Variation of Interstitial Glucose Measurements Assessed by Continuous Glucose Monitors in Healthy, Nondiabetic Individuals

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OBJECTIVE — To characterize glucose levels during daily living using continuous glucose monitors (CGMs) in nondiabetic individuals.

RESEARCH DESIGN AND METHODS — Seventy-four healthy children, adolescents, and adults aged 9–65 years with normal glucose tolerance used a blinded CGM device for 3 to 7 days.

RESULTS — Sensor glucose concentrations were 71–120 mg/dl for 91% of the day. Sensor values were ≤60 or >140 mg/dl for only 0.2% and 0.4% of the day, respectively. Sensor glucose concentrations were slightly higher in children than adults ($P = 0.009$) and were slightly lower during the night than day (95 vs. 99 mg/dl, $P < 0.001$).

CONCLUSIONS — Glucose values ≤60 and >140 mg/dl, measured with CGM, are uncommon in healthy, nondiabetic individuals. CGM may be useful to evaluate glucose tolerance in nondiabetic individuals over time. Furthermore, these data provide a basis for comparison for studies that use CGM to assess glucose control in subjects with diabetes.

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Continuous glucose monitors (CGMs), which measure interstitial glucose concentrations, are increasingly being used in clinical practice and in clinical research in patients with diabetes. However, the variation in glucose levels measured by CGM in healthy, nondiabetic individuals during daily living has not been extensively studied. The aim of this study was to characterize CGM glucose patterns in healthy, nondiabetic individuals.

RESEARCH DESIGN AND METHODS

— The study was conducted at 10 adult and pediatric diabetes centers, after approval by their institutional review boards. Subjects were healthy adults, adolescents, and children who were clinic staff, friends, relatives of clinic staff, or relatives or acquaintances of an individual with type 1 diabetes. Subjects provided written informed consent and children gave assent to study participation. Inclusion criteria were: age ≥8 years old; BMI 10th to 90th percentile for age and sex for subjects <18 years old (based on 2000 Centers for Disease Control and Prevention (CDC) nomogram) and <28 kg/m^2 for subjects ≥18 years old; no significant chronic illness or taking of any medications that might affect glucose metabolism; A1C ≤6.0%; fasting blood glucose 70 to 99 mg/dl; 2-h oral glucose tolerance test (OGTT) level ≤140 mg/dl; and negative anti-GAD, anti-IA2, and anti-insulin antibodies. Of 148 subjects screened for the study, 39 were excluded because of low fasting glucose ($n = 3$), elevated fasting glucose ($n = 16$), elevated 2-h glucose ($n = 5$), positive antibodies ($n = 8$), ineligible BMI ($n = 3$), ineligible A1C ($n = 1$), or insufficient sensor data ($n = 3$).

Subjects used either a Guardian Clinical ($n = 38$; Medtronic MiniMed, Northridge, CA) for 3 days, a FreeStyle Navigator ($n = 36$; Abbott Diabetes Care, Alameda, CA) for 5 days, or a DexCom SEVEN ($n = 35$, DexCom, San Diego, CA) for 7 days. Subjects were instructed on calibration of the devices using a home blood glucose meter. Results using the DexCom sensor were not included in the analysis because of the frequency of missing data because of overnight dropout of sensor function, and because there was a disproportionate number of low and high glucose values compared with the other sensors, which seemed unlikely to represent true extreme values in these nondiabetic individuals. Notably, the current commercially available DexCom device contains newer software than the devices used in our study. The discrepancies between the DexCom results and the other two devices is shown in supplemental Table A-1, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-1971/DC1.

Computed statistics included are mean ± SD for the glucose and medians for the percentage of sensor glucose values in glucose ranges and glucose variability measures overall and in four age-groups: 8 to <15, 15 to <25, 25 to <45, and ≥45 years. The association of A1C,

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*A list of the writing committee can be found in the APPENDIX, and a complete list of the members of the study group is included in the online appendix available at http://care.diabetesjournals.org/cgi/content/full/dc09-1974/DC1.
The study was designed and conducted by the investigators listed in the 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, Inc., 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.

Table 1—*Sensor glucose values and glucose variability by age group and time of day*

	All	Age group				Time of day	
		8–<15	15–<25	25–<45	≥45	Daytime	Nighttime
n	74	20	17	20	17		
A1C (%)	5.3 ± 0.3	5.3 ± 0.2	5.2 ± 0.2	5.2 ± 0.3	5.5 ± 0.3		
Sensor glucose							
Overall*	98 ± 10	103 ± 11	97 ± 7	96 ± 12	95 ± 7		
Daytime†	99 ± 10	103 ± 10	98 ± 7	97 ± 12	97 ± 6		
Nighttime‡	95 ± 13	101 ± 15	97 ± 11	91 ± 12	89 ± 11		
Peak sensor glucose§							
Daytime	131	134	135	125	128		
Nighttime	109	111	111	104	103		
Nadir sensor glucose§							
Daytime	73	74	71	75	79		
Nighttime	80	84	80	77	78		
Distribution of sensor glucose levels							
71–120 mg/dl	91.0%	85.1%	87.9%	91.4%	93.7%	90.4%	90.3%
≤70 mg/dl	1.7%	1.8%	0.6%	2.9%	1.6%	1.1%	2.2%
≤60 mg/dl	0.2%	0.2%	0.0%	0.2%	0.1%	0.0%	0.0%
>120 mg/dl	5.6%	8.2%	8.3%	4.2%	4.4%	5.9%	1.1%
>140 mg/dl	0.4%	1.3%	0.3%	0.3%	0.0%	0.5%	0.0%
Overall glucose variability							
SD (mg/dl)‖	13.7	16.4	13.7	12.6	12.4	13.5	10.9
MARC (mg/dl/min)‖	0.34	0.36	0.34	0.32	0.33	0.37	0.26
Coefficient of variation (%)‖¶	14	16	14	14	13	14	12
MAGE (mg/dl)‖	27.7	28.1	28.3	25.6	26.9	28.0	15.8

Data are means ± SD and medians. *$P = 0.009$ for the association of mean glucose with age, adjusting for device type. †$P = 0.04$ for the association of mean glucose with age, adjusting for device type. ‡$P < 0.001$ for the association of mean glucose with age, adjusting for device type. §The calculation of peak and nadir glucose was restricted to days with ≥12 h and nights with ≥4 h of glucose data. ‖$P < 0.001$ for the association of glucose variability with time of day, adjusting for device type and mean glucose. ¶Coefficient of variation = SD/mean glucose. MARC, mean absolute rate of change; MAGE, mean amplitude of glycemic excursions.

fasting blood glucose, and 2-h postprandial blood glucose with age was assessed using least-squares regression models. The associations of mean sensor glucose and glucose variability measures with age were assessed using least-squares regression models adjusting for device type. The repeated-measures regression models were used to compare mean glucose and glucose variability measures during daytime versus nighttime, adjusting for device type and age. Rank scores were transformed to have a normal distribution, using van der Waerden scores for glucose variability measures because of the skewed distributions. Regression models of glucose variability measures were adjusted for mean glucose as a covariate.

RESULTS — The 74 subjects ranged in age from 9 to 65 years old. Of them, 51 (69%) were female; 55 (74%) were non-Hispanic, Caucasian; 13 (18%) were Hispanic; 1 (1%) was African American; and 5 (7%) were other race/ethnicities. Mean A1C (± SD) was 5.3 ± 0.3% (range 4.7–6.0%), fasting glucose was 86 ± 8 mg/dl, and 2-h post-OGTT was 96 ± 22 mg/dl; none of which varied meaningfully by age. Median BMI percentile was 82nd (interquartile range 62nd to 91st) for subjects <18 years old ($n = 26$) and median BMI was 24.9 kg/m^2 (23.3, 26.3) for those ≥18 years old ($n = 48$).

CGM glucose values were obtained for a mean of 84 ± 21 h per subject. As shown in Table 1, the mean sensor glucose concentration was slightly higher during the day (6:00 A.M. to midnight) than during the night (midnight to 6:00 A.M., $P < 0.001$ comparing day and night). There was a slight association of lower age and higher mean glucose level ($P = 0.009$), which was seen both during the day ($P = 0.04$) and overnight ($P < 0.001$) (Table 1; supplemental Figs. A-1 and A-2). Hourly means ranged from 92 mg/dl from 5:00 to 6:00 A.M. to 103 mg/dl from 8:00 to 10:00 P.M. (supplemental figure A-2). The median percentage of sensor values between 71 and 120 mg/dl was 91%, 0.2% of values being ≤60 mg/dl and 0.4% >140 mg/dl; no subjects had 100% of values between 71 and 120 mg/dl (Table 1; supplemental Tables A-2 and A-3). Except for a slight tendency for a higher rate of change in younger subjects ($P = 0.04$), other measures of glucose variability were not influenced by age (Table 1). Glucose variability was lower at night than during the day ($P < 0.001$; Table 1). Results were similar comparing the Navigator and Guardian Clinical CGM devices (mean glucose 98 ± 11 and 98 ± 9 mg/dl, respectively).

CONCLUSIONS — In this study we have described sensor glucose profiles using the Medtronic and Abbott Diabetes CGM systems in healthy, anti–β-cell antibody–negative subjects across the spectrum of pediatric and adult age ranges. Our mean sensor data were similar to those reported in healthy Chinese subjects using Medtronic's Continuous Glucose Monitoring System (1). However, in that study, sensor values increased with advancing age, contrary to our data, and only subjects >20 years old were included.

Our findings may be useful to clinicians and investigators who are using these devices in patients with abnormal

glucose tolerance or diabetes. Our results describe the frequency of out-of-range sensor glucose values and the degree of glucose variability that are likely to occur in normoglycemic individuals. This provides a better understanding of what constitutes biochemical hypo- or hyperglycemia reported by these devices.

APPENDIX — Lead Authors: Larry A. Fox, MD; Roy W. Beck, MD, PhD; Dongyuan Xing, MPH. Additional members of the writing committee (alphabetical): H. Peter Chase, MD; Lisa K. Gilliam, MD, PhD; Irl Hirsch, MD; Craig Kollman, PhD; Lori Laffel, MD, MPH; Joyce Lee, MD; Katrina J. Ruedy, MSPH; William V. Tamborlane, MD; Michael Tansey, MD; and Darrell M. Wilson, MD.

Acknowledgments— The study was designed and conducted by the investigators listed in the 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, Inc., 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. For a complete conflict of interest statement, please refer to the online appendix available at *http://care.diabetesjournals.org/cgi/content/full/dc09-1974/DC1*. No other potential conflicts of interest relevant to this article were reported.

Parts of this study were presented in poster form at the 69th Scientific Sessions of the American Diabetes Association, New Orleans, Louisiana, 5–9 June 2009.

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Reference

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