrieving data from and recharging the battery of the recording device (Figure 1B), the user interface hosted at https://carelink.minimed.eu/ipro/hcp/login.jsf?bhcp=1 (Figure 1C), and the reports (Figure 1D). Compared to the earlier iPro system, the iPro2 system requires fewer startup steps, is compatible with more blood glucose meters, uses a USB connection, requires no software installation, and is compatible with electronic medical records systems.

The objective of this study was to generate local India evidence to demonstrate that iPro2 studies enable healthcare professionals (HCPs) treating patients with T2D to obtain a better understanding of their patient's metabolic fluctuations and support appropriate therapeutic interventions leading to improved glycemic control.

Methods

Patients

The study was conducted at 11 sites in India. It was approved by all institutions' Ethics

Committees and was registered with Clinical Trials Registry- India (CTRI/2013/03/003499). Written informed consent was obtained from all subjects prior to any study-related activity. Eligibility criteria included a diagnosis of T2D made at least 1 year prior to enrollment, age 19-70 years, a treatment regimen including an oral anti-hyperglycemic medication and/or insulin, and an A1C measurement of >8.0% to < or equal to 10.0% made within 4 weeks of enrollment. The A1C values used to establish eligibility were separate from A1C values determined at the first study visit. Exclusion criteria included lack of experience with self-monitoring of blood glucose (SMBG) and having undergone an iPro study in the past 6 months.

Visit Schedule

Visit 1 included A1C measurement, application of the iPro2 device, and completion of the first set of questionnaires. Visit 2 (day 3-6, 2-6 days after Visit 1) included downloading of the iPro2 data and reviewing of the iPro2 report, initiation of therapy modification(s), and completion of the second set of patient and provider questionnaires. Visit 3 (day 38-52) included application of the second iPro2 device and the third set of patient and provider questionnaires. Visit 4 occurred 3-6 days after Visit 3 (day 41-58), and included downloading of the iPro2 data and reviewing of the iPro2 report, initiation of therapy modification(s), and completion of the fourth set of patient and provider questionnaires. Visit 5 (day 78-92) included blood collection for a second A1C measurement and the fifth set of patient and provider questionnaires.

Using the Reports to Guide Therapy

The iPro2 reports were to be used as part of discussions between patients and their HCPs. The reports were analyzed using standardized guidelines, and treatment recommendations were generated through a combination of clinical experience and the results of the iPro2 report analysis. The suggested steps in iPro2 report analysis included sequential consideration of overnight, pre-prandial, and postprandial intervals. Potential causes for overnight hypoglycemia and hyperglycemia such as prior-evening exercise were evaluated and discussed. Pre-prandial

Table 1: Mean change in A1C (Δ A1C) from visit 1 to end of study according to characteristics of subjects

Characteristic	Number*	†Change in A1C
Age (Years)		
18 - <49	37	-0.9 (1.43)
49 - <55	35	-0.8 (0.79)
55 - <61	36	-0.3 (1.04)
≥ 61	40	-0.6 (1.01)
Gender		
Male	97	-0.6 (1.17)
Female	51	-0.7 (1.00)
BMI (kg/m²)		
< 24.4	37	-0.7 (0.88)
24.4- <27.25	37	-0.4 (0.97)
27.25 - <29.35	37	-0.7 (1.12)
≥ 29.35	37	-0.8 (1.40)
Duration of diabetes (yrs)		
< 8	33	-0.8 (1.36)
8 - < 13	34	-0.4 (0.90)
13 - < 18	36	-0.8 (1.08)
≥ 18	45	-0.7 (1.08)

*Number of subjects with available A1C at Visit 1 and end of study visit; †Mean change in A1C mean (SD)

intervals were to be considered next, followed by postprandial intervals, with similar explorations of potential causes for observed glycemic excursions. Three different report formats (Figure 1D) provided synoptic and fine-grained views of the data. The "Daily Overlay" plot facilitated quick review of glucose excursions and trends, the "Overlay by Meal" plot allowed close examination of 3 critical periods, and the "Daily Summary" plot helped associate patient behaviors with observed effects.

Data Analysis

Descriptive summaries of data are presented. CGM data were analyzed retrospectively. The mean amplitude of glycemic excursions (MAGE) was calculated according to the method of Service et al.[4] and the continuous overall net glycemic action (CONGA) was calculated according to the method of McDonnell et al.[5]

Results

Table 2: Reduction in A1C from baseline to end-of-study

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Statistic	Baseline	End of Study	Δ
Mean ± SD	8.6 ±1.14	8.0 ± 1.06	-0.6 ±1.11
Median	8.5	7.9	-0.6
Min. Max	5,9, 14.2	5.7, 11.0	-7.0, 2.4

A1C values at baseline and at the end of the study from N=148 subjects for whom values were available at both time points

Patient Enrollment and Disposition

Of the 180 subjects who entered the study, 148 completed it. Of the 32 subjects who did not complete the study, 15 were withdrawn by the investigator for unknown reasons, 11 were withdrawn at their own discretion, 5 were lost to follow-up, and 1 refused to undergo study-related procedures. The mean (±SD) age of the enrolled subjects was 54.1 ± 10.1 years, their BMI was 27.1 ± 4.07 kg/m², mean time since diagnosis of T2D, 14.6 ± 8.1 years, and 38.7% were female. Clinically-relevant symptoms noted by HCPs included frequent hyperglycemia in 60.2% of subjects, frequent hypoglycemia in 18.2% of subjects, and erratic blood glucose levels in 48.1% of subjects. Table 1 shows the clinical characteristics of the 148 completers.

A1C and Sensor Glucose Values

Table 2 summarizes completers' A1C values in tabular and graphic form. The 0.6 percentage point reduction in A1C values from 8.6 ±1.14% at baseline to 8.0 ± 1.06% at the end of the study was clinically and statistically significant ($p<0.001$). Sensor glucose (SG) values were obtained from iPro2 studies of 176 subjects who completed an initial test and from 150 who completed a second iPro2 test; the mean (±SD) SG value was 161.2 ± 45.0 mg/dL in the first test and 158 ± 39 mg/dL during the second test. Improved glycemic control during the second iPro2 test was also evidenced by lower area under the curve (AUC) values for hyperglycemic excursions >180 mg/dL. In the first iPro2 test, the mean (±SD) event AUC was 3273+6417.4 mg/dL min, which decreased in the second iPro2 test to 2617±4380.1 mg/dLxmin.

Table 3: Mean change in A1C (ΔA1C) from visit 1 to end of study according to changes to treatment regimen (n=148)

Type of therapy	Subjects experiencing a therapy change % (n)	ΔA1C (SD)
Insulin	70.9% (105)	-0.72 (1.19)
Oral medications	48.0% (71)	-0.66 (1.14)
Diet	67.6% (100)	-0.63 (1.14)
Exercise	48.6% (72)	-0.60 (1.23)
Other medication	38.5% (57)	-0.76 (1.28)

Therapy Adjustments and Changes in A1C

At least one therapy change was made in 142 (95.9%) of the completers. Among these 142, the mean A1C value decreased by 0.69±1.10 percentage points. Among the 6 (4.1%) completers who did not make a therapy change, the mean A1C value increased by 0.28±0.88 percentage points. Table 3 shows therapy adjustments and corresponding mean changes in A1C. The most frequent change was the addition of insulin; many patients also changed their treatment regimens with respect to oral medications, diet, and exercise. The largest decrease in mean A1C was among subjects who were prescribed an additional diabetes medication. Table 4 shows mean A1C changes among insulin-taking patients who experienced a change to their insulin regimen, with respect to either the quantity, timing, or type of insulin. The largest decrease in A1C was among the 35 subjects who adjusted all three aspects of their insulin regimen.

CGM Data Related to Glycemic Variability

Data from the two iPro2 studies allowed calculation of various parameters related to glycemic variability. Data from the first and second sets of studies were

Table 4: Mean change in A1C (ΔA1C) from visit 1 to end of study according to adjustments to insulin therapy regimen

Type of change	Number	ΔA1C (%)	Overall ΔA1C (%)
Quantity/ timing/ type	35	-0.84	
Quantity	51	-0.69	
Quantity/ timing	7	-0.57	-0.72
Quantity/ type	6	-0.43	
Timing	1	0.00	
None	22	-0.25	-0.25

similar with respect to the standard deviation and coefficient of variation of the SG values, MAGE values, and CONGA values using 1-, 2-, and 4-hour time windows (data not shown).

Questionnaire Data from Patients

Visit 1 questionnaires concerned diabetes control and self-management. Regarding the most recent 3 months, 42.5% of subjects reported one or more instances of hypoglycemia (BG <70 mg/dL). Most (53.6%) subjects reported being aware of hypoglycemic events, and 40.4% reported being aware of hyperglycemic events. Only 27.6% of subjects reported checking their own blood glucose values 10 or more times in the past 30 days. The median response to a statement regarding always following their HCP's recommendation regarding their diabetes care was 6.0, indicating a high rate of compliance.

Between Visits 1 and 2, the iPro2 collected and recorded glucose data. Table 5 shows questionnaire responses collected during Visit 2. Mean and median responses support the acceptability and utility of the system. Visit 3 included a brief questionnaire and application of the second iPro2 recorder. Table 6 shows questionnaire responses collected during the third visit, which indicated that patients had implemented therapy changes suggested by their HCP, that the study allowed them to better manage their diabetes than before, that the report provided encouragement to comply with HCP recommendations, and that the iPro2 study was beneficial.

Table 5: Patient survey responses from Visit 2 (review of first iPro2 study)

Characteristic	Mean (SD)	Median	Min, Max
The iPro2 was easy and comfortable to wear	6.1(0.60)	6	3,7
The iPro2 did not interfere with my daily activities	6.2(0.81)	6	1,7
As a result of the review of the iPro2 report, I am now more aware of my Hypoglycemia (Low Blood Sugar below 70 mg/dL) than before.	6.1(0.99)	6	1,7
As a result of the review of the iPro2 report, I am now more aware of my Hyperglycemia (High Blood Sugar, above 200 mg/dL) events than before	6.2(0.88)	6	1,7
The review of the iPro2 report was helpful for me to understand my diabetes better than before	6.2(0.76)	6	1.7
1 understand the recommendations made by my Doctor/ Health Care Professional after reviewing the iPro2 report	6.2(0.67)	6	2,7
After seeing the iPro2 report, I am more likely to follow my Doctor/Health Care Professional's recommendations regarding my diabetes care than before	6.2(0.72)	6	2,7

N=177 for each question. Responses on a scale from 1-7 were allowed, with "1" indicating strong disagreement, "4" indicating neutrality, and "7" indicating strong agreement.

Table 6: Patient survey responses from visit 3 (start of second iPro2 study)

Characteristic	Mean (SD)	Median	Min, Max
I implemented the therapy changes suggested by my Doctor/Health Care Professional after the iPro2 test	6.1(0.64)	6	4,7
The iPro2 evaluation allowed me to better manage my diabetes than before	6.1(0.78)	6	3,7
Information from the iPro2 reports encouraged me comply with doctor/health care professional's recommendations.	6.2(0.68)	6	4,7
Overall, the iPro2 test was beneficial for me	6.3(0.69)	6	4,7

N=151 for each question. Responses on a scale from 1-7 were allowed, with "1" indicating strong disagreement, "4" indicating neutrality, and "7" indicating strong agreement.

Visit 4 responses indicated that patients found the second iPro2 study provided more information in managing their diabetes, and that the review was helpful for understanding their diabetes and the recommendations given by their HCP. Patient responses from Visit 5 indicated that subjects implemented therapy changes recommended after the iPro2 study, that the iPro2 study allowed them to manage their diabetes better than before, that the information in the report encouraged them to comply with treatment recommendations, that the study was beneficial overall, and that another iPro2 study in 6 months would also be valuable.

Questionnaire Data from Physicians

Physicians also completed questionnaires. At each patient's first visit, questionnaire responses from physicians indicated that 78.5% of the patients were unable to maintain tight diabetes control (defined as BG values 70-130 mg/dL before meals and <180 mg/dL 2 hours after meals). Increased A1C was noted for 91.7% of the patients and was seen as the most clinically significant symptom for 62.4% of patients.

Physician questionnaire findings are given in Tables 7 and 8. Physicians expressed agreement with statements that the iPro2 reports were useful; that they accurately revealed hypo- and hyperglycemic events; that they provided more information than SMBG alone; and that they allowed explanation of the patients' diabetes and/or provided more information relevant to managing the disease than before. Most physicians felt that their patients had achieved improved glucose control. More than 80% of them would recommend another iPro2 test for the patient in 6-12 months.

Table 7: HCP survey responses from visit 3 and visit 5

Yes / No questions	Agreement rate - visit 3 (% (n))	Agreement rate - visit 5 (% (n))
After review of the iPro2 results at the previous visit, I feel my patient has improved glucose control	53.0%(80)	53.7%(80)
After review of the iPro2 results at the previous visit, I feel my patient has increased frequency of SMBG	33.8%(51)	42.3%(63)
After review of the iPro2 results at the previous visit, I feel my patient has improved compliance to my recommendations	43.0%(65)	46.3%(69)
After review of the iPro2 results at the previous visit, I feel my patient has no impact	5.3%(8)	4.7%(7)
I would recommend another iPro2 test for this patient after 6-12 months	92.1%(139)	86.6%(129)

Extent of agreement questions	Visit 3			Visit 5		
	Mean (SD)	Median	Min, Max	Mean (SD)	Median	Min, Max
My patient maintained tighter diabetes control (70-130 mg/dl before meals, < 180 mg/dL 2 hours after meals) than before	5.3(0.98)	5	2,7	5.6(1.07)	6	1.0, 7.0
This patient follows my recommendations to conduct their SMBG tests	5.9(0.96)	6	2,7	6.0(0.98)	6	1.0, 7.0
After the iPro2 tests, I feel that this patient now has a better understanding on how to manage their diabetes	5.9(0.96)	6	2,7	5.9(1.02)	6	1.0, 7.0

N=151 for Visit 3 and N=149 for Visit 5. "Yes/No Questions" required yes-or-no answers; "Extent of Agreement Questions" required responses on a scale from 1-7, with "1" indicating strong disagreement, "4" indicating neutrality, and "7" indicating strong agreement.

Table 8: HCP survey responses from visit 2 and visit 4

Characteristic	Visit 2 (N=178)			Visit 4 (N=151)		
	Mean (SD)	Median	Min, Max	Mean (SD)	Median	Min, Max
I found the information from the iPro2 report useful	6.2(0.77)	6	2,7	6.2(0.67)	6	4,7
The iPro2 report accurately revealed hypoglycemic events of my patient	5.7(1.15)	6	2,7	5.8(1.09)	6	3,7
The iPro2 report accurately revealed hyperglycemic events of my patient	6.3(0.82)	6	2,7	6.2(0.82)	6	4,7
The iPro2 test provides more information than SMBG alone	6.3(0.79)	6	2,7	6.2(0.87)	6	3,7
The 3 step methodology was useful for me to make appropriate therapy recommendations for my patient	6.1(0.86)	6	1,7	6.2(0.77)	6	4,7
The iPro2 allowed me to explain, the nature of my patient's diabetes to him/her and/or provided more information in managing this patients' diabetes better than before	6.1(0.85)	6	1,7	6.1(0.73)	6	4,7

Responses on a scale from 1-7 were allowed, with "1" indicating strong disagreement, "4" indicating neutrality, and "7" indicating strong agreement.

Strong agreement was indicated with a statement that patients, after the iPro2 studies, had better understanding on how to manage their diabetes (median response of 6 on a 7-point Likert scale, with 7 indicating strong agreement).

Safety Data

There were no reported serious adverse effects or device complaints that could have led to a serious adverse effect. Of the 7 adverse device effects there were 2 instances of itching, 2 of pain, and 1 each of a pricking sensation, irritation, and bleeding. All were at the site of device application and resolved without complications.

Discussion

The main finding of this study was that structured use of retrospective CGM data can help patients achieve modest but clinically significant A1C reductions within 3 months. Patients who underwent therapy changes after collaborative iPro2 reviews enjoyed larger A1C reductions than those who did not, suggesting that those therapy adjustments were guided and motivated by actionable insights from the iPro2 data. Patients and providers both found the iPro2 results acceptable and useful, and the iPro2 studies were extremely safe.

Results of the current study support and extend earlier results. A recent study of 55 patients in India[6] showed that with iPro2 as a tool in the management of T2D, most patients can achieve A1C reductions and reach the goal of A1C <7.5% without any severe hypoglycemic events. A study of patients with T2D who underwent retrospective CGM studies compared to propensity-matched controls found that the CGM group had significantly more treatment modality changes, and significant improvements in the HbA1c levels at both 3 and 6 months.[7] A similar study of 38 patients with type 1 or T2D provided similar results.[8] Retrospective CGM studies have also proven useful in the context of insulin initiation in T2D,[9] gestational diabetes,[10] pre-diabetes,[11] and children with suboptimally-controlled type 1 diabetes.[12]

Given the rapid improvements in performance characteristics of CGM devices, its role in diabetes management seems destined to increase. The use of CGM in developing countries like India is

still limited and there is a need for data on the use of CGM and also its acceptability to both the patients and HCPs. In this context, this study -provides data from India showing that the iPro2 studies were acceptable to both HCPs and patients and also shows their utility in controlling blood glucose levels.

As was recently shown in the ICMR - INDIAB study, less than a third of patients in India are able to achieve A1C values <7%.[2] With the high prevalence and associated morbidity and cost of poorly-controlled T2D in India and other regions, expanded use of retrospective CGM studies in appropriate patients is warranted.

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