

Reduction in Hemoglobin A_{1c} with Real-Time Continuous Glucose Monitoring: Results from a 12-Week Observational Study

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ABSTRACT

Background: Real-time continuous glucose monitoring (CGM) was studied in 140 adults with diabetes over a 12-week period of home use. Hemoglobin A_{1c} (HbA_{1c}) was measured on day 1 (baseline) and at weeks 6 and 12.

Methods: On day 1, participants received the CGM device (STS[®] System, DexCom, Inc., San Diego, CA) and underwent training on proper use. Insertion of the first sensor was performed under staff supervision. Subjects inserted subsequent sensors on their own. After calibration, the device (a 3-day sensor, receiver, and transmitter) provided users with real-time glucose values updated at 5-min intervals, glucose trend graphs, configurable high/low alerts, and a hypoglycemia alarm (≤ 55 mg/dL). Study participants were given supplies sufficient for 3 weeks of device use. Follow-up visits were performed at 3-week intervals for resupply and to download CGM data, with a final visit at the end of week 12.

Results: Overall, a reduction in HbA_{1c} of $0.4 \pm 0.05\%$ (least squares mean \pm SE) was observed, $P < 0.0001$. Significant HbA_{1c} reductions were observed across subgroups of subjects with both type 1 and 2 diabetes, and those delivering insulin by multiple daily injections and pumps. The largest HbA_{1c} reduction ($1.4 \pm 0.4\%$) was observed in subjects with baseline HbA_{1c} $> 9.0\%$. Increased CGM use was associated with greater reductions in HbA_{1c}.

Conclusions: This observational study showed that home use of real-time GCM was safe and well tolerated and associated with a clinically and statistically significant reduction in HbA_{1c}. Large-scale randomized, controlled outcome studies of CGM are indicated.

INTRODUCTION

IMPROVEMENT IN METABOLIC CONTROL, as measured by reductions in hemoglobin A_{1c} (HbA_{1c}), has been shown to decrease the inci-

dence and progression of both micro- and macrovascular complications of diabetes.¹⁻⁵ In the Diabetes Control and Complications Trial (DCCT), intensive insulin therapy significantly reduced retinopathy (47–76%), microalbumin-

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uria (39%), albuminuria (54%), and neuropathy (60%). Further analysis of DCCT data suggests that HbA1c may not be responsible for all of the improvements seen in the intensively treated group, and the authors went on to suggest that glucose excursions may play a role in the development of complications due to diabetes.⁵ It has also been suggested that glycemic control may be more appropriately expressed in terms of glucose variability in conjunction with HbA1c, rather than by HbA1c alone.⁶⁻⁸

Hypoglycemia is the main limiting factor in the glycemic management of insulin-treated diabetes subjects.⁹ In the DCCT, for instance, attempts to achieve near-normal glucose levels resulted in a 3.3-fold increase in the rate of severe hypoglycemia. Frequent self-monitoring of blood glucose (SMBG) is an integral part of intensive diabetes management that has been shown to improve glycemic control.¹⁰ Patients, however, dislike frequent SMBG because of the associated pain, inconvenience, and intrusive nature of SMBG. Recent availability of continuous glucose monitoring (CGM) devices has given patients the ability to view real-time glucose values, to review trend graphs of recent glucose values, and to receive alarms/alerts of impending hypo- or hyperglycemia. Preliminary clinical evidence suggests that use of continuous glucose data results in reductions in HbA1c.¹¹⁻¹⁹ Most of these studies, however, have relied upon retrospective review of CGM data to modify therapy^{12,15,16,20} or enrolled only pediatric subjects.^{13,14,17,18,21,22}

Two previously published studies involving a 3-day²³ and 7-day²⁴ CGM device (STS[®] System, DexCom, Inc., San Diego, CA) that provides continuous glucose values, trends, and alerts to users in real-time showed significant improvements in the proportion of time spent in target range glycemia coupled with significant reductions in the proportion of time spent both hyper- and hypoglycemic. Herein, we report the results of a study involving the use of the 3-day version of this real-time CGM device by adult subjects with type 1 and type 2 diabetes mellitus. Metabolic control, as measured by HbA1c, was assessed at baseline, at 6 weeks, and at the conclusion of this 12-week study.

SUBJECTS AND METHODS

Study population

One hundred forty subjects were enrolled in this multicenter U.S. study. Individuals younger than 18 years old and those who were pregnant or lactating or with a contraindication to using the CGM (known allergy to medical adhesives or dermatological conditions that would preclude wearing sensors on unaffected skin) were excluded. The protocol was approved by the Institutional Review Boards of all centers, and all subjects provided witnessed, written informed consent prior to enrollment. Subjects were 45.4 ± 13.67 (mean \pm SD) years old, and 64 (45.7%) were men. Subjects had a diagnosis of diabetes for 20.2 ± 11.38 years; 109 (77.9%) had type 1 diabetes, and 31 (22.1%) had type 2 diabetes. Fifty-eight (41.4%) delivered insulin via multiple daily injections (MDI), 75 (53.6%) were on continuous subcutaneous insulin infusion (CSII) pumps, and seven (5.0%) were treated with oral agents only. Height was 169.7 ± 9.4 cm, weight was 82.0 ± 21.6 kg, and body mass index was 28.4 ± 6.8 kg/m². At baseline, subjects reported performing SMBG 5.0 ± 2.6 times per day and had a mean HbA1c of $7.6 \pm 1.2\%$.

Procedures

Real-time CGM with the STS System was studied in adults with diabetes over a 12-week period of home use. HbA1c was measured on day 1 (baseline) and at weeks 6 and 12. Measurement of HbA1c was performed per routine at each enrolling center; no core laboratory was used. On study day 1, participants received the CGM device and underwent training on proper use. Insertion of the first sensor was performed under staff supervision. Subjects inserted subsequent sensors on their own at home. Study participants were given supplies sufficient for 3 weeks of device use. Throughout the study, subjects were instructed to use CGM data as an adjunct to, and not as a replacement for, SMBG fingersticks when making diabetes-related treatment decisions (e.g., insulin dose modifications). Follow-up visits were performed at 3-week intervals for resupply of device-related

materials, to document interval adverse events, and to download CGM data. The final study visit occurred at the end of week 12.

Sensor and transmitter

The STS Sensor consists of an applicator, sensor probe, and transmitter housing as previously described.^{23,24} The applicator is a single-use disposable unit that houses the introducer needle and the sensor probe contained within it. The transmitter housing was adhered to the patient's abdomen, and the needle (containing the sensor probe) was then inserted into the subcutaneous tissue of the abdomen. The needle was retracted, and the applicator was removed, leaving the sensor probe within the subcutaneous tissue. After the transmitter was installed, an averaged glucose signal was wirelessly sent to the receiver via low-powered radiofrequency at 5-min intervals.

Receiver

The STS Receiver is an externally worn pager-sized device. For the purposes of this study, the receiver used uploaded SMBG meter values for calibration (i.e., to convert the glucose signal measured by the sensor into a user-viewable glucose concentration). Two hours after the sensor was first inserted, two SMBG values were uploaded for calibration. Thereafter, patients were instructed to upload at least one SMBG value every 12 h. Once calibrated, the receiver displayed a glucose value that was updated at 5-min intervals. The receiver also displayed glucose trend graphs of the preceding 1, 3, or 9 h and generated high and low glucose alerts and alarms. In this study, subjects were allowed to modify the high glucose alert (range 140–400 mg/dL in increments of 20 mg/dL, or no high alert) as well as the low glucose alert (60–90 mg/dL in increments of 10 mg/dL, or no low alert). A non-modifiable hypoglycemia alarm was triggered at glucose levels ≤ 55 mg/dL.

Statistical analysis

Analyses of HbA1c change from baseline were performed using SAS[®] Software, version

9.1.3 (SAS Institute, Inc., Cary, NC). All statistical comparisons were conducted at the $\alpha = 0.05$ level of significance using two-tailed tests, unless otherwise stated. The P values for HbA1c reductions were calculated using a linear mixed model using the change in HbA1c from baseline as the dependent variable, baseline HbA1c as a covariate, week of measurement as an independent variable, subject as a random effect, and an unstructured covariance model. For exploratory analyses of CGM use relative to HbA1c reduction, the bottom quartile and top quartile of each distribution assessed (1-, 3-, and 9-h trend screen views, and all trend screen views combined) were compared using a two-sample t test of means, using a two-tailed alternative hypothesis at an α level of 0.05.

RESULTS

HbA1c change from baseline

The mean \pm SD number of sensors used per subject over the 12-week study was 23.8 ± 7.8 (approximately two sensors per week). Results of observed HbA1c reductions are presented in Table 1. Over 12 weeks, the overall cohort reduced HbA1c by $0.4 \pm 0.05\%$ ($P < 0.0001$). A reduction in HbA1c relative to baseline was observed in all evaluated subgroups and was statistically significant in all but two subgroups. Table 1 also shows that most of the reduction in HbA1c took place during the first 6 weeks after enrollment, and was sustained through the end of week 12. Both subgroups with baseline HbA1c above target American Diabetes Association values of 7.0% reduced their 12-week HbA1c. Subjects with baseline levels 7.0–9.0% lowered their HbA1c by $0.5 \pm 0.06\%$ (Fig. 1 shows an individual case sample), and those with baseline HbA1c $>9.0\%$ experienced a reduction of $1.4 \pm 0.4\%$.

An exploratory analysis of the relationship between the amount of CGM attention and the magnitude of HbA1c reduction was performed. For all subjects, CGM attention was quantified by calculating the average number of glucose trend screen views (1-h, 3-h, 9-h, and all three combined) performed per day. Sub-

TABLE 1. LEAST SQUARES MEAN \pm SE FOR HbA1c VALUES AND CHANGE FROM BASELINE AT 6 WEEKS AND 12 WEEKS: OVERALL AND IN VARIOUS SUBGROUPS

Subgroup	Number	Week	HbA1c (%) (least squares mean \pm SE)		P value ^a
			Value	Change from baseline	
Overall ^b	139	0	7.6 \pm 1.2		
		6	7.2 \pm 0.9	-0.4 \pm 0.5	<0.0001
		12	7.2 \pm 1.0	-0.4 \pm 0.5	<0.0001
Diabetes type	109	0	7.5 \pm 1.0		
		6	7.2 \pm 0.7	-0.3 \pm 0.05	<0.0001
		12	7.1 \pm 1.0	-0.4 \pm 0.05	<0.0001
Type 1	30	0	7.8 \pm 1.6		
		6	7.3 \pm 1.4	-0.5 \pm 0.1	0.0016
		12	7.2 \pm 1.2	-0.6 \pm 0.1	0.0004
Diabetes therapy	57	0	7.8 \pm 1.4		
		6	7.4 \pm 0.8	-0.4 \pm 0.09	<0.0001
		12	7.3 \pm 1.1	-0.5 \pm 0.09	<0.0001
MDI insulin	75	0	7.4 \pm 0.9		
		6	7.1 \pm 0.9	-0.3 \pm 0.06	<0.0001
		12	7.1 \pm 0.8	-0.3 \pm 0.06	<0.0001
CSII insulin	7	0	7.0 \pm 1.5		
		6	6.8 \pm 1.5	-0.2 \pm 0.1	0.3346
		12	6.8 \pm 1.6	-0.2 \pm 0.1	0.2115
Oral agents (no insulin)	46	0	6.4 \pm 0.3		
		6	6.3 \pm 0.4	-0.1 \pm 0.06	0.0212
		12	6.4 \pm 0.5	-0.05 \pm 0.06	0.3644
Baseline HbA1c <7.0%	78	0	7.8 \pm 0.6		
		6	7.4 \pm 0.6	-0.4 \pm 0.06	<0.0001
		12	7.3 \pm 0.7	-0.5 \pm 0.06	<0.0001
7.0–9.0%	15	0	10.0 \pm 0.7		
		6	9.0 \pm 1.3	-1.0 \pm 0.4	0.0174
		12	8.6 \pm 1.6	-1.4 \pm 0.4	0.0026

^aFor change from baseline.

^bA total of 140 subjects were enrolled; one subject did not have a measured baseline HbA1c.

jects in the top quartile of CGM attention by this measure were compared to those who fell in the bottom quartile. Table 2 shows that, in all cases, the top quartile of CMG users (in terms of frequency of trend screen views) experienced a greater reduction in 12-week HbA1c than those in the bottom quartile ($P < 0.05$ for each comparison).

Safety evaluation

Over the 12-week duration of this study, 41 adverse events were reported for 35 subjects (25.0%). Five hypoglycemic events requiring third-party assistance were experienced by four subjects; three were considered “not related” to the CGM device, and two were

deemed “probably not related” by site investigators. In four of the five instances of hypoglycemia requiring assistance, CGM provided the user with low glucose alerts and alarms; the CGM system was not in calibration during the remaining episode. Overall, four adverse events were considered “probably related” to the CGM device: two were episodes of bleeding, one was erythema at a sensor insertion site, and one was edema at the sensor insertion site. All five of these device-related events were rated as “mild” in severity and resolved without treatment.

In terms of safety, it is also noteworthy that subjects did not increase the amount of time spent hypoglycemic (<70 mg/dL) during study participation. The amount of time spent

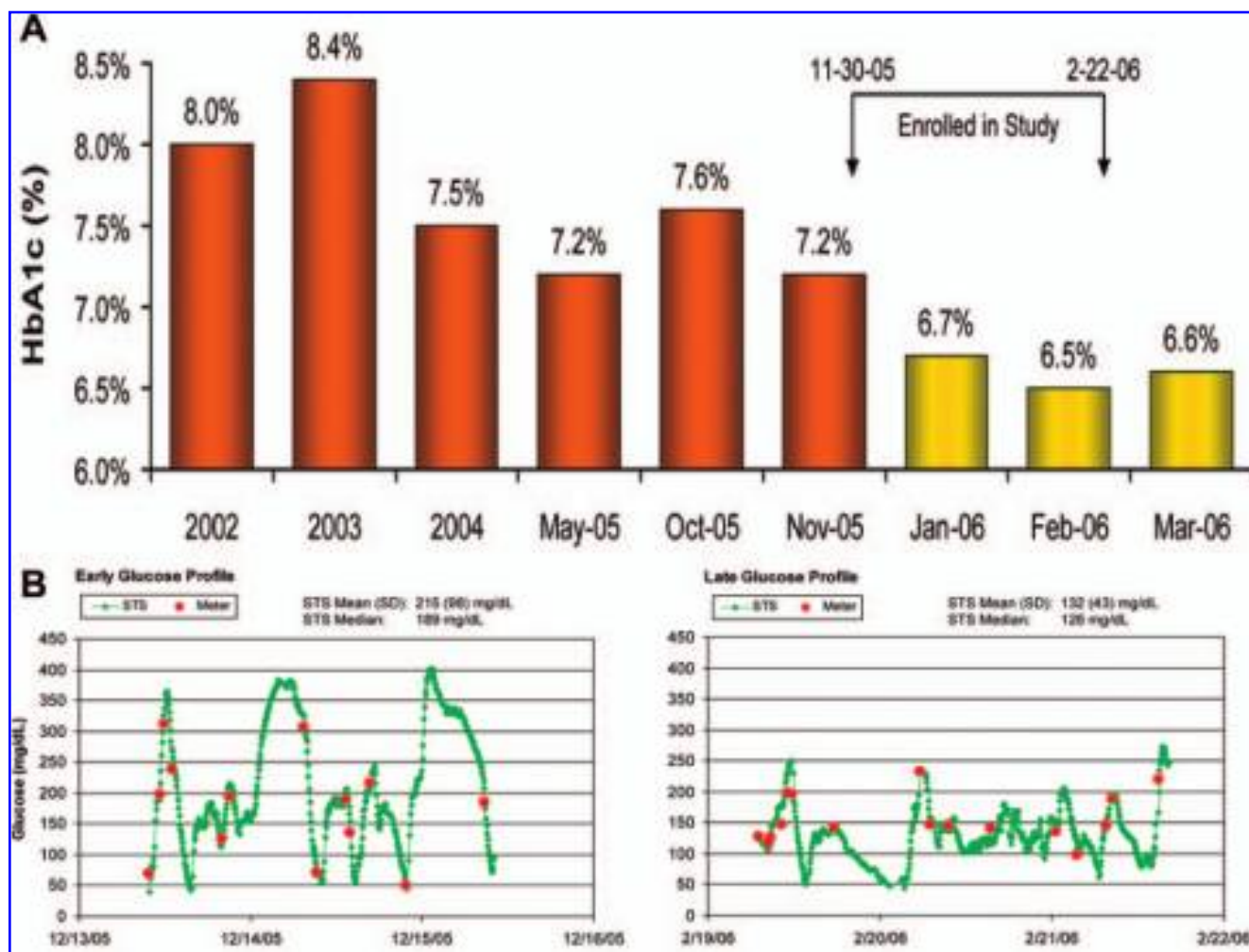


FIG. 1. Sample case. The subject was a 22-year-old woman with a history of type 1 diabetes (for 11 years) on CSII therapy (for 10 years) with no complications due to diabetes. Despite meticulous attention to her diabetes management and a strong support system, she had been unable to attain target HbA1c [her levels varied from 7.2% to 8.4% since 2002 (see HbA1c vs. time, A)]. This subject used 20 sensors during the 12-week study duration, from November 30, 2005 to February 22, 2006. (B) Glucose versus time profiles from early and late periods of study participation. The subject's end-study HbA1c was 6.6%.

TABLE 2. COMPARISON OF BOTTOM AND TOP QUARTILES OF CGM ATTENTION AND HbA1c REDUCTION AT 12 WEEKS

	Bottom quartile (n = 32)	Top quartile (n = 31)	P value
1-h trend screen views per day	9.8 ± 2.7	37.7 ± 11.3	<0.001
HbA1c change at 12 weeks (%)	-0.11 ± 0.61	-0.61 ± 0.76	0.008
3-h trend screen views per day	1.4 ± 0.7	5.8 ± 3.0	<0.001
HbA1c change at 12 weeks (%)	-0.23 ± 0.66	-0.84 ± 0.93	0.006
9-h trend screen views per day	0.9 ± 0.4	3.7 ± 2.3	<0.001
HbA1c change at 12 weeks (%)	-0.19 ± 0.49	-0.78 ± 0.94	0.004
All trend screen views per day ^a	12.2 ± 3.3	47.2 ± 13.4	<0.001
HbA1c change at 12 weeks (%)	-0.08 ± 0.58	-0.61 ± 0.75	0.004

Data are mean ± SD values.

^aCombined number of trend screen views (1-, 3-, and 9-h) per day.

<70 mg/dL for all study subjects was calculated from CGM data during study weeks 1, 6, and 12. This analysis showed that subjects spent a median (25th percentile, 75th percentile) of 1.94 (0.84, 2.95), 1.90 (0.89, 2.97), and 1.50 (0.70, 2.60) h/day <70 mg/dL during weeks 1, 6, and 12, respectively.

CONCLUSIONS

This observational study showed an improvement in metabolic control in adults using real-time CGM at 6 weeks that was sustained at 12 weeks. Earlier reports were either on retrospective CGM systems or involved pediatric subjects using real-time CGM.^{12–18,20–22} From the most recently published data of real-time CGM use in children,²⁵ the DirecNet Study Group concluded that, while the point accuracy of CGM does not yet equal that of SMBG meters, the technology has the potential to be an important adjunct to the management of youth with type 1 diabetes.

In terms of metabolic control, Deiss et al.¹⁹ recently reported an improvement in HbA1c in both adults and children who used real-time CGM over a 3-month period. In that study, however, all subjects had type 1 diabetes and had a baseline HbA1c $\geq 8.1\%$. The present study enrolled subjects with both type 1 and type 2 diabetes who had a broader range of metabolic control at baseline. Results (Table 1) indicate that individuals with type 2 diabetes experienced a significant HbA1c reduction, and subjects with baseline HbA1c in the range of 7.0–9.0% also benefited. The hypoglycemia exposure analysis showed that the overall cohort did not increase time spent <70 mg/dL across the 12 weeks of this study. Hence, the observed reductions in HbA1c were obtained without an increased risk of hypoglycemia. This observation is supported by previous studies^{23,24} that showed improved glycemic control can be accomplished with real-time CGM while significantly reducing hypoglycemic exposure. Most of the observed HbA1c reduction took place within the first 6 weeks of this study, which again is in keeping with prior studies by Garg et al.²³ and Garg and Jovanovic,²⁴ which showed that

improvements in glycemic control were realized within 6 days²³ or 14 days²⁴ of access to real-time CGM data.

Subjects using both MDI and CSII experienced statistically significant reductions in HbA1c. This indicates that use of an insulin pump is not required to derive benefit from real-time CGM. Subjects with baseline HbA1c >9% experienced the greatest reduction in HbA1c ($1.4 \pm 0.4\%$), thereby demonstrating that individuals with poor metabolic control can benefit from real-time CGM. These results indicate that use of real-time CGM need not be restricted to intensively managed patients on CSII therapy. This study's finding that subjects with higher baseline HbA1c experienced a greater reduction in HbA1c is consistent with the pattern previously described by Tsui et al.²⁶

The primary limitation of this study is the fact that it did not enroll a control group; therefore a causal link between CGM use and HbA1c reduction cannot be proven. Nevertheless, the results presented in Table 2 suggest a "dose-response" relationship between the two that provides evidence in favor of causality. These data show that subjects who used CGM more intensively, in terms of frequency of trend screen views, experienced significantly greater reductions in HbA1c relative to subjects falling in the bottom quartile of CGM use.

We feel that the results of this study show that real-time CGM has the potential to help a wide range of individuals with diabetes safely lower their HbA1c. This observational study forms a compelling basis for formal hypothesis testing in large-scale randomized, controlled clinical trials of real-time CGM.

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