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Effect of treatment guidance using a retrospective continuous glucose monitoring system on glycaemic control in outpatients with type 2 diabetes mellitus: A randomized controlled trial*

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Abstract

Objectives: To assess the effect of treatment guidance based on data from a continuous glucose monitoring (CGM) device on glycaemic control, and patient satisfaction, in patients with type 2 diabetes mellitus (T2DM).

Methods: Patients with poorly-controlled T2DM treated with insulin were randomly assigned to the intervention or nonintervention group. Continuous blood-glucose levels were recorded for 4–5 days using a CGM device on three separate occasions during the 8-month study period. The intervention group received treatment guidance based on the CGM data; the nonintervention group received advice based on blood glucose and glycosylated haemoglobin (HbA_{1c}) levels.

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Results: A total of 34 patients were enrolled in the study. The mean ± SD baseline HbA_{1c} was 8.2 ± 1.2% in the intervention group and 8.2 ± 0.9% in the nonintervention group. At the study end, there was no significant difference in the change from baseline of HbA_{1c} between the two groups. There was also no significant difference in the change from baseline in the Diabetes Treatment Satisfaction Questionnaire score between the two groups.
Conclusions: The present study did not demonstrate that treatment guidance using retrospective CGM data was effective for improving glycaemic control and therapeutic satisfaction in Japanese patients with T2DM.

Keywords
Continuous glucose monitoring, type 2 diabetes, insulin therapy

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Introduction

In Japan, the estimated number of people with type 2 diabetes mellitus (T2DM) reached 10.7 million in 2011, which is the sixth largest population of patients with T2DM in the world.[1] Considering the presence of a large number of patients with poor glycaemic control, improvement in T2DM management is an urgent matter in Japan, as it is in other countries.

Continuous glucose monitoring (CGM) technology provides maximum information about fluctuations in blood glucose by the continuous analysis of the interstitial glucose level throughout the day.[2] CGM has the potential to change the approach used to educate patients with T2DM.[3] Since the United States Food and Drug Administration approved a CGM device in 1999, the technology has improved; real-time CGM and insulin pump-integrated systems (with sensor-augmented pumps) have become commercially available in the United States and Europe, in addition to retrospective CGM.[4] A number of important studies have investigated the use of CGM in patients with type 1 (T1DM) and T2DM in the United States and Europe.[5–8] Moreover, the 2014 Clinical Practice Recommendations of the American Diabetes Association stated that the proper use of CGM, in conjunction with an intensive insulin regimen, results in lowering glycosylated haemoglobin (HbA_{1c}) in selected adults (age ≥25 years) with T1DM (level A; clear evidence).[9] In contrast, the history of CGM use in Japan is relatively short, since the device was only approved by the Ministry of Health, Labour and Welfare in 2009, ~10 years after its introduction in the United States. Until the beginning of 2015, only the retrospective CGM device was available in general Japanese hospitals, and in February 2015, a sensor-augmented pump was finally introduced to the Japanese market. However, there are no studies on the usefulness of treatment guidance using CGM for glycaemic control in Japanese patients, especially in those with T2DM. Consequently, the present study investigated whether the iPro®2 (a wireless retrospective CGM device; the most popular CGM in Japan), is useful for glycaemic control and therapeutic satisfaction in Japanese people with T2DM receiving insulin treatment.

Patients and methods

Study population

Patients who fulfilled the following inclusion criteria at registration were included in the study: (i) patients with T2DM on insulin injection therapy; (ii) age > 20 years; (iii) regular visitors to the outpatient clinic at

Juntendo University Hospital, Tokyo, Japan between December 2012 and April 2014; (iv) HbA_{1c} (National Glycohemoglobin Standardization Program [NGSP]) ranged between 6.9% and 11.0% over a period of 3 months prior to study enrolment; HbA_{1c} fluctuations were within $\pm 0.5\%$ over the same time period. The above selected patients with T2DM were excluded from the study when any of the following conditions was diagnosed at registration: (i) proliferative retinopathy; (ii) serious liver disease (aspartate aminotransferase and/or alanine aminotransferase levels >100 IU/l); (iii) serious kidney disease (serum creatinine level >2.0 mg/dl); (iv) acute heart failure; (v) active malignancy; (vi) serious pancreatic disease; (vii) pregnancy; (viii) serious infectious disease; (ix) trauma injury.

Study design

This was an open-label, two-arm, randomized controlled study. Patients meeting the above criteria were assigned randomly by a computer-generated method to either the intervention (I) group or the nonintervention (N-I) group. None of the patients had used a CGM device within 1 year prior to the start of the clinical trial. According to previous reports,[5,10,11] the HbA_{1c} levels decreased from the baseline after intervention using CGM by variable amounts (0.5% – 1.2%). After considering these changes, the difference in HbA_{1c} reduction between the two groups in this study was estimated as 0.7% with an SD of 0.6. Considering a two-sided α-level of 5% and a power (1-β) of 90%, the appropriate number of patients was considered to be 34 (17 patients per study group).

Patients were asked to visit the hospital ~5 days before the start of the study period, and were equipped with a wireless retrospective CGM device (iPro®2; Medtronic, Northridge, CA, USA) with the aid of medical staff.[12] In the present study, all patients applied the CGM to continuously record 4–5 days of data before every visit, including a recording at baseline. This type of recording was repeated twice throughout the duration of the study (~8 months) (Figure 1).

During each 4–5-day CGM recording period using the iPro®2, patients in both study groups were instructed to undertake self-monitoring of blood glucose (SMBG) three times using a handheld blood glucose meter (Glutest® Neo Super; Sanwa Kagaku Kenkyusho, Nagoya, Japan) on the first and last days and four times on the other days for calibration purposes. Patients were also asked to keep a diary that recorded the amount and type of food consumed every day. The proportion of time spent with blood glucose levels <70 mg/dl, 70–140 mg/dl, and >140 mg/dl as determined by CGM was calculated using the following equation: proportion of time spent in range (%) = time spent in range (<70 mg/dl, 70–140 mg/dl, or >140 mg/dl)/total time of measurement $\times$ 100.

At the scheduled outpatient clinic appointment, patients handed the CGM and SMBG data to the study team for downloading. Data from three consecutive days from the second day of the CGM recording period were used to compute the blood glucose levels. For patients in the I group, two trained diabetologists from the study team provided guidance during an interview with the patient of at least a 15-min duration, where they discussed a treatment strategy in terms of lifestyle changes using a printout of the patient's CGM data, in addition to the usual routine clinical examination (range, 5–10 min). This 15-min guidance interview included at least three processes: (i) the trained diabetologists from the study team used a printout of the patient's CGM data to explain when blood glucose levels were >140 mg/dl and/or <70 mg/dl; (ii) the patient was encouraged to find the reasons for high or low blood glucose levels in front of the trained diabetologist from the study team; (iii) the patient was provided with instructions about improving

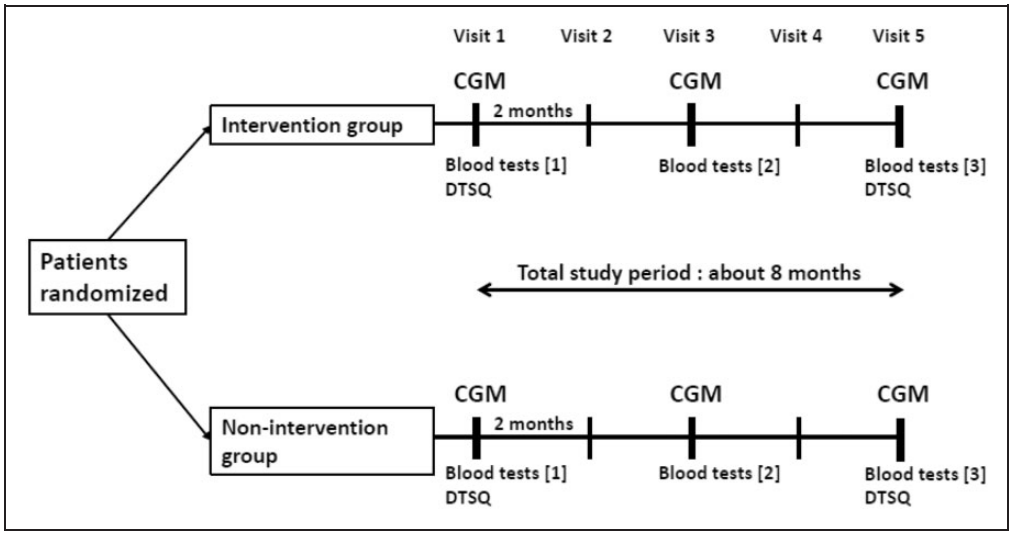

Figure 1. The design of an open-label, two-arm, randomized controlled study that aimed to determine whether a wireless retrospective continuous glucose monitoring (CGM) device is useful for glycaemic control and therapeutic satisfaction in obese Japanese patients with type 2 diabetes mellitus treated with insulin. Patients were randomly assigned to the intervention group or the nonintervention group. Patients visited the hospital every 2 months for blood tests; CGM recording was performed three times prior to these visits throughout the 8-month study period. The patients were also instructed to complete the Diabetes Treatment Satisfaction Questionnaire (DTSQ) at the beginning and end of the study.

his/her blood glucose levels, primarily by changing his/her lifestyle and secondarily by changing the dose of insulin or other medications. Suggestions made by the study team were written down on paper for the patients and physicians. The physician in charge then decided whether or not to adopt the suggestions when they were discussed with the patient during the routine visit. In the N-I group, both the patients and physicians in charge were prohibited from seeing the CGM data until the end of the study, so the treatment strategy for the N-I group was decided based on the results of routine blood tests such as HbA_{1c} and blood glucose analysis.

The routine visit with the physicians in charge was usually scheduled once every 2 months; only the physicians in charge could change the insulin dose and other medications. Blood and urine tests, and measurement of body weight and body mass index, were performed using standard methods at every visit. Blood pressure was measured using routine methods. Serum lipids (total cholesterol, high-density lipoprotein cholesterol, triglycerides) were quantified using an automatic biochemistry analyser (LABOSPECT® 008 Hitachi Automatic Analyzer; Hitachi High-Technologies, Tokyo, Japan). HbA_{1c} (NGSP) was quantified using a high-performance liquid chromatography analyser (HLC-723® G8; Tosoh Bioscience, Tokyo, Japan).

Patients were instructed at the beginning and end of the study to complete the Diabetes Treatment Satisfaction Questionnaire (DTSQ).[13]

The primary endpoint was a change in HbA_{1c} level from baseline. The secondary endpoint was a change in the DTSQ score from baseline. The study protocol was approved by the Human Ethics Committee

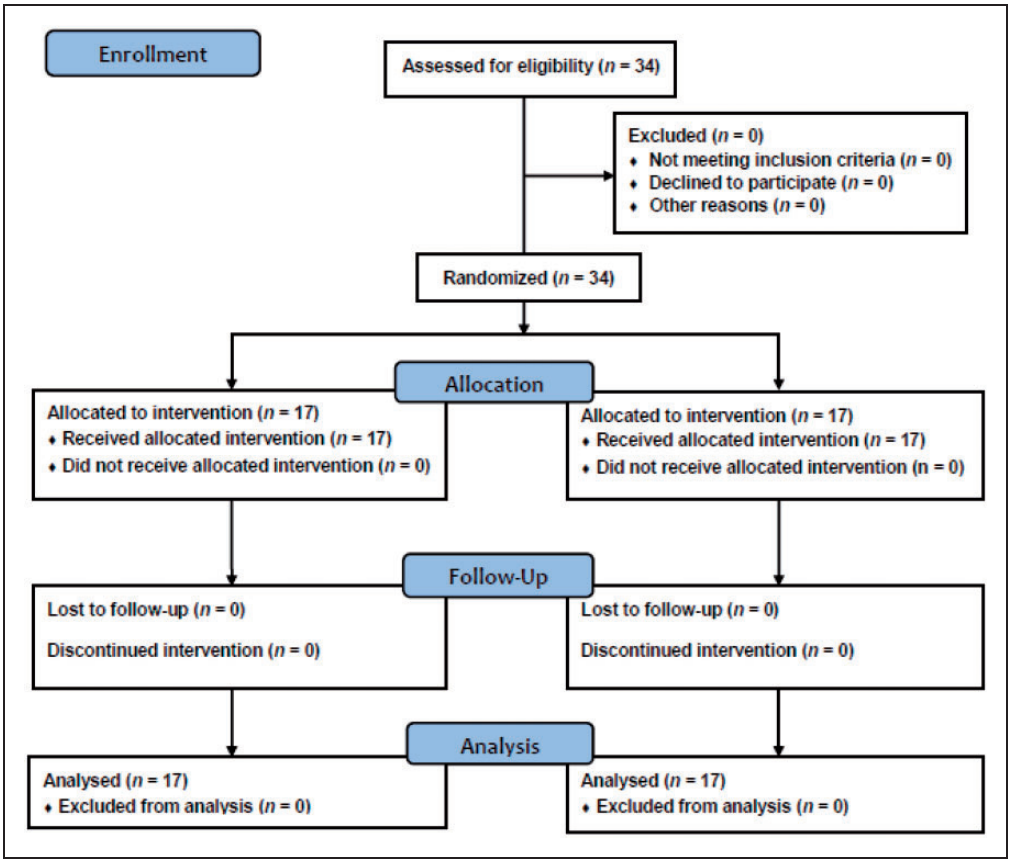

Figure 2. CONSORT flow diagram of Japanese patients with type 2 diabetes mellitus ($n = 34$) included in an open-label, two-arm, randomized controlled study.

of Juntendo University, Tokyo, Japan (No. 25–388). Written informed consent was obtained from each patient before enrolment in the study. This study was registered with the University Hospital Medical Information Network in Japan (UMIN: 000012034).

Statistical analyses

All statistical analyses were conducted using the JMP® statistical discovery software package, version 10.0.2 (SAS Institute, Cary, NC, USA). Data were expressed as mean ± SD for normally distributed data and median (interquartile range) for data with skewed distribution. The Mann–Whitney *U*-test and Wilcoxon signed-rank test were used for data analysis. A *P*-value <0.05 denoted the presence of a statistically significant difference.

Results

A total of 34 patients meeting the inclusion criteria were assigned randomly to either the I group ($n = 17$) or the N-I group ($n = 17$). All of the patients completed the study (Figure 2). Table 1 summarizes the baseline demographic and clinical characteristics of the two study groups. There were no significant differences between the two groups at

Table 1. Baseline demographic and clinical characteristics of Japanese patients with type 2 diabetes mellitus ($n = 34$) included in an open-label, two-arm, randomized controlled study that aimed to determine whether a wireless retrospective continuous glucose monitoring device is useful for glycaemic control and therapeutic satisfaction.

Characteristic	Intervention group $n = 17$	Nonintervention group $n = 17$
Sex, male/female	8/9	12/5
Age, years	59.9 ± 9.0	63.1 ± 8.5
Height, cm	161.8 ± 10.1	164.2 ± 9.5
Body weight, kg	71.4 ± 17.4	73.3 ± 16.1
Body mass index, kg/m^2	27.0 ± 4.7	27.1 ± 5.0
Systolic blood pressure, mmHg	139.4 ± 19.7	137.8 ± 14.7
Diastolic blood pressure, mmHg	80.6 ± 10.0	78.8 ± 12.7
Duration of diabetes, years	16.1 ± 10.7	16.1 ± 7.7
HbA_{1c}, %	8.2 ± 1.2	8.2 ± 0.9
Total cholesterol, mg/dl	183.3 ± 41.9	174.4 ± 29.6
HDL-C, mg/dl	51.1 ± 16.9	44.4 ± 11.9
Triglyceride, mg/dl	125.9 ± 59.7	152.7 ± 103.8
Insulin regimens used		
Intensive	16	15
Bolus	1	1
Basal	0	1
Insulin type used		
Lispro	8	6
Aspart	6	8
Glulisine	2	2
Glargine	12	10
Detemir	3	5
Lispro 50 mix	1	1
Bolus insulin, IU/day	25.0 ± 11.9	26.4 ± 16.4
Basal insulin, IU/day	12.9 ± 7.1	14.8 ± 10.4
Oral therapy for diabetes		
Sulphonylurea	1	1
Metformin	7	8
α-Glucosidase inhibitor	1	4
Thiazolidine	2	0
Dipeptidyl-peptidase 4 inhibitor	4	3
Medications for other diseases		
Antihypertensive drugs	13	10
Lipid-lowering drugs	11	9

Data presented as mean ± SD or *n* of patients.
No significant between-group differences ($P \geq 0.05$); Mann–Whitney *U*-test.
HbA_{1c}, glycosylated haemoglobin; HDL-C, high-density lipoprotein cholesterol.

baseline. The insulin dose was increased by 2.2 ± 4.4 IU/day in the I group and 0.2 ± 3.0 IU/day in the N-I group from baseline to study end (Table 2). There was no significant difference in the insulin dose change between the two groups. Furthermore, one patient in the I group and two patients in the N-I group required the addition of dipeptidyl-peptidase

Table 2. Change from baseline in glycosylated haemoglobin (HbA_{1c}) and insulin dose in Japanese patients with type 2 diabetes mellitus ($n = 34$) who used a wireless retrospective continuous glucose monitoring (CGM) device with or without treatment intervention based on the results of CGM.

Parameter	Intervention group $n = 17$	Nonintervention group $n = 17$
[1] Baseline HbA_{1c}, %	8.2 ± 1.2	8.2 ± 0.9
[2] HbA_{1c} after second CGM recording period, %	8.1 ± 1.3	8.1 ± 0.9
[3] HbA_{1c} after third CGM recording period, %	8.2 ± 1.3	7.9 ± 0.8
Change in HbA_{1c}, %[a]		
Δ[3]–[1]	0.01 ± 1.00	-0.30 ± 0.80
Δ[2]–[1]	-0.1 ± 0.8	-0.1 ± 0.6
Δ[3]–[2]	0.2 ± 0.5	-0.1 ± 0.6
Change in insulin dose [3]–[1], IU/day	2.2 ± 4.4	0.2 ± 3.0

Data presented as mean ± SD.

No significant between-group differences ($P \geq 0.05$); Mann–Whitney *U*-test.

Blood test schedule: [1] blood test at baseline at visit 1; [2] blood test at visit 3; [3] blood test at visit 5 at the end of the study.

[a]Each Δ value represents change of data between each blood test and is presented as the mean of the individual Δ values determined for each patient by subtracting data collected at each visit. These data were not calculated by simple subtraction of the mean values shown in the table for each visit.

4 inhibitors to their treatmentregimen, while α-glucosidase inhibitor therapy was discontinued in one patient in the N-I group.

Changes in HbA_{1c} levels over time are shown in Table 2. Such changes were not significantly different between two groups for any of the time intervals. Other parameters related to diabetes management (such as body mass index, blood pressure, total cholesterol, high-density lipoprotein cholesterol and triglyceride levels) were not significantly different at the end of the study relative to the baseline (data not shown).

Blood glucose concentrations obtained from the CGM devices for the I and the N-I groups are presented in Table 3. There were no significant differences in maximum and median blood glucose levels between the two groups.

Table 3 also shows the percentage of time spent with blood glucose concentrations >140 mg/dl, 70–140 mg/dl and <70 mg/dl within a 24-h time period, based on data from three consecutive days from the second day of the CGM recording period. The percentage of time spent >140 mg/dl decreased from 68.5% at baseline to 56.0% at the end of the study in the I group, and from 63.5% to 51.0% in the N-I group. The percentage of time spent at 70–140 mg/dl increased from 31.5% to 44.0% in the I group and from 36.5% to 46.0% in the N-I group. These changes were not significantly different between the two groups. The percentage of time spent <70 mg/dl was almost 0% in both groups.

Table 4 shows mean ± SD. DTSQ scores at baseline and at the end of the study in the two groups. There were no significant differences between the two groups in terms of their total satisfaction scores or their perception of the frequency of hypoglycaemic events at baseline or at the end of the study. There was no significant difference between the two groups in the scores for perceived frequency of hyperglycaemic events at baseline, but the score was significantly higher in the I group at the end of the study compared with the N-I group (3.8 ± 1.5 versus 2.8 ± 1.1, respectively; $P = 0.042$), although the change from baseline in the perception of the frequency of hyperglycaemic events

Table 3. Blood glucose levels recorded by a wireless retrospective continuous glucose monitoring (CGM) device in Japanese patients with type 2 diabetes mellitus ($n = 34$) who did or did not receive treatment intervention based on the results of CGM.

Parameter		Intervention group $n = 17$	Nonintervention group $n = 17$
Maximum blood glucose, mg/dl	[1]	271.5 (219.5–315.3)	267.5 (233.8–289.5)
	[2]	232.0 (215.0–273.5)	259.0 (221.5–294.5)
	[3]	256.0 (234.5–304.0)	247.0 (223.5–261.0)
Δ[3]–[1]		31.0 (3.0–46.5)	
		32.0 (21.0–40.3)	
Δ[3]–[2]		25.0 (13.5–51.5)	
		20.0 (9.0–51.5)	
Δ[2]–[1]		23.0 (17.5–52.5)	
		15.0 (3.0–34.0)	
Minimum blood glucose, mg/dl	[1]	98.5 (82.3–135.5)	92.5 (77.5–125.0)
	[2]	103.0 (89.5–125.0)	83.0 (76.0–105.8)
	[3]	96.0 (79.0–129.0)	89.0 (76.0–95.5)
Δ[3]–[1]		18.0 (5.5–23.0)	
		18.0 (1.0–39.0)	
Δ[3]–[2]		13.0 (6.0–15.0)	
		17.0 (1.8–31.3)	
Δ[2]–[1]		23.5 (4.5–75.5)	
		11.0 (4.5–30.0)	
Median blood glucose, mg/dl	[1]	173.5 (128.0–216.3)	163.0 (148.5–190.8)
	[2]	155.0 (129.5–202.5)	154.0 (137.8–188.8)
	[3]	153.0 (137.0–201.5)	154.0 (133.5–167.0)
Δ[3]–[1]		−13.5 (−23.3–4.3)	
		2.5 (−17.3–27.0)	
Δ[3]–[2]		9.0 (−19.5–125.0)	
		2.0 (−18.5–34.5)	
Δ[2]–[1]		−10.5 (−40.0–8.3)	
		−2.5 (−23.5–8.0)	
Time spent with blood glucose >140 mg/dl, %	[1]	68.5 (33.5–92.5)	63.5 (43.0–88.3)
	[2]	51.0 (31.5–88.5)	51.5 (45.3–80.3)
	[3]	56.0 (41.0–91.0)	51.0 (35.5–69.0)
Δ[3]–[1]		−6.0 (−22.3–5.3)	
		−0.5 (−16.0–13.8)	
Δ[3]–[2]		−3.0 (−14.8–9.5)	
		2.0 (−9.0–15.0)	
Δ[2]–[1]		−3.5 (−23.8–8.3)	
		−2.5 (−15.5–4.0)	
Time spent with blood glucose within 70–140 mg/dl, %	[1]	31.5 (7.5–61.3)	36.5 (11.8–54.0)
	[2]	49.0 (12.0–66.0)	48.5 (19.0–53.0)
	[3]	44.0 (9.5–59.0)	46.0 (31.0–63.0)
Δ[3]–[1]		7.0 (−4.5–22.3)	
		−1.5 (−9.3–16.5)	
Δ[3]–[2]		0.5 (−9.3–14.8)	
		−2.0 (−13.0–9.0)	

(continued)

Table 3. Continued.

Parameter	Intervention group $n = 17$	Nonintervention group $n = 17$
Δ[2]–[1]	3.5 (−4.0–13.3)	4.0 (−9.3–21.5)
Time spent with blood glucose <70 mg/dl, %	[1] 0 (0–0)	0 (0.0–1.3)
	[2] 0 (0–0)	0 (0–1)
	[3] 0 (0–0)	0 (0–1)
Δ[3]–[1]	0 (0–0)	0 (−1.3–0.3)
Δ[3]–[2]	0 (0–0)	0 (0.0–0.8)
Δ[2]–[1]	0 (0–0)	0 (−0.8–0.8)

Data presented as median (interquartile range).
No significant between-group differences ($P \geq 0.05$); Wilcoxon signed-rank test.
CGM schedule: [1] CGM recording period at baseline; [2] second period of CGM recording prior to visit 3; [3] third period of CGM recording prior to visit 5 at the end of the study.
Each Δ value represents the change of data between each period of CGM and is presented as the median of the individual Δ values that were determined for each patient by subtracting the baseline CGM data from data collected from either the second or third period of CGM. These data were not calculated by simple subtraction of the median values shown in the table for each CGM recording period.

Table 4. Change from baseline in the Diabetes Treatment Satisfaction Questionnaire score in Japanese patients with type 2 diabetes mellitus ($n = 34$) who used a wireless retrospective continuous glucose monitoring (CGM) device with or without treatment intervention based on the results of CGM.

Parameter	Intervention group $n = 17$	Nonintervention group $n = 17$	Statistical significance[a]
Total satisfaction, points			
Baseline	19.8 ± 5.5	21.5 ± 7.1	NS
Study end	20.6 ± 4.8	24.0 ± 5.0	NS
Perception of frequency of hyperglycaemic events, points			
Baseline	3.4 ± 1.4	3.3 ± 1.4	NS
Study end	3.8 ± 1.5	2.8 ± 1.1	$P = 0.042$
Perception of frequency of hypoglycaemic events, points			
Baseline	1.2 ± 1.3	0.9 ± 0.8	NS
Study end	1.7 ± 1.4	2.2 ± 1.2	NS
Δ Total satisfaction score, points[b]	0.8 ± 7.1	2.4 ± 8.0	NS
Δ Perception of frequency of hyperglycaemic events, points[b]	0.4 ± 1.6	−0.5 ± 1.8	NS
Δ Perception of frequency of hypoglycaemic events, points[b]	0.4 ± 1.6	1.2 ± 1.5	NS

Data presented as mean ± SD.
[a]Mann–Whitney *U*-test. NS, no significant between-group difference ($P \geq 0.05$).
[b]Each Δ value represents the change at the end of the study relative to baseline and is presented as the mean of the individual Δ values that were determined for each patient by subtracting the baseline data from data collected at the end of the study. These data were not calculated by simple subtraction of the mean values shown in the table for each time period.

did not show a significant difference between the two groups.

Discussion

The present study investigated the effects of changes in treatment based on retrospective CGM data on glycaemic control and treatment satisfaction in patients with T2DM treated with insulin. In these patients, the results indicated that treatment guidance using retrospective CGM data was not useful with regard to improving people's therapeutic outcome, specifically their HbA_{1c} levels.

In this present study, the mean BMI of the study population was $27\,kg/m^2$. According to data from the Japan Diabetes Clinical Data Management Study Group, the mean BMI of Japanese patients with T2DM was $22.7\,kg/m^2$ for men and $23.3\,kg/m^2$ for women.[14] In comparison, the patients in the present study were relatively obese. In addition, the baseline HbA_{1c} was >8% and the duration of T2DM was >16 years, indicating that patients in this present study were obese with poorly controlled T2DM. CGM data showed that over half of the 24-h blood glucose sampling period was spent with a blood glucose concentration >140 mg/dl, but almost none of the time was spent with blood glucose concentrations at hypoglycaemic levels (<70 mg/dl). Given that CGM is useful for detecting unrecognised episodes of hypoglycaemia, it is likely that these patients tried to avoid hypoglycaemia during treatment, probably based on advice from their physicians.

In a study of patients with T1DM, the use of real-time CGM and intensive insulin regimens resulted in reduced HbA_{1c} levels.[9,15] Another study also showed the usefulness of retrospective CGM for T1DM.[6] In the case of patients with T1DM, the dose of insulin can be easily increased if levels of hyperglycaemia suggest a deficiency of the insulin effect. In this present study, physicians increased the insulin dose by 2.2 ± 4.4 IU/day in the I group and 0.2 ± 3.0 IU/day in the N-I group throughout the study period. This change in insulin dose was not clinically meaningful with regard to causing an improvement in glycaemic control. The small change in insulin probably reflected the physicians' desires to avoid further body weight gain (caused by overdosing of insulin) in obese patients. It is also possible that physicians preferred their patients to change their lifestyles regarding diet and exercise rather than try aggressive insulin titration. However, no significant body weight reduction was noted in this study, indicating that the clinical management aided by the CGM data used in this study did not satisfactorily change the lifestyle of patients. There are some important studies indicating that CGM is useful for specific populations such as pregnant women[5] and patients on haemodialysis.[8] In contrast, unstructured retrospective use of CGM does not provide any benefit for glycaemic control in people with uncontrolled diabetes.[7]

Based on changes in DTSQ scores, CGM intervention did not significantly improve patient satisfaction. There was a tendency for less satisfaction expressed by patients in the I group compared with the N-I group at the end of the study, although the difference between the two groups was not significant. This could be due to the fact that the score for the perception of the frequency of hyperglycaemia at the end of the study was significantly increased in the I group compared with the N-I group. Patients in the I group could have become much more conscious about blood glucose levels based on the close observation of their CGM data, and they were not satisfied with the results of treatment because of the psychological burden.

Patients with diabetes are at risk of emotional problems, such as depression and diabetes-related distress.[16–18] Studies have found that SMBG increased the likelihood of depression and did not improve diabetes control.[19,20] However, in the Structured

Testing Program (STeP) study, strictly 'structured SMBG' for three consecutive days tended to have a positive impact on psychosocial outcome and reductions in HbA_{1c} relative to the control group.[21] In the STeP study, patients received training before the study on how to respond to the results of SMBG.[21] Each of the participating physicians also received training on the correct interpretation of the structured data and was provided with an algorithm that described various pharmacological and lifestyle treatment strategies.[21] This suggests that 'structured SMBG' seems to be the true key for improvement. The intervention in the present study involved 15-min consultations with instructions provided by the trained diabetologists, but the patients and physicians in charge did not receive training before the study. It is possible that the three 15-min consultations throughout the study course did not help patients in making meaningful interpretations of their blood glucose levels measured by the CGM, or in improving their diabetes control. If patients in this current study were unable to manage their blood glucose levels using the CGM data, it would be understandable that they might have felt guilty about having high blood glucose levels and then subsequently experienced dissatisfaction during the study. Construction of 'structured CGM' with some algorithms, for the physicians and the patients, describing various treatment strategies to improve psychosocial and diabetes control might be necessary.

This present study had a number of limitations. First, it did not evaluate the usefulness of CGM for avoiding nocturnal hypoglycaemia based on proper basal insulin titration, because almost none of the patients presented with hypoglycaemia. Secondly, the study did not evaluate lifestyle changes made in response to the CGM data. Thirdly, the sample size was small and further studies that include larger populations are needed to confirm the present findings.

In conclusion, this present study showed that treatment guidance using retrospective CGM data neither improved glycaemic control nor therapeutic outcome in obese poorly-controlled patients with T2DM treated with insulin at an outpatient clinic. To elucidate the usefulness of CGM data, further studies are needed to develop effective interventions by using retrospective or real-time CGM for the improvement of diabetes control and therapeutic satisfaction, in Japanese outpatients with T2DM.

Declaration of conflicting interest

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References

1. Whiting DR, Guariguata L, Weil C, et al. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* 2011; 94: 311–321.
2. Klonoff DC. The need for separate performance goals for glucose sensors in the hypoglycemic, normoglycemic, and hyperglycemic ranges. *Diabetes Care* 2004; 27: 834–836.
3. Allen NA, Fain JA, Braun B, et al. Continuous glucose monitoring in non-insulin-using individuals with type 2 diabetes: acceptability, feasibility, and teaching opportunities. *Diabetes Technol Ther* 2009; 11: 151–158.
4. Sato J, Hirose T and Watada H. Continuous glucose monitoring system: is it really accurate, safe and clinically useful? *J Diabetes Investig* 2012; 3: 225–230.
5. Murphy HR, Rayman G, Lewis K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. BMJ 2008; 337: a1680.
6. Miele A, Weiland K and Dungan KM. Clinical outcomes associated with referral-based continuous glucose monitoring using a central standardized interpretation strategy. *Diabetes Technol Ther* 2012; 14: 765–771.
7. Pepper GM, Steinsapir J and Reynolds K. Effect of short-term iPRO continuous glucose monitoring on hemoglobin A1c levels in clinical practice. *Diabetes Technol Ther* 2012; 14: 654–657.
8. Joubert M, Fourmy C, Henri P, et al. Effectiveness of continuous glucose monitoring in dialysis patients with diabetes: the DIALYDIAB pilot study. *Diabetes Res Clin Pract* 2015; 107: 348–354.
9. American Diabetes Association. Executive summary: standards of medical care in diabetes–2014. *Diabetes Care* 2014; 37(Suppl 1): S5–S13.
10. Cooke D, Hurel SJ, Casbard A, et al. Randomized controlled trial to assess the impact of continuous glucose monitoring on HbA(1c) in insulin-treated diabetes (MITRE Study). *Diabet Med* 2009; 26: 540–547.
11. Vigersky RA, Fonda SJ, Chellappa M, et al. Short- and long-term effects of real-time continuous glucose monitoring in patients with type 2 diabetes. *Diabetes Care* 2012; 35: 32–38.
12. Yates CJ, Fourlanos S, Colman PG, et al. Divided dosing reduces prednisolone-induced hyperglycaemia and glycaemic variability: a randomized trial after kidney transplantation. *Nephrol Dial Transplant* 2014; 29: 698–705.
13. Bradley C. Diabetes treatment satisfaction questionnaire (DTSQ). In: Bradley C (ed) *Handbook of Psychology and Diabetes: A guide to psychological measurement in diabetes research and practice*. Chur, Switzerland: Harwood Academic Publishers, 1994, pp.111–132.
14. Sone H, Yoshimura Y, Tanaka S, et al. Cross-sectional association between BMI, glycemic control and energy intake in Japanese patients with type 2 diabetes, Analysis from the Japan Diabetes Complications Study. *Diabetes Res Clin Pract* 2007; 77(Suppl 1): S23–S29.
15. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, Bode BW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008; 359: 1464–1476.
16. Speight J, Browne JL and Furler J. Challenging evidence and assumptions: is there a role for self-monitoring of blood glucose in people with type 2 diabetes not using insulin? *Curr Med Res Opin* 2013; 29: 161–168.
17. Ali S, Stone MA, Peters JL, et al. The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. *Diabet Med* 2006; 23: 1165–1173.
18. Snoek FJ, Pouwer F, Welch GW, et al. Diabetes-related emotional distress in Dutch and U.S. Diabetic patients: cross-cultural validity of the problem areas in diabetes scale. *Diabetes Care* 2000; 23: 1305–1309.
19. Farmer A, Wade A, Goyder E, et al. Impact of self monitoring of blood glucose in the

management of patients with non-insulin treated diabetes: open parallel group randomised trial. *BMJ* 2007; 335: 132.
20. O'Kane MJ, Bunting B, Copeland M, et al. Efficacy of self monitoring of blood glucose in patients with newly diagnosed type 2 diabetes (ESMON study): randomised controlled trial. *BMJ* 2008; 336: 1174–1177.
21. Polonsky WH, Fisher L, Schikman CH, et al. Structured self-monitoring of blood glucose significantly reduces A1C levels in poorly controlled, noninsulin-treated type 2 diabetes: results from the Structured Testing Program study. *Diabetes Care* 2011; 34: 262–267.