

Daily stress and glycaemic control in Type 1 diabetes: individual differences in magnitude, direction, and timing of stress-reactivity

Afsane Riazi [a,1](#), John Pickup [b](#), Clare Bradley [a](#)

[a](#) Department of Psychology, Royal Holloway, University of London, Surrey, UK

[b](#) Department of Chemical Pathology, Guy's, King's and St. Thomas' School of
Medicine, Guy's Hospital, London, UK

1 Corresponding author. Present address: Department of Human
Sciences, Brunel University Uxbridge, Middlesex UB8 3PH, UK.

Tel.: +44-1895-274000/4652; fax: +44-1895-203018.

E-mail address: afsane.riazi@brunel.ac.uk (A. Riazi).

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Abstract

The aim of this study was to investigate the relationships between daily stress and glycaemic control in 54 people with Type 1 diabetes over 21 days. Measures included daily reports of stress (hassles), four-times-daily blood glucose measurements, and HbA1c levels. Time-series analyses revealed considerable variation between individuals in the nature and extent of blood glucose response to stress (stress-reactivity). In approximately one-third of the sample, stress was significantly associated with either same- or next-day blood glucose levels (r -range: -0.79 to 0.58). The majority of stress-reactive individuals (20.4% of the sample) demonstrated a positive association between hassles and same-day blood glucose levels. A much less common effect was found in two individuals (3.7%), where hassles were related to decreased same-day blood glucose. 'Stress-reactive' individuals tended to have high HbA1c values at baseline ($t(52) = 2.2$; $P < 0.05$), and significant relationships between emotion-focused coping and blood glucose levels ($r = 0.93$; $P < 0.01$). In conclusion, although a significant majority of this sample was resistant to the effects of stress, marked individual differences were found in the nature and extent of stress-reactivity. Our study goes beyond other published results as it is longitudinal, uses time-series analyses and includes a relatively larger sample. Clinicians need to be aware of these individual differences in order to advise patients about anticipating and preventing stress-related disruptions of glycaemic control.

1. Introduction

The relationship between psychological stress and glycaemic control has received substantial attention over the last few decades. Psychological stress may affect metabolic control in Type 1 diabetes in at least two ways [1,2]:

(i) a direct psychophysiological effect via stimulation of sympathetic nervous system and pituitary gland activity, which results in the elevation of circulating catabolic hormone levels and the suppression of anabolic hormones. In people with Type 1 diabetes, this results in increased blood glucose levels.

(ii) stress leads to behavioural changes capable of disrupting self-care. For example, time urgency may make blood glucose monitoring impracticable, leading to disruptions in metabolic control. Additionally, stress may also result in comfort seeking or compensatory behaviour, such as increased food intake and reduced exercise [3] or alcohol intake [4]. These behaviours may also lead to disruptions in metabolic control in people with diabetes.

Both laboratory and naturalistic settings have been used to study the relationship between psychological stress and glycaemic control. Some laboratory studies using acute stress (e.g. mental arithmetic) found changes in blood glucose levels as a result of stress [5–9], but not others [10–14]. It has been pointed out [2,15] that studies with nonsignificant findings tended to report group, rather than individual data. Individual differences in response to acute exercise stress have also been found in children with diabetes in a laboratory setting [16]. This study found a subgroup who showed increases in blood glucose levels under exercise, which also

correlated with increased release of stress hormones (norepinephrine). Furthermore, such increases seemed to occur in those individuals who identified themselves as being stress-reactive to start with.

Studies in naturalistic settings have incorporated stressors of longer duration, such as major life events (e.g. divorce). Significant associations between increased life events and blood glucose levels have been found [17–19], even after controlling for self-care variables. More recent studies have used longitudinal designs whereby minor events ('daily hassles') and blood glucose levels are measured repeatedly over several days or weeks. Such studies have demonstrated individual differences in blood glucose reactivity to stress, (or stress-reactivity) that were also seen in laboratory-based acute stress studies [15].

There is also a growing literature on stress management interventions, especially relaxation training, in people with diabetes. These have met with mixed results, with some studies showing the usefulness of such interventions [20–22], whilst others have not [23]. It is possible that the lack of significant benefits of some stress management programmes may be due to the selection of participants. If the patients are not reactive to stress, stress management cannot be expected to show benefits for blood glucose control. There is evidence of individual differences in response to relaxation training within the same study [24–26].

To date, studies have found an inconsistent relationship between various psychological factors and stress-reactivity. For example, internality concerning health (belief in one's own control over health) and self-esteem did not mediate the relationship between stress and same-day blood glucose levels [27]. There is some

evidence to suggest that the type of coping used by the individual is related stress-reactivity [28]. In particular, emotion-focused coping (such as self-preoccupation and day dreaming) was associated with stress-reactivity [28], whereas task-focused coping (reconceptualising a problem cognitively) was associated with better metabolic outcomes [29]. However, avoidant coping has been associated with better metabolic outcomes in one study [30] and with worse outcomes in another [14]. As coping has been found to be associated with physiological response to stress in the general population [31], it may also be associated with stress-reactivity in people with diabetes.

We therefore conducted a longitudinal study using multiple daily measurements of stress and blood glucose levels, with the aim of investigating individual differences in blood glucose-reactivity to stress in a substantial number of people with Type 1 diabetes than previously studied. We also related psychological factors such as coping style to stress-reactivity.

2. Patients and methods

This was a within-individual longitudinal, prospective study. The 54 adults (25 men and 29 women) with Type 1 diabetes who completed the study were recruited from diabetes clinics at St. Thomas' Hospital, London ($n = 34$), Guy's Hospital, London ($n = 12$) and St. Peter's Hospital, Surrey ($n = 8$). The study was approved by the relevant Ethics Committees. A letter of invitation and information sheet were used for recruitment. An additional 20 volunteers were recruited, but did not complete, or provided insufficient data to be included in the analyses.

2.1. Materials

HbA1c was measured by DCA 2000 (Bayer Diagnostics, Newbury, UK) HbA1c analyser. The normal range is 4.5–6.5%.

Blood glucose was measured by portable Glucometer M (Bayer Diagnostics) meters, unless the patient preferred to use their own. Glucometer M stored test results automatically, with the date and time of the day. The 4-point assessment of blood glucose control was likely to capture glycaemic changes in response to stresses occurring during the day. Daily averages of four blood glucose readings per day were used for analyses. The average was used in order to correlate a single indication of blood glucose control with daily stresses that were measured once a day in the evening.

Daily stress was measured by the Hassles and Uplifts Scale [31]. This scale lists 53 potentially stressful and/or enjoyable aspects of everyday life (e.g. family members, occupational commitments). Patients rated the extent to which the item was ‘a hassle’ on that day on a 4-point scale. The number of hassles was summed to produce the variable “frequency of stress”. The ratings given were summed to produce “intensity of stress”. This measure has been used in numerous studies and with different populations, including people with diabetes [27]. There is evidence for test-retest reliability and construct validity [32] in addition to face validity.

Coping.

Coping inventory for stressful situations (CISS) [33], a 48-item scale, was used to measure coping strategies at baseline. This scale measures three types of coping:

emotion-oriented, task-oriented, and avoidance (16 items each). Task-oriented coping refers to the attempt to understand, define, or solve the problem, by developing new skills or responses to the problem. Emotion-focused coping refers to the attempt to manage the distress by preoccupation with the problem, wishful thinking or expressing feelings about the problem. Each item has Likert response options from 'not at all', 1, to 'very much', 5. Higher scores indicate greater use of the particular coping style when faced with a stressful situation. High reliability and construct validity have been reported [33]. Furthermore, acceptable psychometric properties and factor structure of the measure have been reported in people with diabetes [34].

2.2. Protocol

Following informed consent, patients completed the questionnaires and a capillary blood sample taken for measurement of HbA1c. Patients were then trained in the use of the Glucometer M blood glucose meter by one investigator (AR), except for eight patients who preferred to use their own meter. Patients were asked to complete the Hassles and Uplifts Scale each night, and measure their blood glucose levels four times a day (before breakfast, before lunch, before dinner and before going to bed) for 3 consecutive weeks. Patients using their own meters without memory capacity noted the result and the date and time of the tests. The patients were contacted by phone each week to discuss progress.

2.3. Statistical analyses

Time-series analysis (SPSS Trends) was used to preserve the temporal relation of variables that were assessed daily. Because even nonsignificant autocorrelations may inflate statistical significance in subsequent analysis [35], a generalised least squares (GLS) procedure with the Prais–Winsten algorithm was employed.

This transforms the regression equation to remove first-order autocorrelation and provides an effect size for the magnitude of autocorrelation [36]. Thus, the resulting within-individual correlation between each patient's stress and same-day (or next-day) mean blood glucose concentrations during the study period, is calculated with the first-order correlations removed. The statistical significance of the number of people shown to be stress-reactive was assessed using the binomial probability distribution [37].

T-tests and chi-square analyses were used to compare the stress-reactive ($n = 8$) and non-stress-reactive ($n = 46$) groups on various clinical and psychobehavioural features. To reduce the risk of Type 1 error, $P < 0.005$ was the criteria for significance. Correlations between variables within the subgroups were assessed by Pearson's method.

3. Results

Table 1 shows the clinical and psycho-behavioural features of our sample.

Additionally, all patients were white, 32 (59.3%) were married, and 40 (74.1%) had full-time occupations. Forty-two (77.8%) patients had no other illness apart from diabetes, and 39 (72.2%) did not have any complications of diabetes. All patients were receiving multiple insulin injections comprising a 'basal/bolus' regimen.

3.1. Intra-individual relationships between hassles and blood glucose concentrations

The majority did not appear to be stress-reactive. That is, the majority did not show significant associations between stress and blood glucose levels. However, 8 (two men and six women) out of the 54 patients showed a significant association between the intensity of stress ratings and same-day blood glucose levels, and 11 (two men and nine women) showed a significant association between the frequency of stress and same-day blood glucose levels. Six patients were reactive to both intensity and frequency of stress. Taking into account these six overlapping patients, 13 (24.1% of the sample) patients showed relationships between either frequency or intensity of stress and same-day blood glucose. For 2 of the 13, stress was significantly related to decreases in same-day blood glucose (Table 2). The overall pattern of 8 of 54 who showed a relationship of glycemia to intensity of stress on the same day was statistically significant (binomial probability distribution, $z = 5.2$; $P < 0.0001$), as was the 13 of 54 patients being stress-reactive on the same day ($z = 6.44$; $P < 0.0001$).

Four people (7.4%) only showed next day reactivity. For these people, stress was associated with either increased or decreased blood glucose on the next day but not on the same day. Three people (5.6%) showed both same day and next day elevated readings. For these people, increased blood glucose concentrations continued to be raised into the next day (Table 2).

3.2. Comparison between stress-reactive and non-stress-reactive individuals

Patients with significant association between intensity-of-stress ratings and same-day blood glucose concentrations ($n = 8$) were compared to patients without such association ($n = 46$). The stress-reactive group had higher HbA1c levels at baseline ($9.5 \pm 2.0\%$ versus $8.3 \pm 1.2\%$; $t(52) = 2.2$; $P = 0.031$), though this did not reach significance. The mean blood glucose concentrations over the 21 days were also higher in the stress-reactive group (10.8 ± 3.5 versus 8.5 ± 1.9 ; $t(52) = 2.7$; $P = 0.009$), but again, this finding was non-significant. The stress-reactive individuals did not report more stress over the 21 days, nor did they experience more variation in stress during the study period.

3.3. Associations between coping styles, stress and blood glucose levels

Within the stress-reactive group ($n = 8$), a strong significant correlation between stress (measured by mean intensity of stress over the 21 days), and emotion-focused coping ($r = 0.93$; $P < 0.01$) was found. In the non-stress-reactive group ($n = 46$), there was no relationship between stress and emotion-focused coping ($r = 0.30$; $P = 0.06$). Baseline emotion-focused coping was significantly associated with glycaemic control (average of the daily mean blood glucose levels) in stress-reactive group ($n = 8$) ($r = 0.84$; $P < 0.01$), suggesting that stress-reactive patients who use more emotion-focused coping have higher blood glucose levels. This effect was not seen in the non-stress-reactive individuals ($r = 0.20$; $P > 0.05$).

4. Discussion

An important finding of this study was the considerable variation between individuals in the nature and extent of the stress-blood glucose relationship. Although the majority of the patients did not display an association between stress and blood glucose levels, there were differences between individuals in the magnitude, direction and timing of blood glucose reactivity to stress, suggesting that group analysis may be misleading. The recognition of individual differences in stress-reactivity is not restricted to diabetes. There is evidence of individual differences in response to stress in other patient groups, both in the laboratory [38,39] and in naturalistic settings [40,41].

Stress-reactivity in diabetes has been predicted by being female, having chronically elevated blood glucose levels, and high variability of stress and blood glucose concentrations [15]. The present study did not find stress-reactivity to be associated with variability of stress, though some associations with worse glycaemic control (higher HbA1c) were found. The stress-reactive group also tended to have poorer blood glucose control at baseline, and during the study period, although these findings were not significant.

Emotion-focused coping discriminated between stress-reactive and non-stress-reactive patients. For the stress-reactive individuals, emotion-focused coping was associated with more stress, and with higher blood glucose levels. Thus, emotion-focused coping seems to play some role in stress-reactivity. However, the 'stress-reactive' group consisted of a very small sample ($n = 8$), and these findings must be

viewed cautiously. Recruiting a substantial number of stress-reactive people in future studies such as this is challenging, as there are fewer such individuals.

A minority of our patients showed decreased, rather than increased blood glucose levels in response to stress. This is consistent with studies involving laboratory-induced stress [9,42] and Type 2 diabetes [5]. The reasons for stress-related blood glucose decreases in a naturalistic setting are difficult to explain. However, it is possible that stress leads to errors of diabetes management such as a missed meal, which might lead to hypoglycaemia.

The number of people with significant relationships between stress and blood glucose levels were significantly greater than chance alone. This supports the findings of Aikens et al. [27] ($n = 25$) and Halford et al. [43] ($n = 8$), who also identified a significant proportion of 'stress-reactive' people in their samples. Both studies, however, suffered methodologically from small sample sizes. Our study goes beyond other published results as it is longitudinal, uses time-series analyses, measures coping and also examined individual blood glucose response to stress in a larger sample than has been studied previously.

There are several limitations to this study due to the numerous methodological difficulties in a naturalistic study of this kind. Identification of blood-glucose reactivity was dependent on patients experiencing stress during the study period. Further investigation is needed to determine whether individuals display a consistent pattern of 'stress-reactivity' over a prolonged time course, though there is evidence that stress-response profiles are moderately consistent over time [7].

Although the term 'stress-reactive' was used throughout, the results do not demonstrate a causal relationship between stress and blood glucose levels. Additionally, our sample may not be representative of the population, and this will need to be investigated in future larger-scale trials. The sample size, although larger than some previous studies, was still small. Thus the clinical significance of the findings must be treated with caution. The differences between the subgroups studied must also be considered preliminary, as the differences in sample size between the groups may have biased the results.

There are many other variables that influence blood glucose regulation, which by their sheer number and complexity mean they cannot be controlled in any one study. For example, there are variations in the absorption rate and action of the same type and amount of insulin that are dependent on site, temperature, and whether the mixture is shaken (amongst others). Furthermore, it is not possible to determine whether differences amongst individuals are due to differences in injection techniques across the stressful days.

Although the time frame of our study (21 days) is by no means small compared to other studies of this type [17], more sophisticated methods of time-series analyses, such as ARIMA modelling (autoregressive integrative moving average model), could have been used with longer time frames (i.e. >50 days). Such analysis can remove other non-first-order autocorrelations and moving averages that may have affected our results. Finally, as more than half our sample were women, longer time frames would have captured the effects of the menstrual cycle, which may impact on glycaemic control. Future studies should incorporate longer time frames, although this will further increase the burden for patients. This may also increase the possibility

that the testing period itself may be a confounding factor in any findings. Most individuals commented that self-monitoring on such a regular basis for the study period (3 weeks) was not problematic, but some also commented that a longer time frame could have been difficult.

Despite these methodological shortcomings, the results here demonstrate a clear need to pursue this avenue of research, as it has the potential to offer a route of significant gain for patients. In conclusion, although most of the sample was resistant to the effects of daily stress, this research has highlighted individual differences in stress-reactivity. We have used a longitudinal design with daily assessment of stress and blood glucose levels, time-series analyses for our data and included a relatively large number of patients compared to previous studies. However, due to the methodological limitations inherent in studies of this kind, clinical significance of the results is limited. Nevertheless, recognising these differences in stress-reactivity is an essential first step to optimal management of diabetes. If stress-reactive individuals can be identified and helped to understand, predict and perhaps prevent unwanted blood glucose responses to stress, improvements in their overall diabetes control, as well as quality of life, are likely to follow.

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Tables

Table 1: Clinical and psycho-behavioural features of people with type 1 diabetes studied

Total number	54
Sex (M/F)	25/29
Age (years)	38.1 ± 12.0 (17.0 - 70.0)
Diabetes duration (years)	20.8 ± 10.0 (12.5 - 37.5)
Mean blood glucose (mmol/l)	8.9 ± 2.1 (2 - 22)
HbA1c (%)	8.5 ± 1.4 (5 - 14)
Frequency of stress	7.7 ± 3.0 (0 - 39)
Intensity of stress rating	12.7 ± 5.1 (0 - 90)
Baseline coping (CISS)*	
Task-focused	51.9 ± 11.9 (22-78)
Emotion-focused	38.8 ± 12.1 (18-65)
Avoidance	34.4 ± 10.8 (17-62)

Data are mean ± SD (range) or number.

* Higher scores denote greater use of specified coping

Table 2: Results of time-series analyses of daily stress with same-day mean blood glucose levels

*=p<0.05 **P<0.01

Participant no.	Correlation of daily mean blood glucose with			
	Frequency of stress		Intensity of stress	
	Same-day bg	Next-day bg	Same-day bg	Next-day bg
1	-.19	.38*	-.07	.47*
2	.31	.54**	.30	.54**
3	.58**	.39*	.42*	.38*
6	.38*	.30	.35	.39*
7	-.73**	.01	-.79**	-.11
9	.39*	-.05	.35	.00
17	.49*	-.35	.39*	-.31
19	-.23	-.36	-.28	-.41*
24	.45*	.26	.29	.45*
26	.37*	.04	.21	.03
33	.48*	.27	.48*	.27
36	-.51*	-.28	-.48*	-.16
40	.40*	-.09	.39*	.06
43	-.23	-.38*	-.20	-.21
44	.35	.13	.40*	.09
46	.44*	.11	.33	.10
49	.22	-.22	.38*	-.04