Sustained Benefit of Continuous Glucose Monitoring on A1C, Glucose Profiles, and Hypoglycemia in Adults With Type 1 Diabetes

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OBJECTIVE — To evaluate long-term effects of continuous glucose monitoring (CGM) in intensively treated adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS — We studied 83 of 86 individuals ≥25 years of age with type 1 diabetes who used CGM as part of a 6-month randomized clinical trial in a subsequent 6-month extension study.

RESULTS — After 12 months, median CGM use was 6.8 days per week. Mean change in A1C level from baseline to 12 months was −0.4 ± 0.6% ($P < 0.001$) in subjects with baseline A1C ≥7.0%. A1C remained stable at 6.4% in those with baseline A1C <7.0%. The incidence rate of severe hypoglycemia was 21.8 and 7.1 events per 100 person-years in the first and last 6 months, respectively. Time per day with glucose levels in the range of 71–180 mg/dl increased significantly ($P = 0.02$) from baseline to 12 months.

CONCLUSIONS — In intensively treated adults with type 1 diabetes, CGM use and benefit can be sustained for 12 months.

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In a 6-month randomized trial of intensively treated individuals with type 1 diabetes and baseline A1C ≥7.0%, adults ≥25 years of age benefited from use of continuous glucose monitoring (CGM) compared with adults using conventional blood glucose monitoring (1). In a contemporaneous parallel study of individuals with type 1 diabetes who had A1C levels <7.0%, those in the CGM group had a reduction in biochemical hypoglycemia compared with those in the control group while maintaining A1C levels in the target range (2). This report describes the 12-month follow-up of adult subjects in the two randomized trials' CGM groups.

RESEARCH DESIGN AND METHODS

— The protocol has been described in detail (1–3). We analyzed 12-month follow-up data for 83 of the 86 adults (≥25 years of age) who were initially randomized to the CGM group in either the ≥7.0% ($n = 49$) or <7.0% ($n = 34$) baseline A1C cohorts; 2 subjects discontinued study participation during the first 6 months and one after completion of the 9-month visit. An insulin pump was used by 75 (90%) subjects and multiple daily injections (MDIs) of insulin by 8 (10%). Subjects were provided with either a DexCom SEVEN (DexCom, San Diego, CA), MiniMed Paradigm REAL-Time System (Medtronic MiniMed, Northridge, CA), or FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA). Follow-up visits during the extension study occurred at 9 and 12 months postrandomization. A1C was measured at the University of Minnesota using the Tosoh A1C 2.2 Plus Glycohemoglobin Analyzer method (4). Severe hypoglycemia was defined as an event that required assistance from another person to administer resuscitative actions (5).

The amount of CGM use was determined from CGM downloads. Statistical testing was performed with a paired *t* test for measures with an approximate normal distribution and with a signed-rank test for other measures. Changes in glucose variability were evaluated in least squares regression models based on van der Waerden rank normal scores.

RESULTS

— Median CGM use was 7.0 days/week (interquartile range 6.3–7.0) at 6 months and 6.8 days/week (interquartile range 5.8–7.0) at 12 months (see online appendix supplemental Table S1, available at http://care.diabetesjournals.org/cgi/content/full/dc09-0846/DC1). Use at 12 months did not vary with baseline A1C level (Spearman $r = -0.10$; $P = 0.38$).

Among subjects with baseline A1C ≥7.0%, mean change in A1C from baseline to 12 months was −0.4 ± 0.6% ($P < 0.001$), similar to the change from baseline to 6 months. The reduction in A1C occurred mainly in the first 8 weeks and then remained relatively stable through the next 44 weeks (supplemental Fig. S1). Among subjects with baseline A1C <7.0%, A1C remained within the target range over the entire 12 months of the study (6.4, 6.3, and 6.4% at baseline, 6 months, and 12 months, respectively; $P = 0.42$ for change from baseline to 12 months).

A severe hypoglycemic event was experienced by 8 (10%) of the 83 subjects (9 events) during the first 6 months and 3 subjects (4%; 3 events) in the second 6 months. The rate of severe hypoglycemic events fell from 21.8 events per 100 person-years during the first 6 months to 7.1 events per 100 person-years (95% CI

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*The members of the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group are included in the APPENDIX. A complete list of the clinical centers and investigators is available in the online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-0846/DC1.

Table 1—*Clinical features and metabolic control measures*

	Overall			Baseline A1C >7.0%			Baseline A1C <7.0%			*P**
	Baseline†	Month 6	Month 12	Baseline†	Month 6	Month 12	Baseline†	Month 6	Month 12	
n	83	83	83	49	49	49	34	34	34	
Body weight (kg)	77 ± 15	78 ± 16	79 ± 15	79 ± 16	80 ± 17	81 ± 17	75 ± 13	75 ± 13	76 ± 13	<0.001
Daily insulin dose (U/kg body wt)	0.5 ± 0.1	0.5 ± 0.2	0.5 ± 0.1	0.5 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.72
Blood glucose meter tests per day‡	7.0 ± 2.4	6.4 ± 3.1	5.7 ± 2.1	6.5 ± 2.3	5.7 ± 2.3	5.5 ± 2.0	7.6 ± 2.4	7.3 ± 3.9	6.0 ± 2.2	<0.001
A1C (%)	7.1 ± 0.8	6.8 ± 0.6	6.9 ± 0.7	7.6 ± 0.5	7.1 ± 0.5	7.2 ± 0.5	6.4 ± 0.5	6.3 ± 0.5	6.4 ± 0.6	<0.001
CGM glucose measures (*n*)§	81	81	81	49	49	49	32	32	32	
Mean glucose (mg/dl)	151 ± 25	148 ± 21	148 ± 23	162 ± 24	157 ± 22	158 ± 23	136 ± 18	134 ± 12	133 ± 13	0.22
Glucose level (min/day)										
71–180 mg/dl	983	1,026	1,066	866	962	966	1,151	1,139	1,135	0.02
≤70 mg/dl	62	55	58	53	53	49	82	65	72	0.06
≤60 mg/dl	30	16	19	23	16	14	38	13	25	0.003
≤50 mg/dl	7	4	5	7	3	4	6	6	5	0.002
>180 mg/dl	385	321	293	483	378	422	219	231	211	0.12
>200 mg/dl	246	202	188	335	252	289	133	137	116	0.05
>250 mg/dl	77	48	49	121	61	78	28	33	19	0.02
Summary values										
Hypoglycemia area under the curve‖	0.5	0.3	0.3	0.4	0.3	0.3	0.6	0.3	0.4	0.002
Low blood glucose index¶	1.2	1.0	1.0	0.9	0.9	0.9	1.6	1.3	1.3	0.01
Hyperglycemia area under the curve#	11.6	8.6	8.1	16.0	11.0	12.5	5.4	5.5	4.8	0.05
High blood glucose index¶	5.6	4.8	4.6	6.6	5.5	6.2	3.3	3.7	3.4	0.08
Variability										
Standard deviation (mg/dl)	56	52	52	61	57	55	46	47	45	0.02 (0.03)
Mean amplitude of glycemic excursion (mg/dl)	107	101	97	114	106	107	91	89	93	0.03 (0.04)
Mean absolute rate of change ($mg \cdot dl^{-1} \cdot min^{-1}$)	0.63	0.65	0.65	0.69	0.67	0.69	0.57	0.58	0.63	0.11 (0.03)
Coefficient of variation**	0.36	0.35	0.34	0.37	0.37	0.35	0.35	0.33	0.33	0.07 (0.10)

Data are means ± SD or median. **P* values for the comparison of baseline vs. month 12 for all subjects pooled. For variability, the unadjusted and adjusted *P* values for mean glucose are both given: unadjusted (adjusted). †Baseline data are from blinded CGM use for approximately 4–7 days prior to randomization. ‡Self-reported blood glucose meter monitoring. §Subjects required to have at least 24 h of glucose data at all three time points to be included in analysis. One subject with zero use in month 12 and one subject whose CGM use in month 12 was imputed with the self-reported data at the month 12 visit as a result of a missing download data were excluded. ‖Total area under the curve <70 mg/dl reflects both percentage and severity of glucose values in the hypoglycemic range. ¶Blood glucose index (ref. 8). #Total area under the curve above 180 mg/dl. **SD divided by mean glucose.

0–16.7) during the second 6 months ($P = 0.18$). The rate was not associated with baseline A1C (Spearman $r = -0.004$; $P = 0.97$). In subjects with baseline A1C ≥7%, the incidence fell from 20.5 events per 100 person-years in the first 6 months to 12.1 events per 100 person-years in the second 6 months, whereas in the A1C <7% cohort, the incidence fell from 23.6 events per 100 person-years to no events during the second 6 months (supplemental Fig. S2).

The median amount of time per day with glucose in the range of 71–180 mg/dl increased significantly ($P = 0.02$) from baseline to 12 months, reflecting a decrease in both hypoglycemia and hyperglycemia. Similar trends were seen both in subjects with baseline A1C ≥7.0% and in those with baseline A1C <7.0% (Table 1). The increase in time in range was seen during both daytime and nighttime (supplemental Table S2). Variability assessed with the SD of glucose values ($P = 0.02$) and mean amplitude of glycemic excursions ($P = 0.03$) was reduced with CGM use from baseline to 12 months. Body weight, daily insulin dose, and frequency of daily blood glucose meter tests did not change meaningfully during the study.

CONCLUSIONS — In this 6-month extension to a randomized clinical trial, we found that most adults ≥25 years of age continued to use CGM on a daily or near-daily basis and had sustained benefits of improved glucose control noted by A1C levels and the amount of time sensor glucose values were in the target range. These benefits persisted despite less-intensive follow up, designed to approximate usual clinical practice, than that during the 6-month randomized phase of the study.

An additional important observation was the remarkably low rate of severe hypoglycemic events during the extension phase of the study. The rate of severe hypoglycemia in our CGM subjects with a mean A1C of 6.8% during the 6-month extension phase was markedly lower than the rate of severe hypoglycemia in the Diabetes Control and Complications Trial (DCCT) intensive treatment group, which had mean A1C of 7.1% (7 vs. 62 events per 100 person-years) (6). The total absence of severe hypoglycemia during the second 6 months of the study in the subjects who had a baseline A1C <7.0% is particularly striking, especially because these subjects were able to maintain a mean A1C of 6.4%.

It is possible that the decline in severe hypoglycemic events during the second 6 months of the study resulted from learning from prior experience, including appropriate setting of the low alarms, glucose targets, and titration of basal and bolus insulin doses. It is also intriguing to speculate that the reduction in exposure to biochemical hypoglycemia over the 12 months of the study may have protected subjects from severe hypoglycemic events by enhancing their counterregulatory hormone defense mechanisms against hypoglycemia (7).

Our findings demonstrate that the benefits of CGM can be sustained for at least 12 months in motivated adults with type 1 diabetes practicing intensive diabetes management. In such individuals, CGM provides the ability to achieve target A1C levels much more safely than previously reported.

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The study was designed and conducted by the investigators listed in the online appendix, who collectively wrote the manuscript and vouch for the data. The investigators had complete autonomy to analyze and report the trial results. There were no agreements concerning confidentiality of the data between the Juvenile Diabetes Research Foundation and the authors or their institutions. The Jaeb Center for Health Research had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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APPENDIX — The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group writing committee members are as follows: lead authors Bruce Bode, MD, Roy W. Beck, MD, PhD, and Dongyuan Xing, MPH; and additional authors Lisa Gilliam, MD, PhD, Irl Hirsch, MD, Craig Kollman, PhD, Lori Laffel, MD, MPH, Katrina J. Ruedy, MSPH, William V. Tamborlane, MD, Stuart Weinzimer, MD, and Howard Wolpert, MD.

References

1. The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008359:1464–1476
2. The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care 2009;32:1378–1383
3. JDRF CGM Study Group. JDRF randomized clinical trial to assess the efficacy of real-time continuous glucose monitoring in the management of type 1 diabetes: research design and methods. Diabetes Technol Ther 2008;10:310–321
4. Gibb I, Parnham A, Fonfrède M, Lecock F. Multicenter evaluation of Tosoh glycohemoglobin analyzer. Clin Chem 1999;45:1833–1841
5. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
6. The DCCT Research Group. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. Am J Med 1991;90:450–459
7. Fanelli CG, Epifano L, Rambotti AM, Pampanelli S, Di Vincenzo A, Modarelli F, Lepore M, Annibale B, Ciofetta M, Bottini P. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. Diabetes 1993;42:1683–1689
8. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Clarke W. Symmetrization of the blood glucose measurement scale and its applications. Diabetes Care 1997;20:1655–1658