Glycemic Characteristics in Continuously Monitored Patients With Type 1 and Type 2 Diabetes

Normative values

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OBJECTIVE — The purpose of this study was to generate normative values for periods of euglycemia as well as for daily patterns of glycemic excursions in patients with type 1 and type 2 diabetes monitored continuously for a maximum period of 21 days and blinded to glucose levels.

RESEARCH DESIGN AND METHODS — This was a multicenter, prospective observational study in which 101 consecutive patients with type 1 ($n = 60$) or type 2 ($n = 41$) diabetes underwent blinded continuous glucose monitoring. Serial glucose measurements were divided into periods of euglycemia (70–180 mg/dl), hyperglycemia (>180 mg/dl), and hypoglycemia (<70 mg/dl). The proportions of time patients were hypoglycemic, euglycemic, and hyperglycemic and the total areas under the curves (AUCs) were determined.

RESULTS — During the observation period the 101 subjects contributed an average 287 ± 132 h of continuous glucose values. Subjects remained in the euglycemic range for ~63% of the total day, were hypoglycemic 8%, and were hyperglycemic 29%. Hypoglycemia was more prevalent nocturnally (11 vs. 7%) and hyperglycemia diurnally (31 vs. 25%). Compared with subjects with type 2 diabetes, type 1 diabetic subjects had more frequent hypoglycemic episodes per day (2.1 vs. 1.0; $P < 0.001$) that were of longer duration (1.1 vs. 0.7 h; $P < 0.0001$), reflecting a greater number of hours per day in the hypoglycemic range (2.3 vs. 1.0 h; $P < 0.0001$). The mean hypoglycemic AUC values were >150% higher for type 1 compared with type 2 diabetic subjects (41 vs. 16, respectively; $P < 0.0001$).

CONCLUSIONS — These normative data will assist in study and sample size planning for future investigations of continuous glucose monitoring and allow for qualitative comparisons with trials of therapeutic interventions aimed at reducing the occurrence of glycemic excursions.

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The metabolic perturbations caused by diabetes put the patient at increased risk of cardiovascular disease, as well as severely debilitating conditions such as retinopathy, nephropathy, and neuropathy (1). The prevalence of these complications is likely to rise dramatically over the next several decades if the worrisome upward trend in childhood and adult obesity continues unabated. However, several large controlled clinical trials have demonstrated that intensive therapeutic management aimed at attaining tight glycemic control is associated with a significant reduction in serious diabetes-related complications (2–5),

an improvement in quality of life (6), and a decrease in the economic burden of this disorder to the health care system (7).

Unfortunately, the achievement of tight glycemic control with intensive therapy necessitates frequent blood glucose monitoring (8). The American Diabetes Association (ADA) treatment guidelines recommend maintaining fasting serum glucose values within an optimal range of 90–130 mg/dl (9). However, even with frequent daily self-monitoring of blood glucose, the achievement of consistent euglycemia in this range and the avoidance of hypoglycemic and hyperglycemic excursions remain elusive for many patients with diabetes (10).

Regardless of how often fingerstick blood glucose measurements are undertaken, discrete results offer only a static picture at any point and do not provide a sense of the number, intensity, and duration of glycemic excursions (11). The recent availability of continuous glucose monitors provides the opportunity to match the demands of intensive therapy with a period of equally intensive glucose monitoring (12). The continuous glucose profiles and summary statistics provided by these monitors have been demonstrated to identify periods of previously undetected nocturnal hypoglycemia and postprandial hyperglycemia that allow the clinical management team to suggest specific changes in the timing and dosage of insulin infusion or injection, dietary and physical activity alterations, and changes in the timing and frequency of blood glucose measurements (12–18). Preliminary clinical evidence among small patient groups with both type 1 and type 2 diabetes suggests that utilization of continuous glucose monitoring data to make therapeutic regimen adjustments results in an overall lowering of blood glucose values coupled with a significant reduction in the frequency of glycemic excursions (13,17,19–25). The ability to achieve more consistent glycemic control with continuous glucose monitoring has

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been projected to translate into a reduction in associated health care costs (26,27).

Because continuous glucose monitoring is in its infancy, there remains a paucity of normative data reflecting the typical daily patterns and profiles of normal and abnormal glycemia in patients with both type 1 and type 2 diabetes. The current study aims to fill this gap by providing normative values for glycemic characteristics in a large sample of patients monitored continuously for a maximum of 21 days.

RESEARCH DESIGN AND METHODS

— A prospective observational study was undertaken at seven geographically dispersed medical centers in the U.S. The primary objective was to generate normative values for and characterize periods of euglycemia as well as the daily patterns of glycemic excursions in diabetic patients monitored continuously for a maximum period of 21 days and blinded to glucose levels. Appropriate institutional review board approval was obtained at each clinical site.

All consecutive patients with type 1 or type 2 diabetes were enrolled if they were at least 11 years of age, agreed to comply with the continuous glucose monitoring device instructions for use, provided informed consent, and had no skin abnormalities at the device insertion site or allergies to adhesives. A total of 101 patients qualified for inclusion as study subjects, were trained in the use of the continuous glucose monitor, had the device sensor implanted, and entered a 21-day glucose monitoring period. Subjects also were instructed to perform fingerstick blood glucose measurements 10 times per day with the FreeStyle meter (TheraSense, Alameda, CA) with automatic calibration of the sensor at 1, 3, and 24 h. Study subjects returned to each outpatient clinic on a weekly basis to download electronic data and undergo examination of the sensor insertion site for adverse reactions.

The mean age of the entire study group was 45.3 ± 13.8 years, 53% of subjects (54 of 101) were female, and 59% of subjects (60 of 101) had type 1 diabetes. For subjects with type 1 diabetes, 10% (6 of 60) were <19 years of age, 88% (53 of 60) were between the ages of 19 and 60 years, and 2% (1 of 60) was >60 years of age. The average time since diagnosis of type 1 diabetes was 22.7 ± 12.0 years. All 41 subjects with type 2 diabetes were

>19 years of age and their average time since diagnosis was 7.4 ± 6.2 years.

Study subjects were requested to return to the clinic for a final follow-up visit 1 week after completion of the 21-day observation period to evaluate adverse events. Eighty-nine subjects (88%) returned for this final visit; seven subjects withdrew consent, four were noncompliant, and one had a system malfunction.

Study device

All subjects underwent continuous glucose monitoring with the Navigator device (TheraSense). The accuracy of this device for determining interstitial glucose values has been described previously (28). The device consists of four components: *1*) an electrochemical sensing element that is inserted subcutaneously; *2*) an inserter to implant the sensor in the proper subcutaneous location; *3*) a transmitter that detects the electrical signal generated by the oxidation of glucose in the interstitial fluid at the sensor electrode and conveys the information to a display unit; and *4*) an information display/receiver with a wireless radiofrequency communication link to the transmitter. The sensor is designed to be inserted at a subcutaneous site in either the abdomen or upper arm, and subjects alternated locations with every new sensor during the monitoring period. Each subject's continuous glucose data were recorded every minute and were available for up to 72 continuous h per device sensor. All subjects remained blinded to glucose values, and no therapeutic adjustments were undertaken based on continuous data throughout the duration of the observation period.

Statistical methods

Serial glucose measurements for all subjects were analyzed using summary measures to characterize a subject's glucose profile as recommended by Matthews et al. (29). Briefly, a subject's glucose profile was divided into periods, or episodes, of euglycemia (70–180 mg/dl), hyperglycemia (>180 mg/dl), and hypoglycemia (<70 mg/dl). An excursion into either the hypoglycemic or hyperglycemic range required a duration of at least 10 min to define a definitive episode (30).

For each subject, the proportions of time hypoglycemic, euglycemic, and hyperglycemic were determined from the continuously recorded device data. The total numbers of hypoglycemic and hyperglycemic events were adjusted to 24 h,

and the total area under the curve (AUC) was determined (29). The AUC represents the time-weighted excursion intensity, or magnitude, and is influenced by both the duration of the excursion and the overall glucose levels during the excursion. Glucose measurements also were examined with respect to the ADA optimal range (90–130 mg/dl) (9). The variability in interstitial fluid glucose values for a subject was defined as the standard deviation of all measurements for the subject.

Differences in hypoglycemic and hyperglycemic excursions between sexes and diabetes types were compared using the *t* test, two-tailed. Pairwise Pearson correlation coefficients and their significance values were calculated separately for type 1 and type 2 diabetic subjects for all continuous excursion measures and patient characteristics of age, years since diagnosis of diabetes, and BMI.

Stepwise forward multiple regression analysis was used to explore possible associations between the proportions of time hypoglycemic and hyperglycemic, and overall glucose variability with potentially explanatory factors including age, sex, BMI, diabetes type, and years since diagnosis of diabetes.

RESULTS — During the 21-day observation period, the 101 subjects successfully inserted and used a total of 740 sensors (range 1–12), and contributed an average 287 ± 132 h (range 3–476 h) per subject of device exposure. Overall, more than 1.7 million continuous glucose measurements were obtained. In general, there was excellent compliance with fingerstick blood glucose measurements with an average 9.2 ± 2.3 and 9.0 ± 1.7 fingersticks/day for subjects with type 1 and type 2 diabetes, respectively. There were no significant associations observed between the number of fingersticks per day and age or years since diabetes diagnosis.

Figure 1 illustrates overlaid glucose profiles for three subjects monitored continuously for 72 h, separated into 24-h periods each beginning at 6:00 A.M. There was marked variability both within and among subjects with respect to the duration of time in euglycemia and in the frequency, timing, and magnitude of day-to-day glycemic excursions.

Table 1 provides normative values for various quantitative measures of glycemic status overall as well as by sex and diabetes type, separately. On average, subjects remained in the euglycemic range for ~63% of the total day, in the hypoglyce-
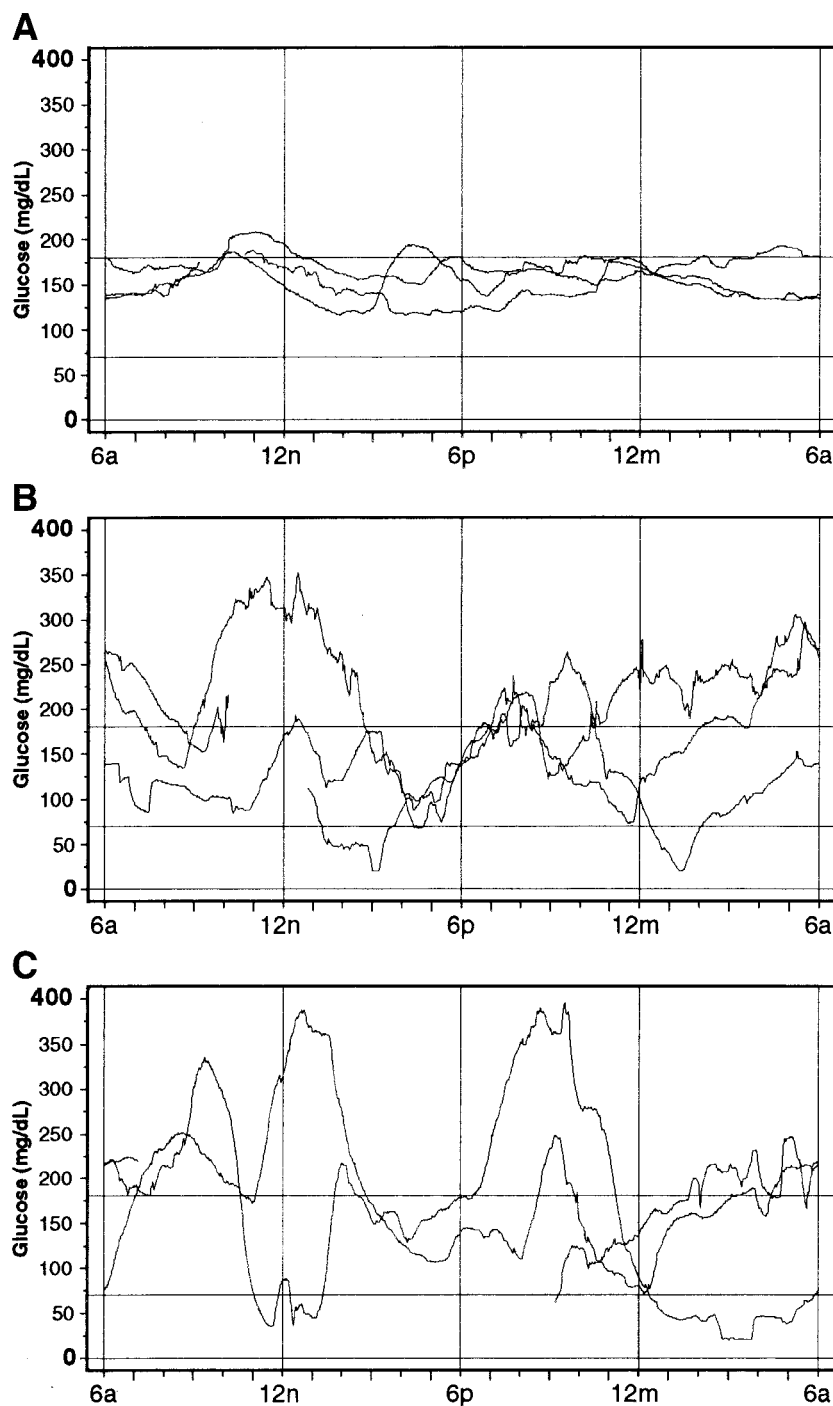
Figure 1— *Overlapping continuous glucose profiles representing 3 consecutive days of monitoring in an obese (BMI 33 kg/m²) 65-year-old type 2 diabetic woman (A), an obese (BMI 31 kg/m²) 29-year-old type 1 diabetic woman (B), and a normal-weight (BMI 22 kg/m²) 14-year-old type 1 diabetic male adolescent (C). There is noteworthy variability both within and among subjects with respect to the duration of time in euglycemia and in the frequency, timing, and magnitude of day-to-day glycemic excursions.*

the hyperglycemic range compared with nocturnal measurements (31 vs. 25%, respectively). Overall, subjects were within the ADA optimal range for ~28% of the time, with almost 55% of the continuous glucose measurements above this range and 18% below this range.

Notably, male subjects, on average, tended to exhibit longer-duration episodes of hyperglycemia than female subjects (2.8 h vs. 2.1 h, respectively), but the difference did not achieve nominal statistical significance ($P = 0.08$) (Table 1). Consequently, male subjects were hyperglycemic almost 2 h more per day than female subjects ($P = 0.08$) and the mean hyperglycemic AUC values were ~45% greater in male than in female subjects (469 vs. 323, respectively; $P = 0.11$). There were no other noteworthy distinctions between sexes for any other measurement of glycemic status.

Compared with type 2 diabetic subjects, subjects with type 1 diabetes had, on average, more frequent hypoglycemic episodes per day (2.1 vs. 1.0; $P < 0.001$) that were of longer duration (1.1 vs. 0.7 h; $P < 0.0001$), reflecting a greater number of hours per day in the hypoglycemic range (2.3 h vs. 1.0 h; $P < 0.0001$) (Table 1). Consequently, the mean hypoglycemic AUC values were >150% higher for type 1 diabetic subjects than for type 2 diabetic subjects (41 vs. 16, respectively; $P < 0.0001$). Type 1 and type 2 diabetic subjects did not differ significantly in the proportion of time their glucose values were in the ADA optimal range ($P = 0.12$). However, there was significantly greater variability in glucose values between type 1 and type 2 diabetic subjects both overall (mean SD 60 vs. 45 mg/dl, respectively; $P < 0.0001$) as well as for diurnal (60 vs. 44 mg/dl, respectively; $P < 0.0001$) and nocturnal (57 vs. 39 mg/dl, respectively; $P < 0.001$) measurements, separately.

Bivariate comparisons between measures of glycemic status and age, years since diagnosis of diabetes, and BMI generally failed to generate any notable or statistically significant associations. The relationship between the number of years with diabetes among type 2 diabetic subjects and the proportion of time in the hypoglycemic range yielded the only significant correlation ($r = 0.32$, $P = 0.045$).

Multivariate analysis found only male sex to significantly ($P = 0.049$) predict the proportion of time per day in hyperglycemia, although this factor accounted for only a small portion of the variability

mic range for 8%, and in the hyperglycemic range for 29%. There was little difference detected in the amount of time spent in the euglycemic range between diurnal (6:00 A.M. to 11:00 P.M.) and nocturnal (11:00 P.M. to 6:00 A.M.) periods (63 vs. 64%, respectively). However, diurnal glucose measurements were less often in the hypoglycemic range compared with nocturnal measurements (7 vs. 11%, respectively) and, conversely, diurnal glucose measurements were more often in

Table 1—*Various glycemic characteristics overall and by sex and diabetes type*

Glycemic measure*	Hypoglycemia†	Euglycemia‡	Hyperglycemia§
Episodes per day			
Overall	1.6 ± 1.3	5.6 ± 1.9	2.8 ± 1.3
Male	1.5 ± 1.3	5.1 ± 2.0	2.8 ± 1.4
Female	1.7 ± 1.3	6.0 ± 1.8	2.8 ± 1.2
Type 1	2.1 ± 1.3	6.3 ± 1.7	3.0 ± 1.0
Type 2	1.0 ± 1.1	4.5 ± 1.8	2.5 ± 1.6
Duration of episode (h)			
Overall	0.9 ± 0.4	3.0 ± 1.6	2.4 ± 1.9
Male	0.9 ± 0.4	3.0 ± 2.0	2.8 ± 2.6
Female	0.9 ± 0.4	2.9 ± 1.2	2.1 ± 1.0
Type 1	1.1 ± 0.4	2.4 ± 0.6	2.3 ± 1.1
Type 2	0.7 ± 0.4	3.8 ± 2.2	2.5 ± 2.7
Maximum value of excursion (mg/dl)			
Overall	49.0 ± 8.2	NA	233.8 ± 27.4
Male	48.0 ± 8.3	NA	238.1 ± 33.7
Female	49.8 ± 8.0	NA	230.2 ± 20.4
Type 1	48.4 ± 7.2	NA	236.9 ± 20.6
Type 2	50.1 ± 9.7	NA	229.5 ± 34.8
Mean departure during episode (mg/dl)			
Overall	57.3 ± 5.8	NA	211.2 ± 17.2
Male	56.7 ± 5.3	NA	213.8 ± 22.0
Female	57.7 ± 4.6	NA	209.0 ± 11.6
Type 1	56.9 ± 4.0	NA	212.7 ± 11.8
Type 2	57.9 ± 6.3	NA	209.0 ± 23.0
AUC			
Overall	31.0 ± 33.9	NA	390.8 ± 432.0
Male	28.4 ± 32.7	NA	468.6 ± 538.9
Female	33.3 ± 35.0	NA	323.1 ± 300.1
Type 1	41.3 ± 31.9	NA	396.8 ± 314.8
Type 2	16.0 ± 31.3	NA	382.1 ± 566.0
Proportion of time			
Overall	0.08 ± 0.07	0.63 ± 0.20	0.29 ± 0.22
Male	0.07 ± 0.07	0.59 ± 0.24	0.34 ± 0.26
Female	0.08 ± 0.07	0.66 ± 0.15	0.26 ± 0.17
Type 1	0.10 ± 0.06	0.61 ± 0.13	0.30 ± 0.16
Type 2	0.04 ± 0.06	0.67 ± 0.27	0.29 ± 0.28
Hours/day			
Overall	1.8 ± 1.6	15.2 ± 4.9	7.1 ± 5.2
Male	1.6 ± 1.6	14.3 ± 5.8	8.1 ± 6.2
Female	1.8 ± 1.6	16.0 ± 3.7	6.2 ± 4.0
Type 1	2.3 ± 1.5	14.5 ± 3.1	7.2 ± 3.9
Type 2	1.0 ± 1.4	16.1 ± 6.6	6.9 ± 6.7

Data are means ±SD. *Sample sizes in all cases are as follows: overall ($n = 101$), male ($n = 47$), female ($n = 54$), type 1 diabetes ($n = 60$), and type 2 diabetes ($n = 41$). †Hypoglycemia indicates episodes of at least 10 min in duration <70 mg/dl, euglycemia indicates 70–180 mg/dl, and hyperglycemia indicates episodes of at least 10 min in duration of >180 mg/dl. NA, not applicable.

in this outcome ($R^2 = 0.04$). No other independent variables achieved nominal statistical significance in multivariate models of measures of hyperglycemia. However, with respect to hypoglycemia, having type 1 diabetes was demonstrated to significantly predict the number of episodes per day of hypoglycemia ($P < 0.0001$, $R^2 = 0.17$), the proportion of time in hypoglycemia ($P < 0.0001$, $R^2 = 0.17$), and the intensity of hypoglycemia as indicated by the AUC <70 mg/dl ($P = 0.0002$, $R^2 = 0.13$). No other independent variables achieved nominal statistical significance in multivariate models of hypoglycemia measures. Lastly, the only independent variable significantly associated with overall glucose variability was diabetes type, with type 1 diabetic subjects demonstrating greater variability than type 2 diabetic subjects ($P < 0.0001$, $R^2 = 0.22$).

CONCLUSIONS — The results of the current study offer a rare opportunity to document the typical glycemic patterns in a large sample of continuously monitored patients with both type 1 and type 2 diabetes. In fact, study subjects contributed, on average, ~12 days of continuous glucose monitoring data with this device. This quantity of continuous monitoring data is unprecedented in the published literature. Moreover, this study was unique in that subjects were blinded to glucose values and profiles provided by the device throughout the observation period without commensurate therapeutic adjustments. However, these results most likely reflect normative glycemic patterns specifically for intensively managed and monitored diabetes patients, as subjects in the current study performed approximately nine fingerstick measurements per day on average, a frequency far higher than commonly encountered among traditionally managed patients.

It was alarming to note that subjects using frequent fingerstick blood glucose measurements and with a variety of treatment options at their disposal only remained in the euglycemic range for ~65% of the day on average. Even more striking was the finding that these subjects were able to achieve strict glycemic control within the ADA optimal range for <30% of the day. This suggests that current methods of monitoring and therapy are inadequate to consistently maintain euglycemia on a day-to-day basis.

Almost 30% of the day was spent in the hyperglycemic range with a greater propensity for hyperglycemia to occur during daytime hours. This finding most likely reflects postprandial periods of hyperglycemia. Previous studies using continuous glucose monitoring have similarly identified distinctive episodes of marked postprandial hyperglycemia despite satisfactory premeal blood glucose levels within or near the target range (10,18). This phenomenon has previously been underappreciated using conventional blood glucose monitoring (10). There is increasing evidence that postprandial hyperglycemic spikes in diabetic patients are an important contributing factor in the development of cardiac disease, particularly atherosclerosis (31,32).

Overall, subjects in this study were

hypoglycemic ~8% of the day, and this finding corroborates previously reported estimates of hypoglycemia prevalence (33). Importantly, however, these periods of hypoglycemia were more likely to occur nocturnally and were significantly more frequent among type 1 diabetic subjects. In fact, type 1 diabetic subjects spent >2 h/day in a state of frank hypoglycemia. This disturbing frequency of nocturnal hypoglycemia often goes undetected by standard self-monitoring of blood glucose and has been recognized previously by other investigators using continuous glucose monitoring in both type 1 and type 2 diabetic patients (10,18,22,23,33–35). Hypoglycemia, often with unconsciousness, appears to be increased in children and adolescents with type 1 diabetes subjected to intensive insulin therapy (36). Moreover, there is evidence that in newborns and infants, brain damage and long-term sequelae ensue after prolonged and severe hypoglycemia (37). Additionally, the occurrence of memory impairment and cognitive function alterations is associated with intensive insulin therapy in children with type 1 diabetes, presumably the result of severe hypoglycemia and consequent medial temporal dysfunction (38). Clearly, hypoglycemic events should be avoided, and continuous glucose monitoring may play a role not only in identifying these episodes but also in assisting in making therapeutic adjustments that will reduce the likelihood of hypoglycemic excursions (13,15,16).

In addition to generating normative values for glycemic characteristics, the current study also examined the potential predictive value for several basic patient background factors including age, sex, BMI, diabetes type, and years since diagnosis of diabetes. The association between these factors and the proportion of time hypoglycemic and hyperglycemic was generally weak in multivariate analyses, accounting for only a small portion of the variability (<20%) in any single glycemic characteristic. It is probable that the large remaining variability in these glycemic characteristics is more likely explained by differences among subjects in dietary and physical activity patterns as well as adherence to drug regimens. However, the current study was not designed to identify other possible predictors of glycemic excursions in continuously monitored patients aside from basic demographic characteristics such as sex and diabetes type. A comprehensive examination of predictors of glycemic excursions would require use of validated physical activity questionnaire instruments as well as diet and medication diaries, an undertaking outside the scope of this study.

The self-monitoring of blood glucose necessary to support intensive therapy is often poorly complied with by patients because of the discomfort, bother, and inconvenience associated with frequent fingersticks, especially during nighttime hours (8). This is particularly true in adolescents with type 1 diabetes and may be reflected, in part, by the significantly greater variability in continuous glucose values among type 1 subjects in the current study. This underscores the need for continuous glucose monitoring as an essential method for achieving and maintaining tight glycemic control.

This study was not designed or conducted to specifically evaluate the diagnostic accuracy of the Navigator continuous glucose monitoring system but to characterize daily glycemic patterns in a large representative sample of persons with diabetes. Nonetheless, a post hoc analysis of the study data was conducted to determine the percentage agreement of hypoglycemic excursions as identified by the continuous monitor with concurrent fingerstick capillary values. For hypoglycemic excursions of at least 1 h in duration as detected by the monitor, there were 604 occurrences in which fingerstick measurements were taken concurrently at some point within the identified boundaries of the excursion. In ~60% (357 of 604) of these patients, both the continuous monitor and the fingerstick measurement indicated a state of defined hypoglycemia (i.e., <70 mg/dl). Moreover, there were 500 instances (83%, 500 of 604) for which the continuous monitor identified a period of hypoglycemia (i.e., <70 mg/dl) and the corresponding fingerstick values were at least <90 mg/dl (i.e., below the ADA optimal range of 90–130 mg/dl).

In summary, the current study provided normative values for periods of euglycemia and characterized the daily patterns of glycemic excursions in a large sample of diabetes patients monitored continuously for a maximum period of 21 days. These normative data will assist in study and sample size planning for future investigations of continuous glucose monitoring and allow for qualitative comparisons with trials of therapeutic interventions aimed to reduce the occurrence of glycemic excursions.

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