Postprandial Glucose Dynamics and Associated Symptoms in Type 2 Diabetes Mellitus

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This research was supported by Eli Lilly & Company, Indianapolis, Ind.

KEY WORDS: postprandial glucose, hyperglycemia, type 2 diabetes mellitus

ABSTRACT

Objectives: This study examined the dynamics of postprandial glucose (PPG) and symptoms among adults with type 2 diabetes mellitus (T2DM) in their natural environment. Using a hand-held computer for 70 trials, 36 adults with T2DM rated symptoms, performed tests, and measured their blood glucose (BG).

Results: The mean peak PPG value was 11.3 mmol/L achieved 2-3 hours after meal, while highest symptom ratings and cognitive slowing were observed within the first hour after meal, at a time corresponding to the steepest slope of PPG increase. Thus, we hypothesized that postprandial symptoms maybe related to a higher rate of BG increase, which was confirmed by high correlations (r = 0.5-0.75) between symptom ratings and BG rate of increase.

Conclusions: We conclude that postprandial symptom elevation is related to the rate of BG increase, thus treatments designed to limit the magnitude of post-meal BG fluctuation may reduce its symptomatic and cognitive consequences.

INTRODUCTION

In nondiabetic individuals postprandial glucose (PPG) fluctuations are limited in both their peak value [rarely exceeding 7.8 mmol/L (140 mg/dL)] and in their duration, with a peak PPG approximately 1 hour after the start of a meal, returning to preprandial levels within 2-3 hours. [1] In individuals with type 1 diabetes (T1DM) or type 2 diabetes mellitus (T2DM) a number of factors, such as inadequate available insulin, delayed insulin action, or abnormalities in glucagon secretion, contribute to delayed peak PPG, and higher and prolonged PPG elevation.[1] The American Diabetes Association Consensus Statement on postprandial hyperglycemia concluded that "in general, a measurement of plasma glucose 2 h after the start of a meal is practical, generally approximates the peak value in patients with diabetes, and provides a reasonable assessment of postprandial hyperglycemia." [1]

However, the dynamics of PPG are complex, dependent on many factors, such

as the amount and the composition of the meal, and still not well understood. Even though a linear relationship between postprandial and post-challenge (after a 75-g oral glucose load) glucose 2 hours after a meal was established in laboratory conditions,[2] the dynamics of this relationship in the field is difficult to assess.[3] Perhaps as a result of the lack of a standard PPG assessment, the usual clinical appraisal of glycemic control includes only better-defined and more stable measures, such as fasting plasma glucose (FPG) and/or glycosylated hemoglobin (HbA_{1c}). However, FPG reflects blood glucose (BG) values after the effect of carbohydrate intake has been eliminated and HbA_{1c} represents the average BG over a certain period of time, which makes both of these measures insensitive to BG excursions throughout the day—in particular to PPG fluctuations. For example, a recent study[4] of more than 800 people with T2DM found that after meals, many subjects had glucose levels >8.9 mmol/L (160 mg/dL) and/or glucose excursions >2.2 mmol/L (40 mg/dL) despite HbA_{1c} <7%. This study also concluded that HbA_{1c} is more related to preprandial than postprandial BG levels.[4] Since there is evidence to the contrary as well,[5] this conclusion remains unclear.[6] Thus, despite being the gold-standard marker of glycemic control,[7-8] HbA_{1c} maybe a poor measure of rapid BG fluctuations.

Mounting evidence, however, points to the importance of BG fluctuations. A number of recent studies found that postprandial hyperglycemia is an independent factor contributing to cardiovascular complications and increased mortality, especially in people with T2DM.[9-14] The Diabetes Intervention Study, the only prospective study considering elevated PPG as a contributor to complications in T2DM, concluded that PPG, but not FPG, was an independent predictor of mortality in T2DM.[15] A recent review of studies in this area concluded that "there are now comprehensive and consistent data from pathophysiological as well as epidemiologic studies that excessive post-load glucose excursions have acute and chronic harmful effects on the endothelium and vessel wall."[3] Thus, an assessment of PPG dynamics in the natural environment would be a valuable tool for evaluation of glycemic control.

In addition to the long-term negative effects of elevated PPG, clinical experience suggests a relationship between postprandial hyperglycemia and acute and transient increases in psychological symptoms and cognitive disruptions.[2,16-18] However, there have been no prospective and objective investigations of the relationship of such symptoms/cognitive dysfunctions with postprandial BG parameters, especially with parameters of postprandial BG dynamics in the natural environment of people with diabetes. For example, it is unclear whether the peak absolute value of PPG is responsible for triggering symptoms, or symptoms are mainly related to the speed and magnitude of BG increase post-meal. This study investigates when BG peaks in T2DM adults following meals in their natural environment, and whether and which parameters of BG dynamics are associated with experienced symptoms and cognitive disruptions.

MATERIALS AND METHODS

Subjects

Forty-four adults with T2DM gave informed consent for participation in this study, which was approved by our institution's Investigation Review Board. Eight of subjects did not complete the data collection: 4 because of difficulty managing the hand-held computer (ages 61, 63, 70, 74), 2 because of being too busy, and 2 because of other medical problems. The average age of the 36 participants was 50 years (SD = 11), average duration of T2DM was 10 years (SD = 9), and average BMI was 34 (SD = 10). There were 21 females; 38% of the subjects used insulin to control their diabetes.

Procedure

Subjects completed a series of psychometric instruments, including the Beck Depression Inventory. They were then instructed to use the Handspring Visor Platinum, (Handspring, Inc, Mountain View, CA) hand-held computer (HHC) immediately before self-monitoring of blood glucose (SMBG). No specific SMBG schedule was given to the subjects; they were required only to complete 70 HHC trials within 3-4 weeks. The HHC was equipped with our custom-developed symptom/behavioral assessment software. At each trial the HHC first collected data on perceived symptoms and cognitive performance. Then, subjects measured and entered their BG level.

Symptoms. At each trial the HHC presented in a random order 16 symptoms and prompted subjects to rate them on a scale from 0 = none to 6 = extreme. There were 6 physical symptoms (need to urinate; sweet/funny taste; dry eyes, nose, mouth; tired/fatigued; thirsty; nausea), 6 mood symptoms (nervous/anxious; irritable/frustrated; restless/jittery; sad/blue; giddy/funny; don't care/apathetic), and 4 cognitive symptoms (difficulty concentrating; difficulty speaking; uncoordinated; slowed thinking).

Cognitive tests. The HHC presented the following tests: (1) 10 mental subtraction problems that used randomly generated 3-digit numbers, with subjects entering answers on a number pad; and (2) 2 levels of the Paced Serial Addition Test (PSAT) presenting a sequence of single-digit numbers for which the subject has to enter the sum of each pair of sequential numbers. Levels 1 and 2 of the test present numbers at 4-second and 2-second intervals, respectively.

Other parameters. The HHC asked subjects to enter the time when "you began eating your last meal" and at the end of each trial, the subjects were prompted to measure and enter their BG. For the latter all subjects used One Touch Ultra glucometers (Lifescan, Milpitas, Calif.). Three precautions were taken to encourage and monitor whether symptom entries and cognitive testing preceded SMBG. (1) Each HHC trial began with the message, "No blood sample yet." (2) The HHC tracked the elapsed time between the prompt "Measure your BG" and the entry of this SMBG reading. Since at least 10 seconds are required for a subject to lance a finger, collect a blood sample, and analyze BG level with the One Touch Ultra, any readings entered in less than 10 seconds were considered invalid. (3) The BG readings entered by the subjects into the HHC were compared to data in the glucometer's memory to ensure accuracy of SMBG results. An earlier version of this HHC routine developed for Psion 250 HHC was used in our previous studies of symptoms and behaviors related to hypoglycemia.[19-21]

Data Analysis

BG values were averaged across all subjects in 10 time intervals post-meal and plotted and compared using univariate ANOVA. To obtain comparable estimates of average BG across these intervals, each time interval was at least one half-hour in duration and was required to contain at least 200 SMBG readings, that is, at least 8% of all HHC/SMBG readings. This approach resulted in approximately equal weights (in terms of number of readings) of the time intervals.

Symptoms and cognitive test performance. In order to eliminate the influence of hypoglycemia, symptom ratings and test results were considered only if BG was greater than 6.7 mmol/L (120 mg/dL). In order to evaluate the magnitude of each individual postprandial symptom its ratings were averaged across subjects at 1-hour time intervals post-meal and compared using univariate ANOVA. The average symptom magnitude in each category, (physical, mood, and cognitive) was computed as well. Similarly, cognitive impairment was assessed using the time to complete 10

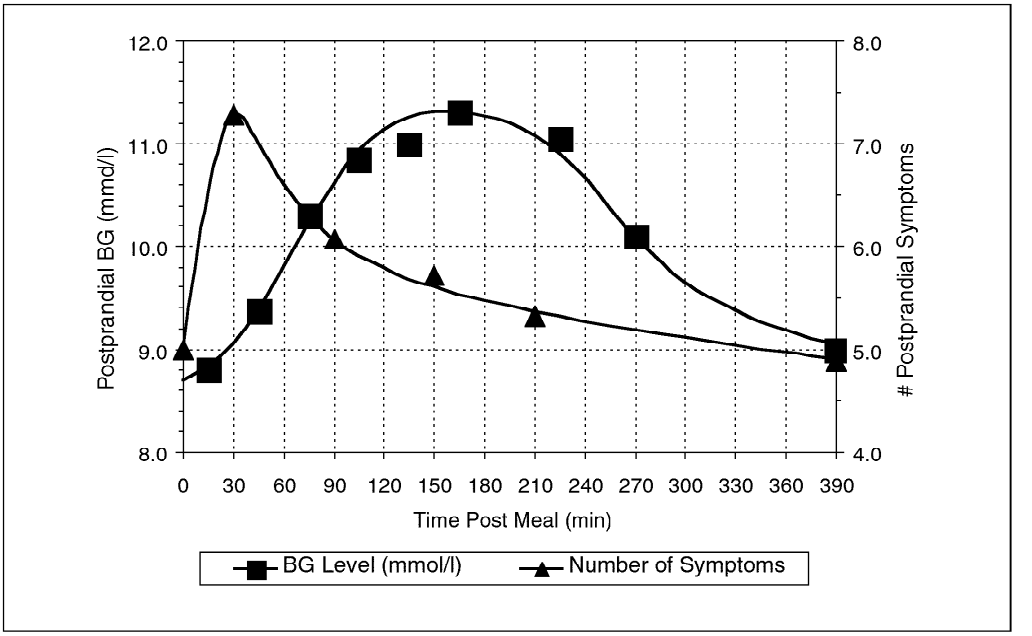

Figure 1. Postprandial blood glucose (BG) levels and postprandial increase in overall symptom reporting are plotted against elapsed time after a meal (x-axis in minutes). The postprandial BG values (black squares) are presented in the primary y-axis and demonstrate a peak PPG value at approximately 2.5 – 3 hours after a meal. The number of elevated postprandial symptoms (symptoms with ratings greater than 0 over the course of PPG) is presented in the secondary y-axis (black triangles) and demonstrates a peak symptom reporting within 1 hour after a meal.

mental subtractions and the number of correct additions on the faster (Level 1) and slower (Level 2) PSAT, averaged at 1-hour intervals post-meal. Average postprandial BG 1, 2, and 3 hours after meal was correlated with corresponding symptom ratings and cognitive performance results. In order to account for multiple tests we used Bonferroni corrections, accepting only results significant at $P<0.01$.

In addition to computing average symptom magnitude and in order to evaluate the overall dynamics of all symptoms combined, the average number of all symptoms rated 1 or greater was computed in several time intervals post-meal and superimposed on the course of PPG. As with PPG, each time interval was required to contain at least 200 HHC trials with BG>6.7 mmol/L.

Rate of BG increase. From each subject's SMBG data collected concurrently with the HHC, we computed an estimate of this subject's BG rate of increase (BGRI). This variable is similar to the previously reported BG rate of change,[22] but takes into account only increases in BG, not overall fluctuations. Specifically, BGRI was computed as the average of the ratios $(BG(t_2)-BG(t_1))/(t_2-t_1)$, where $BG(t_2) > BG(t_1)$ were any two increasing consecutive SMBG readings of a subject taken at times t_2 and t_1 within the same day. In essence, this computation provided an estimate, for each person, of the magnitude and speed of increase of his/her BG levels in mmol/L/h. With this SMBG data set, it was only possible to compute BGRI as a single measure for each individual, not as a measure specific to each individual's postprandial period (the latter would require at least 2 SMBG readings/subject post-meal for several days). However, since fast BG increases are predominantly observed after meals, we assumed that BGRI was mostly influenced by postprandial BG elevation.

Table 1. Average Postprandial Symptom Ratings* and Cognitive Test Performance.

		Pre-prandial	Postprandial Ratings			F (P)
			1 h	2 h	3 h	
Physical symptoms	Need to urinate	1.0	1.7	1.3	1.2	7.7 (<0.001)
	Sweet/funny taste	1.0	1.8	1.3	0.7	38.8 (<0.001)
	Dry eyes, nose, mouth	1.3	2.2	1.8	1.5	13.0 (<0.001)
	Tired/fatigued	1.8	2.1	1.9	1.9	1.0 (NS)
	Thirsty	1.5	2.4	1.9	1.7	11.2 (<0.001)
	Nausea	0.6	1.5	1.0	0.8	13.8 (<0.001)
	Average magnitude of physical symptoms	1.11	1.94	1.56	1.30	18.9 (<0.001)
	Nervous/anxious	0.6	1.2	0.9	1.0	7.8 (<0.001)
Mood symptoms	Irritable/frustrated	0.9	1.2	1.0	1.1	1.4 (NS)
	Restless/jittery	0.6	1.1	1.0	1.1	9.1 (<0.001)
	Sad/blue	0.4	0.8	0.6	0.7	5.5 (<0.001)
	Giddy/funny	0.1	0.5	0.5	0.2	10.6 (<0.001)
	Don't care/apathetic	0.4	0.8	0.5	0.6	8.2 (<0.001)
	Average magnitude of mood symptoms	0.50	0.93	0.76	0.79	9.5 (<0.001)
Cognitive symptoms	Difficulty concentrating	0.5	0.9	0.8	0.7	5.2 (<0.001)
	Difficulty speaking	0.2	0.5	0.4	0.3	6.6 (<0.001)
	Uncoordinated	0.4	0.7	0.6	0.6	4.7 (<0.001)
	Slowed thinking	0.5	0.9	0.8	0.7	8.0 (<0.001)
	Average magnitude of cognitive symptoms	0.39	0.75	0.65	0.61	7.9 (<0.001)
Cognitive tests	Time to complete 10 mental subtractions (sec.)	104	130	110	99	14.9 (<0.001)
	PSAT – Level 1 Number correct answers	3.8	3.4	3.2	3.9	2.4 (NS)
	PSAT – Level 2 Number correct answers	2.4	1.6	2.1	2.5	11.7 (<0.001)

Using a scale from 0 = none to 6 = extreme.
NS = not significant; h = hour.

RESULTS

Postprandial BG Dynamics

Figure 1 presents the average (across subjects) course of BG fluctuations. The peak PPG value of 11.3 mmol/L (203 mg/dL) was achieved between 2.5 and 3 hours after a meal. The average difference between preprandial and postprandial BG was 2.5 mmol/L (45 mg/dL). One-way ANOVA showed that the PPG values were significantly different between the time intervals post meal ($F = 10.3$, $P<0.001$) (see Figure 1, primary axis).

Table 2. Correlations of Average Symptom Ratings* and Cognitive Test Performance with Blood Glucose Rate of Increase.

		Correlation Coefficients**		
		1 h	2 h	3 h
Physical Symptoms	Need to urinate	0.48	-0.02	0.02
	Sweet/funny taste	0.39	0.01	0.08
	Dry eyes, nose, mouth	0.46	-0.05	-0.02
	Tired/fatigued	0.41	0.21	0.18
	Thirsty	0.33	0.08	0.03
	Nausea	0.42	0.02	0.12
	Average magnitude of physical symptoms	0.52	0.06	0.09
Mood symptoms	Nervous/anxious	0.69	0.48	0.43
	Irritable/frustrated	0.56	0.28	0.33
	Restless/jittery	0.50	0.52	0.45
	Sad/blue	0.68	0.53	0.44
	Giddy/funny	0.50	0.07	-0.06
	Not care/apathetic	0.66	0.54	0.37
	Average magnitude of mood symptoms	0.70	0.49	0.44
Cognitive symptoms	Difficulty concentrating	0.60	0.39	0.30
	Difficulty speaking	0.75	0.34	.25
	Uncoordinated	0.76	0.52	.22
	Slowed thinking	0.58	0.34	.31
	Average magnitude of cognitive symptoms	0.74	0.44	0.30
Cognitive tests	Time to complete 10 mental subtractions (sec.)	0.27	0.06	0.02
	PSAT – Level 1 Number correct answers	-0.21	-0.21	0.18
	PSAT – Level 2 Number correct answers	-0.26	-0.02	0.15

* Using a scale from 0 = none to 6 = extreme.

** With this sample size correlations above 0.37 yield P-levels below P= 0.05, while correlations above 0.47 are significant at P = 0.01. The latter are indicated in bold.

Postprandial Symptoms and Cognitive Slowing

Most physical, mood, and cognitive symptoms displayed similar patterns of highest average rating within the first hour after meal and a significant decrease thereafter (Table 1).

Specifically, 5 of the 6 physical symptoms were rated higher post-meal: subjects reported a greater need to urinate ($F = 7.7$, $P<0.001$), sweet taste ($F = 38.8$, $P<0.001$), dry eyes/nose/mouth ($F = 13.0$, $P<0.001$),

thirst (F = 11.2, $P<0.001$), and nausea (F = 13.8, $P< 0.001$). One-way ANOVAs across time ranges were highly significant for all comparisons. Similarly, all mood symptoms (nervous/anxious; irritable/frustrated; restless/jittery; sad/blue; giddy/funny; don't care/apathetic) were significantly elevated within the first hour after a meal, but remained elevated somewhat longer than the physical symptoms. All but one mood symptom (giddy/funny) went up, then down, then up again with a second smaller peak between 2 and 3 hours after meal. This fluctuation, however, was not statistically significant. All four cognitive symptoms (difficulty concentrating; difficulty speaking; uncoordinated; slowed thinking) became significantly elevated during the first hour after meal and receded thereafter (Table 1). The average magnitudes in all symptom categories—physical, mood, and cognitive—were significantly higher in the first hour post-meal (Table 1).

Mental calculations within 1 hour post-meal were almost 30% slower (slowing from a baseline of about 100 to 130 seconds to complete 10 subtractions), with this effect disappearing within 2 hours (F = 14.9, $P<0.001$). The correctness of the mental calculations, however, remained constant throughout all postprandial periods (about 90% correct subtractions). The easier PSAT–Level 1 test did not demonstrate significant impairment post-meal; however, the more demanding Level 2 resulted in approximately 30% fewer correct answers within 1 hour after a meal (from 2.4 to 1.6 correct answers). This effect vanished within 2 hours post-meal (F = 11.7, $P<0.001$) (See Table 1, cognitive tests).

Table 1 demonstrates that most symptoms achieved their highest magnitude within the first hour after meal, before the PPG reached its peak. Thus, symptom elevation was not clearly related to extreme PPG. Indeed, average postprandial symptom magnitudes and test results 1, 2, and 3 hours after a meal did not correlate significantly with PPG values averaged at the same time intervals, with the exception of a few correlation coefficients of approximately 0.4 (approximate $P = 0.02$), which were not considered significant taking into account the large number of simultaneous tests.

In order to more precisely assess the relationship between PPG and overall postprandial symptoms, we superimposed the number of symptoms with ratings greater than 0 over the course of PPG (Figure 1, secondary axis). This superposition confirmed that symptom occurrence was not related to highest PPG and in general preceded the peak PPG values. Figure 1 also implied that more symptoms occurred when PPG increase was fastest, that is, within the first-to-second hour post-meal, where the slope of the PPG curve was steepest. Thus, we formulated the hypothesis that postprandial symptoms are primarily related to a higher rate of BG increase, and less to the absolute value of extreme BG.

Postprandial Symptoms and BGRI

In an attempt to test this hypothesis, we used BGRI as an estimate of the steepness of his slope of BG increase throughout the day for each subject. The average BGRI was 0.78 (SD = 0.60) mmol/L/h and the median BGRI was 0.68 mmol/L/h. The BGRI correlated significantly with all mood and cognitive symptoms at 1-hour post-meal. The correlation with physical symptoms was weaker. Table 2 presents the correlation coefficients with BGRI of all postprandial symptom ratings and cognitive performance results at 1, 2, and 3 hours post-meal.

Taken by symptom category within the first hour post-meal, mood and cognitive symptoms displayed high correlations with BGRI (r = 0.70 and r = 0.74, respectively). The correlation of the average magnitude of physical symptoms with BGRI was weaker (r = 0.52), but still statistically significant at $P<0.01$ (Table 2). For all symptoms (individual and by category) the correla-

tions with BGRI were highest within 1 hour post-meal, and gradually decreased at 2 and 3 hours post-meal. Since PPG increase slowed down at 2 and 3 hours post-meal, and the PPG curve gradually flattened, this was precisely the effect to be expected if symptoms were related to PPG increase and not to extreme PPG values. With this sample size (N = 36) correlations above 0.47 yielded *P*-levels below 0.01 and were considered significant. Several correlation coefficients were above 0.6. For example, the average magnitude of "difficulty speaking" and "uncoordinated" 1 hour post-meal produced a correlation coefficient of 0.75-0.76 with BGRI (see Table 2).

DISCUSSION

This study used new monitoring technology (HHC and custom software) to assess in-the-field dynamics of postprandial BG and associated symptoms and cognitive impairment in adults with type 2 diabetes mellitus. Our data allowed for a reconstruction of PPG dynamics in our subjects' natural environment and confirmed laboratory observations and common knowledge that PPG is most elevated 2-3 hours after meal. [1] In addition, we demonstrated that after meals self-reported physical symptoms and moods became significantly elevated, and that objectively determined cognitive slowing of approximately 30% was apparent.

Surprisingly, however, symptom elevation and cognitive slowing did not follow the course of absolute PPG values. Instead, for most symptoms highest symptom ratings were observed within 1 hour after a meal (Table 1), not when PPG was at its peak 2-3 hours post-meal. Overall, plotting a summary of all symptoms and PPG against the time elapsed after a meal revealed that symptoms generally occurred during the time of steepest slope of PPG increase (Figure 1). Thus, we hypothesized that postprandial symptoms occurred during times when BG increase was fastest. With our data, however, we could not definitely confirm this notion. One limitation in the design of the study was that the BG rate of increase could not be computed strictly for pre-to-postprandial periods, that is, the slope of PPG increase could not be estimated directly. This was due to the lack of sufficient number of BG readings within a pre- and corresponding postprandial period; at least two, pre-and postprandial, readings on several days per subject are needed in order to estimate PPG slope.

Instead, we confirmed a less specific hypothesis: higher postprandial symptoms are related to higher overall BG rate of increase. The BGRI was based on a previously reported measure, BG rate of change,[22] but it took into account only consecutively increasing SMBG readings, not any two consecutive readings. As computed here, BGRI was not specific to postprandial time periods; however, we assumed that it was most influenced by the largest (per hour) BG increases that subjects experienced post-meal. Indeed, it was illogical to expect that large and fast BG elevations could have occurred with no relationship to a preceding significant carbohydrate intake. Thus, we could speculate that the process of PPG elevation contributed to symptoms more than the absolute values of postprandial hyperglycemia. While this speculation may be confirmed (or rejected) by future studies, here we were able to clearly observe two related properties: (1) symptom ratings were higher during the first hour post-meal and this was the period of steepest slope of PPG increase, and (2) postprandial symptoms were highly correlated with subject's overall rate of BG increase.

In fact, the correlations between mood and cognitive symptoms and BGRI were very high, in some cases higher than 0.7 (Table 2). Given that symptom ratings were derived from behavioral self-assessment, while BGRI was derived from concurrent but quite different sets of SMBG data downloaded from the subjects' glucometer memories, correlations of that magnitude imply very strong [linear] relationships.

Thus, the magnitude and speed of BG increase post-meal may be the single most significant determinant of postprandial symptoms.

In contrast to symptoms, reduced performance on cognitive tests, although well expressed in the first hour after meal (Table 1, cognitive tests), could not be explained by absolute PPG peak, or by BGRI. Thus, alternative mechanisms of postprandial cognitive slowing must be considered. For example, there may be a BG threshold, above which these effects occur in a stepwise fashion, or some disruption of metabolic homeostasis may be responsible for the observed cognitive slowing. Further studies will be needed to address these issues.

The results of this study imply that in people with T2DM the most effective time to sample symptoms and cognitive functioning postprandially is during the first 1-2 hours after a meal. This is also the time when fastest BG elevation was observed in this study and documented by others.[0] Since the BGRI was a better correlate of postprandial symptoms than absolute PPG peaks, treatment regiments designed to reduce the magnitude and the speed of PPG fluctuations, such as rapid-acting insulin analogs or complex carbohydrate diets, may reduce the negative symptomatic and cognitive consequences of postprandial glucose excursions.

ACKNOWLEDGMENTS

The authors would like to thank Pamela Erickson, Haya Ascher-Savanum, PhD, and James Malone, MD, for their helpful reviews and suggestions on previous drafts of this manuscript.

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