Responses to Continuous Glucose Monitoring in Subjects with Type 1 Diabetes Using Continuous Subcutaneous Insulin Infusion or Multiple Daily Injections

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Abstract

Objective: We compared changes in response to unmasking of continuous glucose monitoring (CGM) in subjects with type 1 diabetes who use multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII).

Research Design and Methods: Use of real-time CGM (DexCom [San Diego, CA] SEVEN[®]) was studied in 38 subjects using CSII and 26 using MDI. CGM output was masked during Week 1 and unmasked during Weeks 2 and 3. We evaluated changes in 16 criteria for quality of glycemic control and eight criteria for glycemic variability.

Results: All 24 criteria showed highly statistically significant improvement when considered simultaneously ($P < 0.000001$). For subjects using CSII, 18 of 24 criteria improved significantly (nominal $P < 0.05$); for subjects using MDI, 16 of 24 criteria improved significantly ($P < 0.05$). Twelve of the comparisons remained significant ($P < 0.05$) after applying the overconservative Bonferroni correction for multiple comparisons. The percentage of glucose values within the range 80–140 mg/dL increased by 19% and 17% relative to their control values (Week 1) for subjects using MDI and CSII, respectively. Mean glucose, overall SD (SD_T), SD between daily means (SD_{dm}), mean amplitude of glycemic excursion (MAGE), and mean of daily differences (MODD) improved significantly. Responses to CGM display were not significantly different between the MDI and CSII subject groups for any of the 24 criteria considered individually or in groups of eight, 16, or 24.

Conclusion: CGM has similar effectiveness in subjects with type 1 diabetes using either CSII or MDI.

Introduction

USE OF CONTINUOUS glucose monitoring (CGM) has been demonstrated to improve glucose control in a wide range of patient populations.^{1–11} However, there remains a common misconception that CGM is primarily indicated for subjects who are using continuous subcutaneous insulin infusion (CSII) and that it might not be indicated in subjects who are using multiple daily injections of insulin (MDI). The effect of CGM on glycemic variability per se has been less studied^{9–11} despite the numerous clinical and preclinical studies suggesting a linkage between glycemic variability and development of diabetes complications.^{12–17}

Garg and Jovanovic² demonstrated the beneficial effects of CGM in 85 patients with type 1 and type 2 diabetes using either CGM or MDI. We have recently reanalyzed the subset of data from 64 of those subjects with type 1 diabetes and 17 subjects with type 2 diabetes, using 20 criteria for quality of glycemic control and 28 criteria for glycemic variability, in-

cluding several new criteria.⁹ We found highly statistically significant benefits of CGM, with many criteria showing statistical significance conservatively at the level of $P < 0.0001$. The present study was undertaken to examine the question whether CGM with real-time display had similar effectiveness in subjects with type 1 diabetes who use CSII (insulin pump) and those who use MDI. We reanalyzed the data² using newly developed and improved methodologies involving multiple criteria for quality of glycemic control and glycemic variability.

Portions of this study were presented as a late breaking poster at the 69th Annual Scientific Sessions of the American Diabetes Association, New Orleans, LA, June 5–9, 2009.¹⁸

Methods

The characteristics of the patient population and the experimental design have been described previously.² The study involved 64 subjects with type 1 diabetes studied at five

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clinical centers within the United States. Subjects younger than 18 years of age and pregnant or lactating women were not eligible. Institutional Review Board approval and informed consent were obtained in all cases. Subjects were provided with a DexCom (San Diego, CA) SEVEN[®] sensor, transmitter, and receiver for a 3-week period. Display of the glucose sensor results was masked during Week 1 but made available ad libitum on demand during Weeks 2 and 3. Sensors were changed weekly. The subjects were presented with a brief review of the principles of diabetes self-management immediately prior to commencing the study. Subjects were allowed to use the CGM data as they thought appropriate; no specific algorithm or instructions were provided. No other changes were made in patient management.

Subject characteristics

Table 1 summarizes characteristics of the study population.² For subjects with type 1 diabetes mellitus, there were no statistically significant differences between the MDI and CSII groups with respect to any of these eight characteristics using an unpaired two-sided Student's *t* test ($P > 0.05$). The study population was 58.7% women and 89.5% Caucasian, 10% Hispanic. Among subjects using MDI, 52.0% were female, 77.7% were Caucasian, and 7.4% were Hispanic. Among subjects using CSII, 61.5% were female, 100% were Caucasian, and 11.6% were Hispanic.

CGM

Subjects used a sensor for three consecutive 1-week periods as described previously.² Sensor readings were masked dur-

ing Week 1 but displayed during Weeks 2 and 3. Data were downloaded from the sensor devices on a weekly basis. We compared the properties of the glucose time series for Week 1 (CGM sensor masked) and Week 3 (CGM sensor unmasked) within subjects.

Criteria for quality of glycemic control and glycemic variability

We computed 16 criteria for quality of glucose control^{19–26} and 8 criteria for glycemic variability (Table 2), including several new methods.^{22,23} The number of criteria was reduced from 49 to 24 to reduce the problems associated with multiple comparisons, using the most sensitive criteria as identified in our previous studies,⁹ so as to reduce redundancy, and avoid use of criteria that are relatively difficult to interpret.

Measures of quality of glucose control. These included the mean of all glucose values (all days, all times of day), designated Mean $\bar{T}$, percentage of glucose values within three specified target ranges (80–200 mg/dL, 80–140 mg/dL, 70–180 mg/dL), percentage in the hypoglycemic range (below 50 or 80 mg/dL), percentage in the hyperglycemic range (above 180 or 250 mg/dL),² Schlichtkrull's M_{100} ,¹⁹ Wojcicki's J index,²⁰ Kovatchev's Low Blood Glucose Index (LBGI) and High Blood Glucose Index (HBGI),²¹ Rodbard's Index of Glycemic Control (IGC),^{22,23} and Hill's GRADE score.²⁴ (The adjustable parameters for the IGC were set as follows: a target range of 80–140 mg/dL [LLTR = 80, ULTR = 140]; exponent for excursions above ULTR $a = 1.1$; exponent for excursions below LLTR $b = 2.0$; linear scaling factors: $c = d = 30$.^{22,23})

TABLE 1. CHARACTERISTICS OF 81 STUDY SUBJECTS WITH TYPE 1 DIABETES MELLITUS USING CSII OR MDI

	Mean	SD	SEM	Minimum	Maximum
Age (years)					
CSII	42.9	13.4	2.1	20.2	68.4
MDI	36.9	12.7	2.5	19.8	70.0
Duration of diabetes (years)					
CSII	21.9	13.2	2.1	4.0	49.0
MDI	17.0	11.4	2.3	4.0	50.0
Baseline A1C (%)					
CSII	7.3	0.77	0.1	5.8	9.2
MDI	7.9	1.33	0.3	5.9	11.5
Mean CGM glucose during Week 1 (mg/dL)					
CSII	169.0	31.1	5.0	114.1	248.5
MDI	182.1	31.8	6.2	112.8	238.3
Height (cm)					
CSII	169.7	9.8	1.6	137.2	189.8
MDI	171.8	12.6	2.5	147.3	196.2
Weight (kg)					
CSII	75.8	16.3	2.7	54.5	124.4
MDI	82.3	21.8	4.4	54.9	159.0
BMI (kg/m ²)					
CSII	26.2	4.3	0.7	19.3	36.4
MDI	27.8	5.9	1.2	20.1	41.5
SMBG frequency (per day)					
CSII	5.9	1.9	0.3	3.0	10.0
MDI	5.5	2.4	0.5	2.0	10.0

There were no statistically significant differences between the two groups of subjects in any of these eight parameters as evaluated by an unpaired *t* test ($P > 0.05$, difference not significant). BMI, body mass index; ISF, interstitial fluid; SMBG, self-monitoring of blood glucose.

TABLE 2. CHANGES IN MEASURES OF QUALITY OF GLUCOSE CONTROL AND GLYCEMIC VARIABILITY IN RESPONSE TO DISPLAY OF CGM

Column 1: measure	CSII and MDI combined (n = 64)				CSII (n = 38)			MDI (n = 26)		
	Column 2:	Column 3:	Column 4:	P	Column 5:	Column 6:	Column 7:	Column 8:	Column 9:	Column 10:
	mean	SEM	SEM		mean	SEM	P	mean	SEM	P
A. Quality of glucose control										
Mean _T	5.67%	1.97%	0.00274		4.07%	2.50%		7.86%	3.19%	*
M ₁₀₀	18.48%	5.81%	0.00114		17.35%	7.60%	*	19.81%	8.85%	*
I Index	8.88%	3.84%	0.01208		7.07%	4.98%		11.20%	6.00%	*
% 80–200 mg/dL	12.64%	3.17%	0.00009		12.57%	3.65%	***	12.76%	5.65%	*
% 70–180 mg/dL	14.54%	3.61%	0.00008		12.96%	4.14%	**	17.16%	6.61%	**
% 80–140 mg/dL	18.17%	4.87%	0.00020		17.42%	5.68%	**	19.42%	8.76%	*
IGC	19.64%	3.82%	<0.00001		23.13%	4.62%	***	14.59%	6.45%	*
GRADE	12.70%	3.63%	0.00044		12.16%	4.53%	**	13.39%	5.87%	*
% <50 mg/dL	37.88%	8.97%	0.00004		52.34%	7.70%	***	7.20%	22.79%	
% <80 mg/dL	6.10%	8.14%	0.22806		15.35%	8.34%	*	−10.39%	17.33%	
LBGI	10.69%	7.70%	0.08495		21.16%	7.38%	**	−8.95%	17.52%	
Hypoglycemia Index	28.28%	6.72%	0.00004		37.96%	6.76%	***	8.56%	15.30%	**
% >180 mg/dL	16.32%	4.77%	0.00055		14.48%	6.23%	*	18.56%	7.32%	
% >250 mg/dL	20.84%	8.88%	0.01107		21.70%	11.28%	*	19.85%	13.90%	
HBGI	16.69%	5.53%	0.00183		14.88%	7.17%	*	18.83%	8.52%	*
Hyperglycemia Index	17.14%	5.80%	0.00221		15.08%	7.81%	*	19.57%	8.63%	*
B. Glycemic variability										
SD _T	6.16%	2.53%	0.00889		4.67%	3.33%		8.21%	3.95%	*
MAGE	6.82%	2.63%	0.00596		4.61%	3.66%		9.81%	3.79%	**
MODDAVE	9.80%	3.04%	0.00102		7.55%	4.16%	*	12.91%	4.47%	**
CONGA ₂₄	5.32%	2.79%	0.03075		4.18%	3.62%		6.87%	4.49%	
SD _{dm}	19.68%	4.66%	0.00004		20.17%	6.18%	**	18.95%	7.22%	**
SD _b	7.39%	2.79%	0.00513		7.59%	3.65%	*	7.10%	4.42%	
SD _{hh:mm}	10.53%	3.98%	0.04202		8.95%	4.85%	*	12.48%	6.44%	*
SD _{b/l/dm}	4.90%	2.79%	0.04202		3.00%	3.60%		7.51%	4.50%	

Results are shown for the combined group of subjects ($n = 64$) (columns 2–4) including those using either CSII or MDI and for the CSII group (columns 5–7) and MDI group (columns 8–10) individually. There were no statistically significant differences between the two groups of subjects (using CSII or MDI) with respect to any one of these characteristics considered individually.

Levels of statistical significance for the comparisons of Week 1 (masked) and Week 3 (unmasked) for both patient groups combined (CSII and MDI) are shown in column 4: values in bold font are significant prior to applying the Bonferroni correction; values in bold font that are underlined are significant even when using the (overconservative) Bonferroni correction with a correction factor of 24. Even the presence of a single significant (underlined) value implies that the two sets of observations (before and after use of unmasked CGM) are statistically significantly different.

Columns 7 and 10 summarize P values for paired t tests within individual subjects for single criteria without the Bonferroni correction: * denotes < 0.05 , ** denotes < 0.01 , *** denotes < 0.001 .

Measures of glycemic variability. These included three “classical” measures: mean amplitude of glycemic excursion (MAGE),²⁶ mean of daily differences (MODD),²⁶ and the overall or “total” SD (SD_T).^{9,22,23} MODD was originally defined only for a 2-day series,²⁶ so it must be generalized to apply to a multiday series. $MODD_{AVE}$ is the average of MODD obtained by the original method of calculation for all consecutive pairs of days for any subject.^{22,23} We also examined several new types of SD values, including the SD of daily means (SD_{dm}), the SD between days–within time points (SD_b), the SD between days–within time points after correction for changes in daily means ($SD_{b//dm}$), the SD between time points ($SD_{hh:mm}$), and the SD within days (SD_w).^{21,22} We also examined CONGA₂₄.²⁵ Computations were performed using SAS (Cary, NC) software and using a dedicated software program for the calculation of MAGE. An Excel (Microsoft, Redmond, WA) spreadsheet was also developed for computation of the several types of SD (SD_T , SD_{dm} , SD_b , $SD_{b//dm}$, SD_w , $SD_{hh:mm}$) (cf. the supplementary online appendix to Rodbard²³). Interrelationships among these measures are discussed elsewhere.^{22,23}

Hypothesis testing

We first examined the effects of CGM on the entire group of 64 subjects with type 1 diabetes, pooling the data from subjects using CSII and MDI. Comparisons between time periods (Week 1 vs. Week 3) were made using paired *t* tests so that each subject could be used as his or her own control. The mean relative percentage improvement in all 24 criteria, in the 16 criteria for quality of glycemic control, and in the eight criteria for glycemic variability were tested versus the null hypothesis using a one-sided *t* test for the CSII and MDI groups separately. Improvement corresponded to an *increase* in the percentage of glucose values within a specified target range (80–200, 70–180, or 80–140 mg/dL) or a *decrease* in any of the other 21 criteria. The percentage improvement in the mean value of each criterion during Week 3 (within subjects) was calculated as the mean change in each parameter expressed as a percentage of the mean value during the control period (Week 1).

We then evaluated the CSII and MDI groups separately and evaluated the difference in magnitude of responses to CGM using two-sided unpaired *t* tests. The mean percentage improvement for the 24, 16, or eight criteria in the CSII and MDI groups was compared using a two-sided *t* test. After demonstrating that the CSII and MDI groups combined showed a statistically significant change in response to use of CGM, we then tested each of the 24 criteria individually in both groups of subjects. A one-sided *t* test was used when the direction of the change could be predicted a priori. Results are presented as *P* values before application of a Bonferroni correction to compensate for the use of multiple comparisons. In view of the high degree of correlation of the parameters (cf. the supplementary online appendix for Rodbard et al.⁹), the Bonferroni correction is extremely overconservative.

We examined the relationships of changes in criteria between Week 1 and Week 3 to the baseline hemoglobin A1c (A1C). We performed tests to evaluate whether the regression lines for the MDI and CSII groups were compatible by: (a) fitting least-squares regression lines to the two groups separately (involving four parameters, i.e., two slopes and two

intercepts); (b) fitting another regression line after pooling the data from the two groups, involving two parameters, i.e., one slope and one intercept; and (c) comparing the residual sum of squares using an *F* test based on the extra-sum of squares principle.

Results

Table 2 shows comparisons of Week 3 (CGM values unmasked) with Week 1 (masked), for subjects using CSII and for subjects using MDI. When all subjects with are considered simultaneously (combining the MDI and CSII groups), 22 of the 24 criteria were significantly improved after unmasking of the real time display of CGM data, including 14 of 16 criteria for quality of glycemic control and all eight criteria for glycemic variability. When the 38 subjects using CSII are considered, 18 of 24 criteria showed statistically significant improvement; when the 26 subjects using MDI are considered, 16 of 24 criteria improved significantly ($P < 0.05$) between Week 1 and Week 3. There were no statistically significant differences in the percentage improvement observed between Week 1 (masked) and Week 3 (unmasked) for any of the 24 criteria between the MDI and CSII groups, whether one considers each criterion individually, the mean percentage improvement for all 24 criteria, the 16 criteria for quality of glycemic control, or the eight criteria for glycemic variability.

Figure 1 displays the percentage improvement in glucose values in Week 3 relative to Week 1 for 16 criteria—eight reflecting quality of glycemic control and eight reflecting glycemic variability—using each subject as his or her own control, i.e., using a paired analysis within subjects.

We examined the relationships between the changes in response to unmasking of CGM measured for each subject and the subject’s baseline A1C level. There was a statistically significant linear relationship for several parameters. Figure 2 shows a representative example for one criterion, the GRADE score. The magnitude of the benefit derived from unmasking of real-time display of CGM appeared to be linearly related to the baseline A1C. There were no statistically significant differences in the regression lines for the CSII and MDI patient groups. Similar results were observed for all criteria examined (see Supplementary Appendix at www.liebertonline.com/dia). Subjects with elevated baseline A1C values showed the greatest benefit in measures of hyperglycemia, euglycemia, and overall quality of glycemic control. In contrast, for subjects whose baseline A1Cs were close to the target levels of 6.5–7 % at baseline, unmasking of CGM for the brief time frame of only 2 weeks resulted in little or no benefit in terms of measures of hyperglycemia and euglycemia. However, this group (with A1C 6.5–7%) showed the greatest improvement in four measures of hypoglycemia (percentage of glucose values below 80 mg/dL, percentage of glucose values below 50 mg/dL, LBG, and Hypoglycemia Index).

Numerous criteria for evaluation of glycemic control and glycemic variability have been proposed previously. It is not evident a priori which measure or measures are most important and clinically relevant. Accordingly, we have examined the majority of the available measures to identify the ones that are most sensitive to the effect of this particular therapeutic intervention.

FIG. 1. Responses to display of CGM (± 1 SEM) expressed as percentage improvement between Week 1 and Week 3 for measures of (A) quality of glycemic control and (B) glycemic variability. Responses for subjects using CSII are shown in open columns; responses for subjects using MDI are shown in shaded columns. (A) Measures of quality of glycemic control: Mean_T, mean of glucose for all days and all times of day; M₁₀₀, Schlichtkrull's M with a reference value of 100 mg/dL; J Index; IGC (Rodbard's Index of Glycemic Control^{22,23}); GRADE (GRADE score of Hill et al.²⁴); and percentage of glucose values within three specified target ranges. (B) Measures of glycemic variability: MAGE, MODD, CONGA₂₄, SD_T, SD_{dm}, SD_b, SD_{b//dm}, and SD_{hh:mm}.

Measures of quality of glucose control

We first tested whether there was an effect of CGM when the CSII and MDI groups are combined for each of the individual criteria. A significant effect was seen in 14 of 16 criteria at the nominal P value of $P < 0.05$ (Table 2A, column 4). We applied an extremely conservative Bonferroni correction for multiple comparisons, using a factor of 24—the total number of criteria examined in the present study, such that a P value of $0.05/24 = 0.0021$ is required to achieve statistical significance. Ten of the 16 comparisons remained significant and are shown in bold underlined font in column 4 of Table 2A. **M₁₀₀**,

J, HBGI, LBG, IGC, and GRADE improved for the combined group of subjects (CSII and MDI).

Having established the presence of a significant change in response to CGM for the entire group, we then analyzed the CSII and MDI groups separately (Table 2A, columns 5–7 and 8–10, respectively). A similar effect was seen in both the CSII and MDI groups of subjects, with 14 and 11 of the 24 criteria significant at the nominal $P < 0.05$ level without use of the Bonferroni correction. Because of the smaller sample sizes (38 and 26 for the CSII and MDI groups, respectively), the effect of CGM was not statistically significant within either of these subgroups after applying the Bonferroni correction. The

FIG. 2. Relationship of change in one criterion of overall quality of glycemic control, GRADE, versus baseline A1C. Regression lines are shown for the groups of subjects using MDI (solid squares, dashed line), CSII (open circles, thin line), and for both groups combined (heavy line).

percentage of glucose values in the target ranges 80–200, 70–180, and 80–140 mg/dL improved for subjects using either CSII or MDI. The mean glucose (Mean_T) improved significantly ($P < 0.05$) for the MDI group but not in the CSII group. Three criteria for hypoglycemia (LBGI, Hypoglycemia Index, and percentage < 50 mg/dL) improved significantly in the CSII group but not in the MDI group. CGM resulted in an increase in glucose values in the range 50–80 mg/dL but a decrease in percentage of values below 50 mg/dL in the MDI group, corresponding to a reduction in severe hypoglycemia but an increase in moderate degrees of hypoglycemia. This was reflected in discordance in the responses for LBGI and Hypoglycemia Index, which are highly correlated with percentage of glucose values below 80 mg/dL and 50 mg/dL, respectively. The results for IGC also reflect the changes in the Hypoglycemia Index. There is an excellent correlation ($r = +0.88$) between the percentage improvement in 12 criteria for the CSII and MDI groups, when the four criteria for hypoglycemia are excluded (cf. Figure A17 of the Supplementary Appendix at www.liebertonline.com/dia).

Measures of glycemic variability

When one combines results from subjects using CSII and MDI, then all eight criteria for glycemic variability are improved at the nominal $P < 0.05$ level (Table 2B, column 4). After application of the Bonferroni correction using a factor of 24, two criteria, MODD_{AVE} and SD_{dm} , remain significant at the $P < 0.05$ level, indicating a reduction in day-to-day vari-

ability. If we examine the mean relative percentage improvement in all eight criteria considered simultaneously, we find a statistically significant response ($P < 0.01$) in the subjects using either CSII or MDI (cf. Table A2 of Supplementary Appendix at www.liebertonline.com/dia). A t test comparing the CSII and MDI groups did not show any significant difference between groups. Further, there was a very high degree of correlation of the percentage improvement in each of the eight criteria for the CSII and MDI groups. The SD_{dm} decreased significantly in both groups. The total variability, as reflected in SD_T and MAGE, was significantly improved for MDI group but not in the CSII group. The between day-within time point variability (SD_b) improved by a nearly identical 7.59% and 7.10% for the CSII and MDI groups, respectively. However, partly due to the different number of subjects in the two groups, the change in the CSII group was significant at the $P < 0.05$ level, whereas the change in SD_b for the MDI group was not.

Discussion

Selection of criteria for responses to CGM

We utilize 16 measures of quality of glycemic control. Four of these are related to hyperglycemia (percentage of glucose values > 250 mg/dL, percentage > 180 mg/dL, HBGI, and Hyperglycemic Index). Four criteria are related to hypoglycemia (percentage of glucose values < 50 mg/dL, percentage < 80 mg/dL, LBGI, and Hypoglycemia Index). Three are related to “euglycemia” (percentage of glucose values within

80–200, 70–180, and 80–140 mg/dL). Five criteria are “general” indices, including Mean Glucose (M_T), M_{100} , J , IGC, and GRADE. We utilized eight measures of glycemic variability, including measures of total variability (SD_T), within-day variability (MAGE, $SD_{hh:mm}$), and between-day variability ($MODD_{AVE}$, SD_{dm} , SD_b , $SD_{b//dm}$, CONGA₂₄). The definitions, properties, and interrelationships among these measures are described elsewhere (Rodbard et al.⁹ and Rodbard²³). We also examined the responses to six additional criteria, which gave similar results.

Effectiveness of CGM in type 1 diabetes

Several previous studies have reported the effectiveness of CGM in subjects with type 1 diabetes using either CSII or MDI.^{1–11,18,27} Nevertheless, there is a popular misconception among many clinicians that CGM is indicated primarily for subjects using CSII or for subjects already in relatively good to excellent glycemic control. As a result, some health insurance companies have refused to provide reimbursement for CGM in subjects using MDI and for those subjects with relatively poor glycemic control. The present study was underpowered to detect effects in only the MDI or CSII subgroups of subjects. However, when we combine results from both groups, and when we combine results from the multiple (24) criteria, then the benefit of introducing unmasked CGM—without any other specific instructions to the patient as to how best to use the information—is highly statistically significant at the $P < 0.000001$ level. By use of a single comparison, we avoid the problem of multiple comparisons. The effects of CGM are evident in the majority of criteria when examined individually. Even after applying the excessively conservative Bonferroni correction, we find that several comparisons are significant at the $P < 0.05$ level. Thus, the effect of CGM can be clearly and unambiguously demonstrated in both the CSII and MDI groups. The effect of CGM is also evident when we examine individual criteria (Table 2) at the usual or nominal $P < 0.05$ level. However, when examining these criteria individually, the results would not be significant after applying the Bonferroni correction. (The 24 criteria are highly correlated so that one is not making 24 independent comparisons. Accordingly, the Bonferroni correction is overconservative. If all of the criteria were perfectly correlated, then the Bonferroni correction would not or should not be used—all criteria would be giving the same result. In the present data set, several of the criteria show correlations of 0.8–0.9 (cf. online supplementary materials associated with reference 9).

Similarity of response in subjects using CSII versus MDI

The present study (Table 2, Figs. 1 and 2, and Supplementary Appendix at www.liebertonline.com/dia) demonstrates that there are similar and statistically indistinguishable responses to CGM in groups of patients using CSII or MDI. This is true whether we examine each of the criteria individually or in groups of eight, 16, or 24 (see Supplementary Appendix at www.liebertonline.com/dia). The power to detect a difference increases as we use a composite response variable such as mean percentage improvement. The responses for subjects using CSII and MDI are very highly correlated for all eight measures of glycemic variability and for 12 of the 16 measures of quality of glycemic control. Only the four measures of hypoglycemia

display discordance between the results for patients using CSII and MDI. This finding deserves further examination in independent, longer-term studies and may depend on subject selection criteria and the set of instructions provided to the subjects regarding the recommended methods to respond to the information provided by CGM.

Relationship of response to baseline A1C

The recently reported Juvenile Diabetes Research Foundation study indicates the benefit of CGM in subjects with type 1 diabetes who are well controlled ($A1C < 7.0\%$).¹⁰ That study involved 62 patients using CSII and CGM, but only five of these were using MDI, so an analysis by treatment modality is not possible. Similarly, Danne et al.¹¹ have recently reported beneficial effects of CGM in 48 patients with type 1 diabetes, of whom 39 were using CSII and nine were using MDI. For this subject population, Danne et al.¹¹ reported no relationship of improvements in A1C or glucose SD with initial A1C when using a protocol involving 20 days with CGM masked followed by 40 days with CGM unmasked (see Fig. 1 of Danne et al.¹¹). Weinzimer et al.⁸ have also reported that CGM is effective in subjects using MDI.

In the present study, the availability of real-time display of CGM was equally efficacious in groups being treated with CSII or with MDI (Table 2, Fig. 1). The relationships of responses to baseline A1C were also indistinguishable in subjects using CSII or MDI (Fig. 2, and Supplementary Appendix at www.liebertonline.com/dia).

Experimental design

The present study uses the data as reported previously by Garg and Jovanovic.² Patients with type 1 diabetes were selected on the basis of their willingness to utilize CGM for a period of 3 weeks. They were not randomized to a treatment group of CSII or MDI. Hence, there is the possibility that the two groups might differ in terms of various aspects of their diabetes. We examined several characteristics of the two patient groups (Table 1) and did not find any statistically significant differences. However, these subjects might differ in their level of experience with self-management, motivation, education in terms of diabetes management, and ability and willingness to adjust insulin dosages. Although these differences did not reach statistical significance, subjects who use CSII tended to be older, have a longer duration of diabetes, a lower baseline A1C, and use self-monitoring of blood glucose more frequently than the subjects using MDI (Table 1). These and related factors may contribute to the subtle differences between groups, e.g., as related to frequency and severity of hypoglycemia. Accordingly, it would be desirable to repeat the present study, using randomization to assign subjects to CSII or MDI groups. Such an experimental design would entail many practical difficulties, as one would need to recruit subjects who were willing and able to use both CSII and MDI, preferably using a crossover experimental design.

Statistical methods

We have used a variety of statistical methods to examine a modest-sized dataset. We first confirmed the effect of CGM in the subset of subjects with type 1 diabetes using either CSII or MDI. (Our previous analyses of these data examined these

same subjects combined with 17 subjects with type 2 diabetes.^{9,27}) We were able to confirm the effect of CGM using individual criteria (Table 2) and using the Bonferroni correction. We then examined the effects of CGM separately for the CSII and MDI groups, using individual criteria (Table 2). Finally, we used the composite variables (percentage improvement) for eight, 16, or 24 criteria for CSII and MDI separately and compared the responses for the two groups using an unpaired *t* test (Tables A1, A2, and A3 of supplementary Appendix at www.libertonline.com/dia). The results obtained were remarkably consistent irrespective of the statistical methods used.

The present study provides new insights regarding the clinical utility of CGM with real-time display of glucose levels in subjects with diabetes and provides insights into the performance of both "classical" and recently described criteria for quality of glucose control and glycemic variability, in terms of their relative sensitivity for detection of changes in response to a therapeutic intervention, i.e., unmasking of CGM. These insights should be helpful in the design and analysis of future studies.

Conclusions

Subjects with type 1 diabetes showed significant improvement in 16 measures of quality of glycemic control and eight measures of glycemic variability in response to unmasking of real-time displays of CGM data irrespective of whether they were using CSII or MDI. There were no significant differences between the responses in the CSII and MDI groups for any of the 24 criteria examined. The magnitude of improvement was generally greater in subjects with a higher baseline A1C in this short-term study, with identical relationships for the CSII and MDI groups of subjects.

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