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ORIGINAL ARTICLE

Interindividual and Intraindividual Variations in Postprandial Glycemia Peak Time Complicate Precise Recommendations for Self-Monitoring of Glucose in Persons with Type 1 Diabetes Mellitus

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Abstract

Background:

In glycemic control, postprandial glycemia may be important to monitor and optimize as it reveals glycemic control quality, and postprandial hyperglycemia partly predicts late diabetic complications. Self-monitoring of blood glucose (SMBG) may be an appropriate technology to use, but recommendations on measurement time are crucial.

Method:

We retrospectively analyzed interindividual and intraindividual variations in postprandial glycemic peak time. Continuous glucose monitoring (CGM) and carbohydrate intake were collected in 22 patients with type 1 diabetes mellitus. Meals were identified from carbohydrate intake data. For each meal, peak time was identified as time from meal to CGM zenith within 40–150 min after meal start. Interindividual (one-way Anova) and intraindividual (intraclass correlation coefficient) variation was calculated.

Results:

Nineteen patients were included with sufficient meal data quality. Mean peak time was 87 ± 29 min. Mean peak time differed significantly between patients ($p = 0.02$). Intraclass correlation coefficient was 0.29.

Conclusions:

Significant interindividual and intraindividual variations exist in postprandial glycemia peak time, thus hindering simple and general advice regarding postprandial SMBG for detection of maximum values.

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Abbreviations: (ADA) American Diabetes Association, (CGM) continuous glucose monitoring, (HbA1c) hemoglobin A1c, (ICC) intraclass correlation coefficient, (SMBG) self-monitoring of blood glucose, (T1DM) type 1 diabetes mellitus

Keywords: blood glucose self-monitoring, continuous glucose sensors, hyperglycemia, postprandial period, type 1 diabetes mellitus

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Discussion

Self-monitoring of blood glucose (SMBG) by spot finger prick capillary blood measurements at home is recognized as an important and powerful way to improve self-efficacy, self-care, and glycemic control of patients with diabetes.[1,2]

In daily life, SMBG is used as a key input for patients' decisions on meal insulin bolus dosing from meal to meal and for assessment of hypoglycemia risk. The patient's record of SMBG is also pivotal in doctor–patient communication because, together with measurement of hemoglobin A1c (HbA1c), it provides a measure of glycemic control. The American Diabetes Association (ADA) recommends that patients with type 1 diabetes mellitus (T1DM) perform SMBG at least three times per day when on insulin regimens of multiple daily doses or on continuous subcutaneous insulin infusion pump. To facilitate meal insulin bolus dosing from the current blood glucose level, SMBG must be performed before both insulin injection and meal, i.e., preprandially.

Postprandial SMBG may also have a role to play in monitoring and optimizing glycemic control as it reveals the accordance of exogenous insulin dose and timing with the endogenous insulin requirement. The impact of postprandial hyperglycemia on the progression of late diabetic complications and thus the need for its postprandial detection have been examined in several studies.[3–5] No firm evidence exists on the link between postprandial hyperglycemia and development of microvascular late diabetic complications,[5,6] possibly because of rather short follow-ups in the relevant studies. Also, interactions from mean blood glucose or HbA1c may explain some indications of the lower late diabetic complications (micro- and macrovascular) development rate in T1DM patients with postprandial euglycemia versus T1DM patients with postprandial hyperglycemia.[6,7] Indirect evidence of the hazards of postprandial hyperglycemia is stronger. Hyperglycemia-induced elevations in tumor necrosis factor-α and interleukin-6[8] indicate a possible pathway for microvascular complications as they have an inflammatory etiology.[9,10] Oxidative stress may be the biochemical link between hyperglycemia and inflammation.[8,11–13] The strong correlation between HbA1c and postprandial blood glucose is furthermore a reason for attention to postprandial glycemia, as HbA1c, yet measured routinely two to four times per year, provide only nonspecific and infrequent evaluation of glycemic control.[14,15]

Self-monitored blood glucose detection of postprandial hyperglycemia for corrective purposes, such as careful dietary interventions (low glycemic index foods), or pharmacological interventions requires measurements to be performed at the zenith blood glucose value, despite significant interindividual and intraindividual variations in absorption profiles in all insulin types.[16–18] Thus, advice to diabetes patients on when to measure postprandial blood glucose to detect blood glucose zenith is crucial. Peak time (time from meal start to highest blood glucose value) as well as variation due to meal type and time (breakfast, lunch, dinner), have been explored and published previously. Mean peak time values determined from continuously measured interstitial glucose [continuous glucose monitoring (CGM)] systems range from 57 to 100 min.[19–21] Great variations in peak time in different studies and between meals are evident, peak time ranging from 0 to 300 min,[20,21] and standard deviation (SD) is reported to be around 30 min.[19] This could reflect variations in meal composition, meal duration, insulin doses, insulin timing, and insulin absorption, as well as other causes. Though previous reports are based on normal-life-like conditions, little is still known about inter- and intrapatient variation of glycemic peak time after main meals, making it difficult to advise patients on when to measure. Current guidelines from the ADA mention postprandial SMBG measurement time to be 1–2 h postprandially, the wide window indicating the difficulty in recommending postprandial SMBG time.[22]

The aim of the present retrospective study was to examine inter- and intrapatient peak time correlation for postprandial blood glucose in general and after main meals.

Methods

We retrospectively assessed CGM profiles of T1DM patients. Data were collected from four clinical centers (Medical Department M, Aarhus University Hospital, Denmark; Profil Institute for Metabolic Research, Neuss, Germany; German Diabetes Research Institute at the Heinrich–Heine University of Duesseldorf, Germany; and Department of Pharmaceutical Technology and Biopharmacy, University Center of Pharmacy, University of Groningen, The Netherlands). All centers participated in the clinical development of the SCGM 1 system (Roche Diagnostics, Mannheim, Germany).

Participants

A total of 22 subjects were included in the study. Subjects were recruited from their respective outpatient clinics. The data sets of these subjects were collected from a larger population of more than 200 series in two phases. First, other researchers unfamiliar with the present study's aim and methods selected data for further evaluation based on the following criteria: (1) sufficient technical quality of the measurements, (2) elimination of artifacts, studying all recordings manually, (3) T1DM, and (4) data collection in inpatient setting, resulting in a pool of 91 subjects with relevant data quality and characteristics regarding CGM data. Next, we inspected records of insulin and carbohydrate intake to discriminate between subjects eligible for analysis and subjects with insufficient data amounts. During data collection, all subjects were encouraged to live their normal everyday lives, maintaining and controlling their normal therapy (primarily insulin) as usual, using their own glucose meters. They were further encouraged to maintain their normal level of physical activity on all study days, walking or indoor cycling in the ward. They were not given access to CGM or other experimental data during data collection.

All subjects received written and oral information according to the Declaration of Helsinki II and signed consent forms. The study was approved by the local ethics committees of the four centers participating in the study and was performed according to Good Clinical Practice guidelines.

SCGM 1 System

The SCGM 1 system is based on the glucose oxidase principle and consists of a sensor unit device and a belt-held sensor holding the microdialysis system. The system allows up to 120 h of minutely dialysate glucose measurements. Data are stored by custom-designed software, and online display of dialysate glucose is transferred wirelessly from the sensor unit to the portable data manager. Additional information (insulin administration, meals, exercise, etc.) can be entered as separate events in the data managing device. The sensor unit uses a roller pump that provides a push–pull flow, resulting in a perfusion of the microdialysis membrane with 0.3 μl/min. The perfusion fluid (Ringer chloride, sodium ion, 147 mmol/liter; potassium, 1.4 mmol/liter; serum calcium, 2.3 mmol/liter; chloride, 156 mmol/liter, pH 6; osmolality, 290 mosmol/kg) passes through the catheter, achieving approximately 95% equilibration with the interstitial fluid. Glucose oxidase is mixed with the dialysate and passes the *ex vivo* sensor, creating a current in the nanoampere range. The current is averaged over 60 s, and data are stored.

Study Procedure

The microdialysis probe was inserted into the subcutaneous abdominal adipose tissue after skin puncture with a 16 G needle. At the end of each experiment, the last half hour of *in vivo* measurement was discarded to avoid inclusion of data derived after the explantation of the catheter. Subsequently, the membrane was placed in glucose of a known concentration, and repeated calibration procedures were performed to assess the individual lag time of each catheter.

In order to calibrate the dialysate glucose values to capillary blood glucose, spot measurements were performed up to 20 times per day as described later. On the basis of the spot measurements performed throughout the experiment and the lag time-corrected (inherent physical microdialysis lag time of 31 min) corresponding interstitial values, a linear regression approach was used to calibrate the system.

Assays

Hemoglobin A1c was measured by high-performance liquid chromatography at all sites (normal range 4.8–6.2). Spot measurements of capillary blood glucose were performed by the glucose oxidase method on a Glucotrend™ blood glucose monitoring device (Roche Diagnostics, Mannheim, Germany).

Data Analysis and Statistics

The sensor glucose profiles were calibrated by fitting the paired meter data and sensor data to a line and adjusting the sensor data to the gain and offset identified by the fitting.

Meals were detected from the recordings of carbohydrate and insulin intake. The highest carbohydrate intake close (± 2 h) to the times 8 a.m., 12 a.m., and 6 p.m. was classified as a main meal. Two events of carbohydrate intake separated by less than 15 min, of which one was a main meal, were summed to one main meal, whereas main meals were excluded if subsequent meals followed within 16–120 min. Subjects with less than three includable main meals in the recording period were excluded.

For each main meal, peak time was identified as the time elapsed between meal time and the time of the highest CGM value in the interval 40–150 min after meal start.

Interindividual variation in mean peak time was calculated using one-way Anova (including only the first three meals of each subject). Intraindividual variations in peak time were calculated as the intraclass correlation coefficient (ICC), one-way random (including only the first three meals of each subject). All statistical analyses were done using SPSS (SPSS 19, IBM, Chicago).

Results

Subjects

Out of the 22 subjects, 19 subjects were included in the study. Three subjects were excluded because of insufficient meal records or because they had less than three includable meals. **Table 1** shows the clinical characteristics of included subjects. For included subjects with includable meals, mean ± SD duration of CGM profiles was 6781 ± 840 min.

Peak Time

The distribution of peak times is given in **Figure 1**.

As shown in **Table 2**, mean peak time including all meals was 87 ± 29 min, and mean peak time including only the first three meals was 88 ± 31 min ($p = 0.7$).

Interindividual and Intraindividual Variation

One-way Anova revealed significant differences between mean peak times between subjects, including three meals from each subject ($n = 19$, $p = 0.02$). Intraclass correlation coefficient was 0.29.

Discussion

Attention to the relevance of postprandial hyperglycemia as a predictor of late diabetic complications is currently accompanied by recommendations and studies as to the timing of SMBG to detect the condition.[19–21] Interindividual differences in peak time may complicate general advice. Our primary findings of significant differences in peak time between subjects ($p = 0.02$), including three meals, indicate the existence of important interindividual variation in postprandial peak time, thus probably eliminating the convenience of one suggestible peak time for all patients, and only 67% of the peak times reported in the present study fall within the 1–2 h window suggested by ADA. Our findings of significant interindividual variation is supported by previous work.[19,20] Interindividual differences can be handled in practice by suggesting that diabetes patients perform postprandial SMBG systematically with short intervals after one meal of each type, given intraindividual variations are very limited. The same can be achieved using CGM systems for a few days, which is consistent with the major dissemination of this promising technology yet to come. Our findings of significant ICC between peak times when three meals are included

Table 1.
Clinical Characteristics

	Total population
N	19
Gender (male/female)	15/4
Age (years)	38.0 ± 12.2
Diabetes duration (years)	18.4 ± 10.5
HbA1c (%)[a]	8.0 ± 1.5
Body mass index (kg/m^2)	26.6 ± 4.7

All data are expressed as mean ± SD.
[a] Normal range: 4–6%.

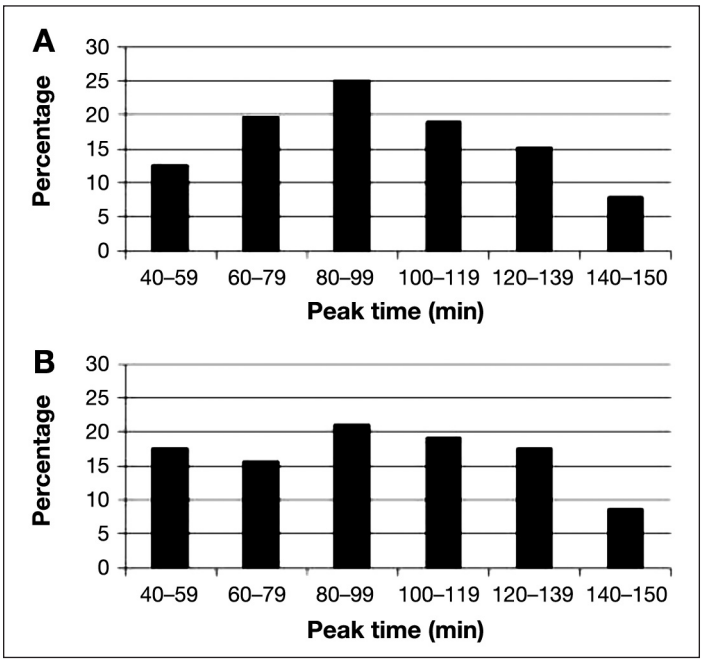

Figure 1. Histograms for **(A)** all subjects, all peak times, and **(B)** all subjects, three first peak times.

Table 2.
Peak Time

	Total population ($n = 19$)	
	All meals	First 3 meals
Peak time	87 ± 29	88 ± 31
n meals	111	57

All data are expressed as mean ± SD.

(ICC = 0.29, n = 57 meals, 19 subjects), indicating a high intraindividual variation in peak time, seem to limit this elegant and efficient solution. Our findings of high intraindividual variation are consistent with the reports from Daenen and colleagues[19] of an intraindividual coefficient of variance of 49% and a standard error of the mean of >20 min. Sophisticated methods exist to calculate the number of observations necessary to limit attenuation at specific level,[23] but this requires large amounts of data not consistent with the rather work intensive data collection using CGM systems.

Our findings in the study presented here evolve from data collected in rather controlled conditions. In the everyday lives of persons with diabetes, an equal level of uniformity among days and patients cannot be assumed. This may have been a reasonable assumption earlier when efficient diabetes treatment enforced diabetes patients into a life governed by strict routines, but today's diabetes population seek flexibility and the ability to exhibit impulsive behavior to the same extent as healthy persons.[24] Clear evidence on the impact of postprandial glycemic levels on overall glycemic control is unlikely to change this and introduce frequent postprandial SMBG measurements with dubious promises of detection of postprandial hyperglycemia, so more flexible approaches to the management of this important aspect of glycemic control is indicated. Continuous glucose monitoring systems may pose a solution but only on the days when it is worn.

Conclusions

The optimal time to measure postprandial blood glucose cannot be easily determined, as significant variations occur between meal types and subjects, as well as within subjects.

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Disclosures:

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