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Is Psychological Stress a Factor for Incorporation Into Future Closed-Loop Systems?

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Abstract

Background: The relationship between daily psychological stress and BG fluctuations in type 1 diabetes (T1DM) is unclear. More research is needed to determine if stress-related BG changes should be considered in glucose control algorithms. This study in the usual free-living environment examined relationships among routine daily stressors and BG profile measures generated from CGM readings.

Methods: A total of 33 participants with T1DM on insulin pumps wore a CGM device for 1 week and recorded daily ratings of psychological stress, carbohydrates, and insulin boluses.

Results: Within-subjects ANCOVAs found a significant relationship between daily stress and indices of BG variability/instability (r = .172 to .185, P = .011 to .018, r^2 = 2.97% to 3.43%), increased % time in hypoglycemia (r = .153, P = .036, r^2 = 2.33%) and decreased carbohydrate consumption (r = –.157, P = .031, r^2 = 2.47%). Models accounted for more variance for individuals reporting the highest daily stress. There was no relationship between stress and mean daily glucose or low/high glucose risk indices.

Conclusions: These preliminary findings suggest that naturally occurring daily stressors can be associated with increased glucose instability and hypoglycemia, as well as decreased food consumption. In addition, findings support the hypothesis that some individuals are more metabolically reactive to stress. More rigorous studies using CGM technology are needed to understand whether the impact of daily stress on BG is clinically meaningful and if it is a behavioral factor that should be considered in glucose control systems for some individuals.

Keywords
blood glucose variability, continuous glucose monitoring, psychological stress, type 1 diabetes

It has long been recognized that acute psychological stress may affect blood glucose (BG) levels in type 1 diabetes (T1DM) through both direct and indirect mechanisms.[1-3] The direct impact is mediated by stress-induced activation of adrenergic hormones and cortisol, which can increase glucose production and increase insulin resistance.[3-5] Indirect effects can occur secondary to stress-related deterioration in diabetes management behaviors such as under- or over-eating, checking BG less often, and skipping exercise. In spite of these recognized mechanisms, the glycemic impact of acute stress in T1DM has proven difficult to demonstrate. Laboratory studies have yielded inconclusive results, with some studies finding no stress effect,[6,7] and other studies finding increases in BG for some people and decreases in BG for others, in response to the same stressful situation.[8,9] These

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idiosyncratic stress responses have led to the conclusion that certain individuals are "stress-reactive" while others are not.[10] Metabolic state at the time of stress occurrence also appears to contribute to the glycemic impact. Specifically, recent studies found that, when stress occurred after food intake, there was a significant delay in postprandial glucose recovery, but there was no effect when stress occurred in the fasting state.[11-13] These findings may be partially explained by research showing that, in nondiabetic people, cortisol levels increase more when stress occurs after glucose intake.[4,14]

It is important to understand whether routine, daily psychological stressors have clinically significant effects on BG levels and if these effects have implications for diabetes management and control. Moreover, the effects of stress may have implications for the development of automated closed-loop systems operated by control algorithms. These systems must be able to respond to glycemic challenges by recognizing and predicting glucose excursions triggered by situational or behavioral factors. This, as well as accounting for the delay in action by rapid acting insulin means closed-loop systems need to include "meal announcements" so that insulin delivery adequately matches postprandial insulin requirements,[15] or "exercise announcements" to adapt to these changing metabolic needs.[16] If acute stress has a significant impact on glycemic status, then glucose control systems may need to consider these effects to control more precisely stress-related changes in BG.

In this preliminary study, adults with T1DM participating in a multicenter randomized crossover closed-loop study collected outpatient continuous glucose monitoring (CGM) data for at least 1 week and completed daily diaries to record stress, carbohydrates and insulin boluses prior to the clinical trial.[17] The purpose of the study was to investigate relationships between routine daily stressors, glucose levels, and diabetes management behaviors obtained in a naturalistic setting using CGM data to generate glycemic profile measures. Because this study was exploratory and because CGM data offers the ability to compute numerous different glycemic variables, we investigated a wide variety of measures of glucose control, including average daily BG levels, % time in and out of target ranges, area under the curve, BG risk indices and BG variability. For each measure, we hypothesized that stress would be associated with more disruption in daily glucose levels.

Methods

Participants

Inclusion criteria for participants were age 21-65 years, with type 1 diabetes for at least 1 year, use of an insulin pump for at least 6 months, and an HbA1c ≤ 10%. Exclusion criteria included pregnancy, diabetic ketoacidosis in the past 6 months, severe hypoglycemia with seizure or loss of consciousness in the past 12 months, and medical conditions or medication use that increase the risk of hypoglycemia. Thirty-eight participants completed the study protocol, with no dropouts; however, 5 individuals were excluded from data analysis for reporting no variation in daily stress ratings. For the remaining 33 participants (51.5% women), age ranged from 25-62 (mean = 46.2 ± 11.2), and HbA1c ranged from 5.7 – 9.9% (mean = 7.3 ± .95) with average duration of diabetes of 27.1 ± 13.0 years. All participants were white non-Hispanic or Latino individuals. Participants wore the CGM for a period of 7-15 consecutive days (mean = 8.9 ± 1.8) prior to the closed-loop study. For each participant, all CGM readings and Daily Diary data for all days of outpatient data collection were included in the analyses.

Procedure

Participants were solicited for this study through advertisements in diabetes clinics, speaking engagements, social media, and word of mouth. All individuals in the study were participating in a multicenter randomized crossover closed-loop control (artificial pancreas) project. The parent study required collecting at least a week of outpatient data prior to beginning a clinical trial to test the effect of initialization of basal rate and insulin to carbohydrate ratio of a zone-Model Predictive Control based on a priori individual data collection.[17] This outpatient data was also used in the present study. After giving written informed consent, a physical examination and laboratory analysis were performed to ensure enrollment criteria were met.

During outpatient data collection, participants wore CGM devices (Dexcom G4 Platinum, Dexcom, San Diego, CA) which were downloaded along with insulin pump data at the end of the week. For those participants who did not normally use CGM, the devices were blinded so that glucose readings were not displayed and alarms were disabled. Those participants who used CGM prior to the study continued to use their devices as they normally did to avoid changing their diabetes management routines. Sensors were changed according to manufacturer instructions (once per week) unless malfunction required replacement sooner. CGM devices were calibrated according to manufacturer instructions (2 start-up samples, at 12-hour *calibration* prompts, and whenever sensors were inaccurate).

All participants completed daily diaries consisting of a stress rating, as well as grams of carbohydrate consumed for each meal and snack, and the dose and timing of all insulin boluses. For all participants, outpatient data was collected prior to the beginning of the clinical trial. Participants attended an orientation meeting with a project coordinator where the study was explained, questions answered, and informed consent obtained. Institutional Review Boards for each research site (University of Virginia; Mayo Clinic, Rochester, MN; William Sansum Diabetes Center, Santa Barbara, CA) approved the study protocol. Participants were compensated $100 for completing the enrollment and outpatient data collection.

Measures

Daily Diary Variables. Participants completed paper-and-pencil Daily Diaries for at least 7 consecutive days and, at the end of this period, returned to the study site to turn in their diary data. To quantify global daily stress levels, the diary contained the question "How stressful was today?" which was rated on a 5-point Likert-type scale where 0 = *none* and 4 = *extreme*. Total grams of carbohydrate were recorded for each daily meal and snack, as well as the timing and dosage of each meal and correction bolus. The outpatient Daily Diary collection occurred prior to the clinical trial of the parent study during a period of time when participants were at home and following their normal routines (eg, not traveling or on vacation).

BG Summary Measures. We summarized CGM readings into the following daily glucose measures for comparison to daily stress ratings:

1. Average daily glucose
2. Daily low glucose %: Percentage of CGM readings ≤ 70 mg/dl (3.9 mmol/l).
3. Daily high glucose %: Percentage of CGM readings ≥200 mg/dl (11.1 mmol/l).
4. Total area under the curve (TAUC): TAUC gives an estimate of the magnitude of BG values throughout the day. Research indicates that statistical differences between AUC estimation methods are not clinically relevant; therefore we opted for the simplicity of trapezoidal estimation to compute this value.[18] Because the additive nature of TAUC results in bias against days where participants wore the CGM for less time (ie, study initiation and closure), we only analyzed days with 95% of possible readings .
5. Daily low and high blood glucose risk indices (LGBI and HGBI): The LGBI and HGBI are weighted algorithms that take into consideration the daily magnitude and frequency of low and high BG excursions, respectively.[19]

Indices of daily BG variability and instability were also computed, including:

1. Daily glucose standard deviation (GSD): GSD is a simple, if imperfect, measure of variability because the BG measurement scale is highly skewed toward hyperglycemia, resulting in fewer possible values for lower ranges.[20]
2. Daily blood glucose risk index (BGRI): BGRI is defined as the sum of the average LGBI and average HGBI. BGRI has advantages over GSD because its computation is based on a symmetrical BG measurement scale.[20,21]
3. Daily risk range (DRR) is computed by adding the maximum daily LGBI and maximum daily HGBI values.[22]
4. Daily BG rate of change SD: BG rate of change measures how rapidly glucose levels are increasing or decreasing at the time of each CGM reading. It is computed by subtracting the reading 15 minutes prior to each reading, then dividing this difference by 15 to obtain the change in mg/dl (mmol/L)/minute.[20] High SDs of these values indicate increased BG variability.

Statistical Analysis

To adjust for individual differences in glycemic patterns and profiles, Analyses of Covariance (ANCOVA) were used to compute within-subjects correlation coefficients.[23] In this method, daily stress rating is an independent variable (IV) used to predict dependent variables including daily glucose measures, postprandial measures, daily carbohydrates, or daily insulin dose as dependent variables. The participant was treated as a covariant categorical factor. Daily insulin bolus and daily carbohydrate intake were also included as covariates when predicting the daily glucose measures (there was no evidence of multicollinearity). In contrast, when daily insulin or daily carbohydrate was the dependent variable, these were excluded as covariates in the model. In the analysis, variation from each included covariate is removed, and then the variance accounted for by stress is tested against the remaining residual variance using an F test. The degrees of freedom increase because each stress rating is treated as an observation, rather than individual participants. Equation 1 shows how the within-subjects coefficient is calculated. The square of this statistic represents the proportion of remaining variance accounted for in the dependent variable (DV) by stress ratings. The direction of the correlation is determined by the sign of the regression coefficient for stress, while controlling for participant, in the multivariate model predicting the DV. All ANCOVA analysis was performed in R version 3.1.2.[24]

$$\textit{Within} - \textit{Subjects}\ \textit{Correlation Coefficent} = \sqrt{\frac{\textit{Sum of Squares for Stress}}{\textit{Sum of Squares for Stress} + \textit{Residual Sum of Squares}}}$$

In addition, SD criteria were used to select and compare participants whose daily stress varied at different levels during the study. Separate analyses examined participants with daily stress SDs > 0.0 (minimal variation), ≥ 0.5 (moderate variation), and ≥ 1.0 (high variation), with SDs computed based on individual participant mean stress ratings. The more inclusive criterion of SDs > 0.0 includes the largest number of stress ratings, resulting in higher degrees of freedom and an increased ability to detect statistical differences. In contrast, participants with higher variability in stress (≥1.0 SD)

Table 1. Overview of ANCOVAs Testing the Relationships Between Daily Stress Ratings and BG Profile and Diabetes Management Measures for Participants Meeting Daily Stress SD > (≥) 0.0, 0.50, and 1.00 Criteria.

Measure	Daily stress SD criteria (≥)	Participants meeting criteria (n)	Number of stress ratings (n)	Within-subjects *R*	Within-subjects R^2 (%)	*P* value
BG summary variables						
Average glucose	0.00	33	246	.048	0.23	—
	0.50	29	218	.063	0.40	—
	1.00	11	82	.061	0.37	—
High BG %	0.00	33	246	.117	1.36	.090*
	0.50	29	218	.123	1.52	.091*
	1.00	11	82	.186	3.46	—
Low BG %	0.00	33	246	.153	2.33	.026**
	0.50	29	218	.153	2.33	.036**
	1.00	11	82	.206	4.26	.086*
HGBI	0.00	33	246	.072	0.52	—
	0.50	29	218	.081	0.66	—
	1.00	11	82	.098	0.97	—
LGBI	0.00	33	246	.115	1.33	.094*
	0.50	29	218	.103	1.06	—
	1.00	11	82	.143	2.05	—
TAUC	0.00	28	104	.182	3.29	—
	0.50	24	90	.182	3.33	—
	1.00	10	35	.320	10.25	—
BG variability						
GSD	0.00	33	246	.169	2.85	.014**
	0.50	29	218	.185	3.43	.011**
	1.00	11	82	.240	5.77	.045**
BGRI	0.00	33	246	.143	2.05	.037**
	0.50	29	218	.138	1.91	.058*
	1.00	11	82	.194	3.78	—
DRR	0.00	33	246	.172	2.94	.012**
	0.50	29	218	.185	3.43	.011**
	1.00	11	82	.249	6.20	.038**
BG rate of change	0.00	33	246	.148	2.20	.031**
	0.50	29	218	.172	2.97	.018**
	1.00	11	82	.189	3.58	—
Diabetes management factors						
Total daily carbs	0.00	33	246	–.162	2.64	.018**
	0.50	29	218	–.157	2.47	.031**
	1.00	11	82	–.227	5.15	.057*
Total daily insulin bolus	0.00	33	246	.044	0.20	—
	0.50	29	218	.041	0.16	—
	1.00	11	82	.020	0.04	—

*Shows a trend according to $P < .10$ criteria. **Significant according to $P < .05$ criteria.

might exhibit more pronounced associations that fail to achieve statistical significance due to lower sample size. The analyses presented in the Results section below use the criterion of ≥0.5 SD to represent the best estimate of associations between stress and the dependent variables. However, findings using the >0.0 and ≥1.0 SD criteria are also presented in Table 1. Because of the exploratory nature of this study and the desire to minimize Type II errors, alpha levels were not adjusted for multiple variable testing and trends toward significant findings ($P < .10$) are presented in Table 1.

Results

BG Summary Measures

Table 1 presents the overall results of ANCOVAs testing the relationships between stress rating and BG Summary Measures for each of the stress SD criteria groups. Looking at the results for the ≥0.5 SD group, there was no relationship between stress ratings and average daily glucose, LGBI, HGBI, high BG%, or TAUC. However, stress ratings were positively related to low BG% ($r = .153$, n = 218, $P = .036$, $r^2 = 2.33\%$),

indicating that increased stress was associated with a greater percentage of BG readings in the hypoglycemic range.

BG Variability Measures

Table 1 also displays the ANCOVA results for BG variability measures. There were significant positive relationships for GSD (r = .185, n = 218, P = .011, r^2 = 3.43%), DRR (r = .185, n = 218, P = .011, r^2 = 3.43%), and BG rate of change (r = .172, n = 218, P = .018, r^2 = 2.97%), with a trend for BGRI (r = .138, n = 218, P = .058, r^2 = 1.91%). Taken together, these findings indicate that increased stress is associated with elevated BG variability.

Diabetes Management Factors

There was a negative relationship between daily stress ratings and total carbohydrate consumption (r = –.157, n = 218, P = .031, r^2 = 2.47%), and no relationship between stress and total daily bolus insulin (see Table 1). This suggests that participants reduced carbohydrate intake on days with higher stress levels but did not alter total daily bolus insulin.

Discussion

Using CGM technology to collect glucose data, this study during free living found significant positive relationships between stress and several different measures of BG variability, including GSD, the BGRI, DRR, and daily BG rate of change. These findings suggest that increases in psychological stress during routine daily activities are associated with greater glycemic instability. There was also a significant relationship between higher stress ratings and increased frequency of hypoglycemia, but no significant relationships between stress ratings and indices of increased high glucose readings and hyperglycemic risk. This suggests that stress-related increases in glycemic variability generally reflect more frequent and/or extreme hypoglycemic excursions, although it should be noted that this study did not find significant associations between stress and other measures of hypoglycemic risk.

Previous laboratory research that controlled meal timing, carbohydrate content, and the timing and severity of stress exposure found that stress significantly delayed postprandial glucose recovery.[11-13] Because the current study assessed only 1 global daily measure of stress, it was not possible to investigate relationships between stress and discrete glycemic responses at different times of the day in relation to meals. However, there was a relationship between higher stress and decreased daily carbohydrate consumption, although these findings may also indicate decreased entry of carbohydrate data on higher stress days, or increased consumption of low-carbohydrate foods. More research is needed to investigate the relationship between daily stress, food intake, and postprandial glucose recovery. In addition, it is important to point out that these results do not necessarily support a unidirectional causal relationship in which stress influences glycemic parameters. The relationship between stress and glucose is almost certainly bidirectional. Although stress and its concordant physiological effects may have a glycemic impact, daily glucose fluctuations should also affect daily stress levels. For example, the individual who is struggling with hypoglycemic episodes or increased BG variability during the course of a particular day is more likely to experience higher stress levels that day, which, in turn, may have additional effects on glycemic status.

The clinical significance of the relationship between psychological stress and glycemic profiles must also be carefully considered. In the data analysis including all participants (ie, stress rating SD > 0.0), psychological stress accounted for only 2% to 3% of the residual variance in BG variability, and only 2.6% of the residual variance in carbohydrate consumption. Such a minimal impact may not be clinically relevant, especially within the context of other factors which have far greater effects on glycemic parameters, such as carbohydrate intake and insulin. However, for the third of participants who showed the highest stress rating lability (SD ≥ 1.0), daily stress accounted for close to 6% of the residual variance in BG variability and just over 5% of the variance in carbohydrate consumption, which could be clinically meaningful. These findings also support previous conclusions that there are important individual differences in the relationship between psychological stress and daily glucose levels in T1DM, and that some individuals may be more metabolically reactive to stress than others.[10] For these reactive individuals, the relationship between psychological stressors and glycemic control may be clinically, as well as statistically, significant. If so, psychological stress may warrant further examination as a potential contributor to predictive algorithms and models of daily glycemic patterns and control. CGM technology offers a new and more sophisticated methodological approach for studying the relationships between psychological stress and BG, and possibly for identifying those individuals who are significantly more stress-reactive.

Although these results suggest that psychological stress is associated to some degree with daily glucose variability, the findings and conclusions are preliminary and there are several methodological limitations to consider. The first limitation is the relatively small number of participants and the highly select subject sample in this study, all of whom were using CSII and participating in an artificial pancreas clinical trial. Another major limitation is that only a single daily stress measure was used, which was global and therefore unable to detect more discrete changes in stress throughout the day or the type and context of stressful events. A more appropriate experimental approach would be momentary ecological assessment,[25,26] which involves multiple measures of stress, as close as possible to the time of the stress occurrence, throughout the day. This approach can reduce biases in recall and provide more information on the real-time

experience of stress. Electronic data collection that is date and time stamped would help ensure that self-reported ratings are completed each day as instructed. Because highly stressful events may occur at a relatively low base rate, longitudinal and prospective studies over longer time periods would also be a methodological improvement. This study also does not address the possibility of cumulative stress effects for individuals. We did perform exploratory regressions in this study using average stress ratings to predict glucose variables across the study period. Findings were not significant, which may be because these between-subject analyses were unable to detect idiosyncratic stress-glucose associations. In spite of these limitations, however, these preliminary findings support the need for more research to understand the complex relationships between acute daily stressors and diabetes control. Baseline psychological stress assessment during a data gathering period, and eligibility for closed-loop control based on baseline stress stratification, would enable testing of the impact of psychological stress on closed-loop control.

Conclusions

We used CGM technology and daily ratings of psychological stress to investigate the relationship between naturally occurring increases in stress and glycemic profile measures. Stress ratings were significantly associated with increased measures of BG variability, increased frequency of hypoglycemic excursions, and reduced carbohydrate consumption, especially for those individuals who reported higher variation in daily stress. More methodologically rigorous research is needed to clarify whether the impact of acute psychological stressors on glucose levels is clinically meaningful and how to identify those individuals who may be most vulnerable to the negative effects of routine daily stress on glucose profiles.

Abbreviations

ANCOVA, analysis of covariance; AUC, area under the curve; BG, blood glucose; BGRI, blood glucose risk index; CGM, continuous glucose monitoring; DRR, daily risk range; DV, dependent variable; GSD, glucose standard deviation; HGBI, high blood glucose index; IV, independent variable; LGBI, low blood glucose index; TAUC, total area under the curve; T1DM, type 1 diabetes.

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Declaration of Conflicting Interests

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