Interstitial Glucose Level Is a Significant Predictor of Energy Intake in Free-Living Women with Healthy Body Weight[1,2]

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ABSTRACT The relative contribution of circulating glucose to meal-to-meal variability in energy intake is not known. In 8 free-living young (median age 26.5 y) women with healthy body weight (median BMI 22.2 kg/m^2), we measured glucose in the interstitial space by an automated monitoring procedure (continuous glucose monitoring system, CGMS™) for up to 3 consecutive days (mean 706 glucose readings per subject). We examined the association between interstitial glucose (which lags blood glucose by ~10 min), self-reported hunger, satiety, desire for a meal, and nutrient intakes. Participants reported consuming a typical Western diet (59% carbohydrate, 27% fat, 14% protein). Median (interquartile range) interstitial glucose was 5.2 mmol/L (4.7–5.8). Using repeated-measures techniques in univariate analyses, desire for a meal ($r = 0.45$, $P < 0.0001$), hunger ($r = 0.37$, $P = 0.0002$), satiety ($r = -0.40$, $P < 0.0001$), low interstitial absolute mean glucose up to 25 min before eating ($r = -0.23$, $P = 0.02$), and a large decline in glucose between 40 and 5 min before eating ($r = -0.17$, $P = 0.08$) were all associated with meal energy intake. In multivariate regression analyses, desire for a meal ($P < 0.0001$) and hunger ($P = 0.02$) were the strongest independent contributors to meal energy intake, whereas absolute mean glucose measured in the period 15 to 0 min before eating was marginally significant ($P = 0.08$). In conclusion, absolute glucose level is a significant predictor of energy intake in nonobese women. However, desire for a meal and hunger are quantitatively more important, emphasizing the importance of both glucose signals and nonglucose (internal or environmental) factors in within-subject variability in energy intake. In addition, the CGMS may have utility in understanding the role of circulating glucose in energy regulation in free-living subjects under a wide range of different nutritional conditions. J. Nutr. 135: 1070–1074, 2005.

KEY WORDS: • *glucose* • *energy* • *hunger* • *satiety* • *free-living*

An epidemic of overweight and obesity has developed in the United States during the past 20 years, with nearly two thirds of U.S. adults now overweight (1). Although the pathogenesis of overweight and obesity is clearly multifactorial, factors influencing energy intake are thought to play a central role (2). Thus, further understanding of the mechanisms and signals that regulate energy intake may lead to interventions with improved efficacy.

Multiple internal (physiologic) and external (environmental) factors are known to interact with each other in complex ways to regulate energy intake and maintain energy homeostasis (2–4). Among the internal factors, blood glucose has long been assumed to be an important determinant of energy intake, due primarily to its tight regulation and its dominant role as an energy source for the central nervous system (5,6). The glucostatic theory, first proposed in the 1950s, suggested that hunger and spontaneous meal initiation are stimulated at least in part by changes in circulating glucose, as subsequently demonstrated in controlled experimental settings in rats (5,7–9) and humans (10,11). However, as our understanding of energy homeostasis has broadened to include multiple additional internal pathways and external factors, the relative contribution of glucose dynamics to overall energy regulation in free-living individuals is unclear.

The primary objectives of the present study were as follows: *1*) to determine the utility of interstitial glucose measurements for studies of glucose homeostasis and energy regulation in free-living individuals; and *2*) to examine the relative contribution of glucose levels, hunger, satiety, and desire for a meal to energy intake in nonobese free-living individuals allowed to lead their normal daily lives and eat according to their typical pattern.

SUBJECTS AND METHODS

Subjects. Healthy women aged 18–40 y, weight-stable and with a BMI in the range of 18.5–24.9 kg/m^2 were recruited from the

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hospital community at Tufts-New England Medical Center (Tufts-NEMC).[4] Potential volunteers were asked to come to the General Clinical Research Center (GCRC) at Tufts-NEMC for screening with a general health history questionnaire and dietary restraint questionnaire (Three-Factor Eating Questionnaire-Restraint, TFEQ-R) (12). Women were excluded if they had irregular daily eating patterns (defined here for protocol convenience as > 3 major meals per day), or had a dietary restraint score > 11 (12), a history of diabetes, hypertension, heart disease, cancer, cachexia, eating disorders including bulimia and anorexia, depression, AIDS, alcoholism, or inflammatory disorders. Other exclusion criteria included pregnancy, weight loss or gain > 5 kg over the previous year, significant endurance training (participation in sports for > 6 h/wk), child bearing within the past year, and current cigarette smoking.

Study design. The study protocol was approved by the Human Investigation Review Committee at Tufts-NEMC and all participants gave informed consent before participation. Women accepted as subjects came to the GCRC after a 12-h overnight fast. Weight (kg) and height (cm) were measured while wearing a hospital gown only and the glucose measurements were started as described below. Subjects were given instructions on how to fill out the questionnaires to report hunger, satiety, desire for a meal, and dietary intake before being discharged with instructions to continue their normal routine during the next 3 d (except that they were required to refrain from exercise).

Glucose measurements. Glucose measurements were performed with the continuous glucose monitoring system (CGMS™, Medtronic-Mini Med). The CGMS, a device approved by the U.S. FDA for clinical use, provides measurements of mean glucose level in the interstitial tissue every 5 min and is worn without any discomfort during all normal daily activities including taking a shower (13). Medical personnel place a small catheter in the subject's interstitial tissue in the abdominal area. The catheter contains a sensor, which is attached to a small plastic disk about the size of a dime, which is taped to the skin to hold the sensor in place. The sensor continuously detects and converts glucose from the subject's interstitial tissue into an electrical signal, whose strength is proportional to the amount of glucose present. A thin cable connects the sensor to a pager-sized glucose monitor, which records and stores glucose values in memory. The monitor receives the electrical signal from the sensor every 10 s and stores an average glucose measurement every 5 min. The sensor transmits glucose values to the monitor automatically, 24 h/d, for up to 3 d, before requiring a catheter change; this translates into up to 288 readings over 24 h or 864 readings over 72 h. The CGMS requires glucose measurement by finger-pricking (one finger-prick at baseline and 3–4 finger-pricks daily) for calibration. The subjects do not have access to real-time glucose values. The CGMS was tested on patients with diabetes and close correlation between sensor measurements and blood glucose values was demonstrated ($r = 0.92$, CV 5%) (14). Glucose values measured in the interstitial fluid lag the blood glucose concentration by a mean of 10 min, especially when blood glucose is rising or falling rapidly (15,16). A computer program (Solutions CGMS Sensor Software, Version 3.0A, Medtronic-MiniMed) was used for downloading and analyzing the glucose data.

Trained nursing personnel inserted the CGMS catheter/sensor in the interstitial tissue in the abdomen or flank area, and the device was calibrated with capillary blood glucose obtained through finger pricking. Subjects returned to the GCRC in 72 h. The catheter with the sensor was removed and the insertion site was checked for any signs of infection. Questionnaires with self-reported information were collected and the study was terminated.

Visual analog scales. Assessment of hunger ("how hungry are you now?"), satiety ("how full or satiated do you feel right now?") and desire for a meal ("how would you describe your desire for a meal right now?") was performed using 100-mm visual analog scales (17). Self-assessment of hunger, satiety, and desire for a meal was recorded every 3 h while awake, and before every meal/snack. The date and time were recorded for each data point.

Dietary intake. The women's usual dietary intake was assessed with diet records, which were kept by each subject during the entire time that the CGMS monitor was worn. The women were given verbal and written directions on how to keep the diet records, which included instructions on how to be as specific and complete as possible when recording their food intake and to include the date and time of each eating occasion, brand names, recipes, names of restaurants, etc. Diet records were analyzed for total energy intake (kJ) and macronutrient composition (g) using the Nutrition Data System for Research (NDS-R), software version 4.05_33, developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN, Food and Nutrient Database 33, released 2002 (18).

Statistics and data analysis. The data were analyzed using repeated-measures techniques. Univariate within-subject correlation coefficients were calculated between variables of interest (glucose level, hunger, satiety, desire for a meal as the predictor variables and energy intake as the outcome) as described by Bland and Altman (19). This method let us examine whether a change in a predictor variable (e.g., glucose) within an individual was associated with a change in the predictor variable (e.g., energy intake) by removing the differences between subjects and looking only at changes within. We examined glucose values in relation to self-reports in various ways. First, we examined the absolute mean glucose level measured in the interstitial space over a 5-min period immediately before an event. Because this glucose value may not necessarily be the best correlate of the event, correlation analyses were repeated with inclusion of various other glucose levels (absolute mean levels and changes over time) within a 60-min period before self-reporting of an event. Because measurements obtained with the CGMS lag the blood glucose concentration, we also examined the interstitial glucose level 5 and 10 min after the meal, which reflects the blood glucose measurement immediately before the meal.

Multivariate regression analyses were performed to determine the contribution of the independent variables (glucose level, hunger, satiety, and desire for a meal) that predict outcomes of interest (energy intake), corrected for age, BMI, and dietary restraint (based on TFEQ-R). We used an exchangeable (compound symmetric) correlation structure in our analyses. Although only 8 subjects were studied, given the multiple data points available per subject, we were able to fit regression models with repeated-measures analyses. Statistical significance was set at $\alpha = 0.05$. Values are expressed as median (interquartile range; IQR) unless otherwise specified. Statistical analysis was done using SAS version 8.2.

RESULTS

Descriptive statistics. Subject characteristics are shown in **Table 1**. The low dietary restraint score of the subjects indicated that as a group, they were not inclined to control their food intake cognitively.

The median (IQR) duration of continuous glucose monitoring sampling per subject was 65.2 (26.8) h with a range of 33.3 to 72 h for a total of 5645 glucose observations out of a possible 6912. Five subjects did not complete the full 72 h due to technical problems (accidental removal of the cable, inter-

TABLE 1

Subject characteristics of the 8 young Caucasian women with healthy body weight

	Median	IQR
Age, *y*	26.5	23.5–29.0
Weight, *kg*	59.8	55.2–62.5
Height, *cm*	163	157–167
BMI, *kg/m*^{2}	22.2	21.3–23.3
Dietary Restraint Score[1]	6	4.5–10

[1] The Dietary Restraint Score was obtained from the TFEQ-R (12).

[4] Abbreviations used: CGMS, continuous glucose monitoring system; GCRC, General Clinical Research Center; IQR, interquartile range; TFEQ-R, Three-Factor Eating Questionnaire-Restraint; Tufts-NEMC, Tufts-New England Medical Center.

mittent bending of the cable). **Figure 1** shows representative daily curves obtained with the CGMS device from 2 of the women. While the women were ambulatory, the median glucose level as measured in the interstitial fluid throughout the study was 5.22 mmol/L **(Table 2)**. The median (IQR) energy intake per meal for all subjects was 1398 (783–2165) kJ and the macronutrient composition was typical of the American diet (Table 2).

Univariate correlation between glucose level, hunger, desire for a meal, satiety, and subsequent energy intake. We examined whether there were within-subject univariate correlations between glucose levels, self-reported measures of hunger, desire for a meal, and satiety (as independent variables), and subsequent energy intake (as dependent variable). As discussed above, correlation analyses included various glucose levels (absolute levels and declines) from CGMS measurements within a 60-min period before self-reports. After examining scatter plots of individual subjects, we log-transformed the energy intake data. In simple linear univariate regression, desire for a meal ($r = 0.45$, $P < 0.001$), hunger ($r = 0.37$, $P < 0.001$), satiety ($r = -0.40$, $P < 0.001$), and various glucose levels all were correlated with subsequent energy intake **(Table 3)**. Absolute glucose values that showed the best correlation with subsequent energy intake were those measured in the interstitial space between 0 and 15 min before the meal ($r = -0.23$, $P = 0.021$), which reflects blood glucose 10–25 min before the meal. Various absolute mean glucose values up to 25 min before the meal also showed good correlation. Interstitial glucose levels measured 10 min after the meal, which reflect the blood glucose concentration immediately before the meal, were not significant (Table 3). We also

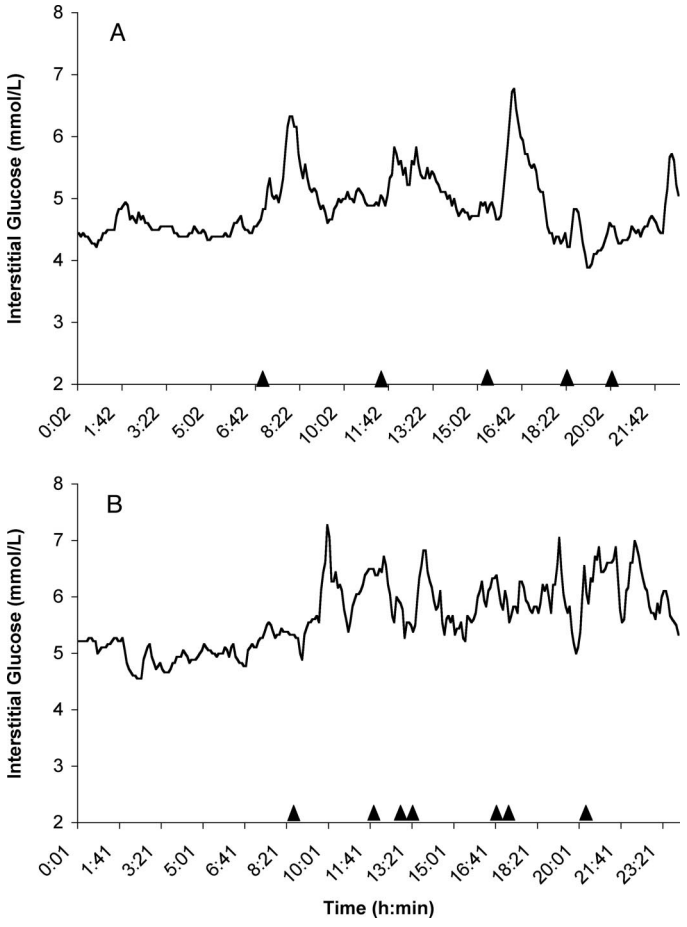

FIGURE 1 Interstitial glucose 24-h profiles in healthy young women obtained with the CGMS from 2 of the women (*A* and *B*). Meals and snacks containing energy are shown as ▲.

TABLE 2

Glucose level and meal energy intake and composition for 8 healthy young women during the 3-d observational study period

	Total number of observations	Median	IQR
Glucose level,[1] *mmol/L*	5645	5.22	4.66–5.77
Energy,[2] *kJ/meal*	107	1398	783–2,165
Macronutrient composition			
Carbohydrate, *% meal energy*	107	59	43–73
Fat, *% meal energy*	107	27	16–38
Protein, *% meal energy*	107	14	9–19
Total fiber, *g/meal*	107	3.0	1.3–6.7

[1] Glucose level measured in the interstitial space by the CGMS.
[2] Energy, macronutrient composition and fiber content were calculated from self-reported food records.

TABLE 3

Within-subject univariate correlates of energy intake in 8 healthy young women[1]

	Energy intake		Log of energy intake	
Independent variables	*r*	*P*	*r*	*P*
Desire for meal	0.45	<0.001	0.56	<0.001
Hunger	0.37	<0.001	0.43	<0.001
Satiety	−0.40	<0.001	−0.42	<0.001
Absolute mean glucose values in relation to self-reports of meal initiation[2]				
Glucose −45 to −30 min	−0.18	0.1	−0.18	0.09
Glucose −30 to −25 min	−0.17	0.11	−0.18	0.09
Glucose −30 to −15 min	−0.21	0.05	−0.21	0.04
Glucose −15 to 0 min	−0.23	0.02	−0.22	0.03
Glucose −5 to 0 min	−0.22	0.03	−0.22	0.04
Glucose 0 to +5 min	0.24	0.03	−0.22	0.04
Glucose +5 to +10 min	−0.04	0.71	0.02	0.91
Magnitude of change in glucose values in relation to self-reports of meal initiation[3]				
Glucose −40 to −20 min	0.15	0.17	0.13	0.21
Glucose −40 to −5 min	0.17	0.08	0.14	0.17
Glucose −40 to 0 min	0.17	0.11	0.14	0.18
Glucose −30 to 0 min	0.16	0.13	0.14	0.19
Glucose −20 to 0 min	0.07	0.5	0.05	0.64

[1] *r* is the within-subject correlation coefficient, calculated with analysis of covariance techniques. Glucose was measured in the interstitial space by the CGMS™.
[2] Mean interstitial glucose over the specified time period in relation to self-report of meal initiation, e.g., glucose −30 min to −15 min is the mean glucose for the 15-min period between 15 and 30 min before eating. Glucose measured in the interstitial space reflects the blood glucose concentration ~10 min before the interstitial measurement.
[3] Difference between glucose values at the beginning and end of the specified time periods.

TABLE 4

Multiple regression analysis for log of energy intake in 8 healthy young women as the dependent variable

Independent variables	Estimate[1]	*P*
Desire for meal	$+2.8 \times 10^{-2}$	<0.001
Hunger	-1.7×10^{-2}	0.02
Absolute mean glucose, −15 to 0 min[2]	-0.8×10^{-2}	0.08

[1] Adjusted for age, BMI, and dietary restraint score based on TFEQ-R (12).

[2] Mean interstitial glucose for the 15-min period between −15 and 0 min before meal initiation. The variable satiety is not included in the analysis because of its high colinearity with the variable desire for meal.

examined the importance of change in glucose by looking at the difference between 2 glucose values. The difference in the interstitial glucose value between 40 and 5 min before a meal was the strongest predictor of subsequent energy intake ($r = 0.17$, $P = 0.08$) but, in general, it appeared that change in blood glucose was consistently a weaker predictor of energy intake than were absolute glucose levels.

Multivariate regression. We next performed contextual multiple regression analyses with energy intake as the dependent variable and glucose level, hunger, satiety, and desire for a meal at the beginning of the meal as independent variables, to determine the best model for predicting energy intake and the partial contributions of each variable to subsequent energy intake. After correcting for age, BMI, and the dietary restraint score, desire for a meal ($P < 0.001$) and hunger ($P = 0.02$) were the strongest independent contributors to subsequent energy intake, whereas absolute mean interstitial glucose measured in the 15-min period before energy intake was marginally significant ($P = 0.08$) **(Table 4)**.

DISCUSSION

In this study of 8 healthy free-living nonobese women, we showed that glucose measured in the interstitial space by a continuous glucose-monitoring device was a significant determinant of meal size, but other factors such as desire for a meal were quantitatively more important. Our study also demonstrated the utility of measuring interstitial glucose by the CGMS in the study of the regulation of food intake in free-living individuals leading their normal daily lives.

The glucostatic theory, first proposed by Mayer in the 1950s, states that hunger and spontaneous meal initiation are stimulated at least in part by changes in glucose patterns, as shown in controlled experimental settings in rats (5,7–9,20) and humans (10,11,21,22). To our knowledge, our data are the first on the role of blood glucose in determining meal size within individuals who are leading their normal daily lives, and strongly indicate that there is a significant but small role for lower blood glucose values within the normal range in promoting increased energy intake. As such, our studies support and extend the early theories of Mayer on the centrality of blood glucose in energy regulation (5,6).

One area of controversy in the previous literature on blood glucose and energy regulation in humans is whether absolute blood glucose level or change in blood glucose is the primary glucose parameter that contributes to increased hunger and energy intake. For example, data from clamp studies comparing low and high blood glucose levels suggested that high absolute glucose concentrations are associated with lower appetite (as measured by hunger, fullness, prospective feeding intentions) and energy intake (23–25). Intracellular glucopenia, induced by 2-deoxy-D-glucose, an inhibitor of intracellular glucose utilization, also increases appetite and food intake, providing further evidence of the role of absolute glucose levels in hunger and regulation of energy intake (26,27). However, in other human studies, absolute glucose levels did not correlate with hunger (11).

Other studies in controlled experimental settings have suggested that declines in glucose levels (rather than absolute levels) are associated with meal initiation and energy intake. This was first demonstrated in rats where meal initiation was preceded by transient declines in blood glucose starting 5–12 min before the meal (7,8,20,28). Glucose decline had to be of a high degree (5% from maximum value) and duration (over 5 min) for a meal initiation to occur. In general, meal initiation occurred within 20 min of the decline in glucose (20), and meal initiation was often observed as the blood glucose slowly rose back to normal. There is also some evidence in humans that expression of hunger, measured by changes in hunger ratings and spoken meal requests, are preceded by transient (postabsorptive and postprandial) or dynamic (rapid declines following a peak inducing by meal ingestion) declines in blood glucose (10,11,21,22). On the basis of these studies, a causal relation between blood glucose dynamics, hunger, and meal initiation was proposed. The relation between glucose dynamics and size of meal or timing of meal termination is less clear.

In the present study, we found a stronger association between absolute glucose levels and energy intake than between glucose declines and energy intake. This may be due in part to the greater measurement error associated with measuring a change in glucose compared with a mean absolute value. Additionally, there may have been critical differences in experimental designs between previous studies and the current one. Previous human studies were conducted under highly restrictive experimental settings in which subjects were deprived of environmental and time cues. By design, these studies attempted to minimize nonphysiologic influences that might be important in initiation and size of meal, thereby potentially making subjects more sensitive to internal regulation signals than they would be in everyday life. In contrast, our study is the first attempt to characterize the relation between glucose dynamics and energy intake in the free-living setting in the normal context of eating behavior. We did not control for and did not specifically measure all potentially contributing environmental factors, and further studies in this area are warranted.

The mechanism by which glucose level before a meal may predict the amount consumed in the meal is not clear. Because hypoglycemia and reductions in blood glucose above hypoglycemia were shown to correlate with self-reported hunger (10), low glucose levels may predict a large amount of food consumed indirectly through increased hunger. In our study, glucose had an effect on the size of a meal independent of sensations subjects can define as premeal hunger, satiety, or desire to eat. The glucose level may be a signal (direct or indirect) for postmeal satiety and meal termination, and there is indeed evidence suggesting that in humans, hyperglycemia induces satiety (24). It is therefore conceivable that subjects with lower glucose before a meal may need a larger energy intake to elevate their postprandial glucose enough to reach a satiety threshold that will terminate the meal. In our study, we did not evaluate postmeal measures and we were unable to test this hypothesis.

Our findings of a significant contribution of glucose level to energy intake in univariate analyses and a reduced, marginal significance of glucose to energy intake in multivariate analyses is consistent with the suggestion of an important and perhaps dominant role for environmental factors in determin-

ing variability in energy intake between different meals. Factors such as variety (which could not be modeled in this study due to the complexity of the variable and our small number of subjects) are known to have a substantial effect on energy intake (29,30), as do eating out (31), palatability (32), and perhaps dietary composition and energy density (33,34). On a meal-to-meal basis, these factors may override physiologic stimuli for food seeking and meal initiation such as glucose level. Our variable "desire for a meal" may be used as a proxy for a constellation of external and internal contributing factors, and was a strong predictor of energy intake. Indeed, our finding that self-reported desire for a meal was quantitatively the most important variable contributing to energy intake emphasizes the combined importance of both internal (physiologic) mechanisms and external (environmental) factors in energy intake regulation.

Certain limitations of the study must be noted. First, the CGMS device measures glucose in the interstitial space; its correlation with blood glucose level measured by glucose analyzer varies from 0.76 to 0.92 (13,35). Although the device has been approved to examine glucose trends in patients with diabetes who tend to have wide blood glucose fluctuations, it may be less sensitive at distinguishing small fluctuations in glucose such as those seen in nondiabetic individuals. Indeed, there is evidence that the correlation between glucose measured by CGMS and blood glucose is smaller in subjects with the narrowest range in daily glucose levels (35). Second, glucose level measured by CGMS lags behind blood glucose ~10 min on average (15,16). To account for this, in our analyses, we examined various measurements of glucose in relation to the event of interest. Finally, our study included only women of normal weight; therefore, our results cannot be generalized to men or those with a BMI > 25 kg/m^2. Overweight or obese individuals may exhibit differences in terms of the contribution of their glucose levels to measures of appetite and energy intake.

In conclusion, we showed that in nonobese free-living women absolute levels of interstitial glucose were a significant predictor of energy intake in univariate analyses, but desire to eat and hunger sensation were more significant determinants of subsequent energy intake in multivariate analyses. These findings emphasize the importance of both blood glucose and nonglucose (internal or external) factors in the regulation of energy intake. Finally, the monitoring of interstitial glucose with the CGMS device permits studies of the role of glucose in energy regulation in the free-living state, and may therefore have utility in studies of energy regulation in different population groups and the effects of different dietary compositions.

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