The Association of Cortisol Stress Response with Early Adversity and Diabetes Control in Adolescents with Diabetes

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Abstract

**Objectives:** The hypothalamic-pituitary-adrenal (HPA) axis has been implicated in the relationship between increased stress and poor diabetes control in children with type 1 diabetes mellitus (T1DM).

The objectives of this study were two-fold: (1) To evaluate the effectiveness of the Trier Social Stress Test for Children (TSST-C) in inducing psychosocial stress in children with T1DM; (2) To investigate predictors of the cortisol stress response to the TSST-C.

**Methods:** Seventeen adolescents with T1DM were exposed to the TSST-C. Salivary cortisol was sampled pre-TSST-C and at six 10-minute intervals following the stress procedure. Measures of anxiety, depression, family functioning and early adversity were completed.

**Results:** The TSST-C induced a significant increase in cortisol response (p<0.01). Early adversity predicted cortisol response to the stressor (p=0.01). Early adversity was also associated with poorer diabetes control (p=0.05).

**Conclusion:** The TSST-C was effective in producing a stress response in children with diabetes. Whereas previous research has emphasized psychological pathways which contribute to the relationship between psychosocial stressors and poor diabetes control, this study suggests that biological dysfunction may also underlie the association.

**Keywords:** Child maltreatment; Child psychiatry; Cortisol stress response; Diabetes

Introduction

Type 1 Diabetes Mellitus (T1DM) is associated with multiple sources of stress for affected youth and their families, with increased levels of stress associated with poorer diabetes control [1]. Investigators examining predictors of poor metabolic control have identified family structure [2,3] (i.e. married, biological parents) and family function [4] (a routine-oriented, structured household) as more frequently lacking in families of children with poor diabetes control. Additional family factors, including decreased parental involvement in diabetes management [5], increased family conflict, and decreased family cohesion [6] have also been correlated with poorer disease control. The nature of the relationship between diabetes control and psychological stress, including stressful life events, however, is unclear [7,8]. One area of potential shared pathophysiology may be hypothalamic-pituitary-adrenal (HPA) axis dysfunction.

The HPA axis acts to maintain homeostasis in the face of stress. Activation of the HPA axis results in the secretion of cortisol [9]. The functional changes of the HPA axis in specific psychological distress states, such as depression, anxiety and post-traumatic stress disorder, are well described [10-12]. Moreover, exposure to early life stress (for example, abuse in childhood) has been shown to result in HPA dysfunction which persists, even after the inciting stressor has been eliminated [12,13]. Cortisol acts in times of hypoglycemia, and in response to both physiological and psychological stressors, to increase plasma glucose levels [14]. The action of cortisol is thus opposite to the action of insulin, which lowers plasma glucose levels. In the non-diabetic state, plasma glucose levels are tightly controlled by these balanced systems. At times of stress in the diabetic state, however, there is insufficient insulin production such that hypercortisolemia results in hyperglycemia [15].

The specific aims of this study were to (1) evaluate the ability of a psychosocial stressor to induce an adequate stress response among adolescents with T1D; (2) examine predictors of stress responsiveness in this population and (3) evaluate the relationship of these factors with diabetes control. Based on previous research demonstrating the ability of a psychosocial stressor to elicit a cortisol response among children with a chronic inflammatory disorder, we hypothesized that the Trier Social Stress Task for Children (TSST-C [16,17]) would be an adequate stressor that causes a significant and reliable increase in cortisol levels among adolescents with T1DM. Further, we hypothesized that greater burden of stressful life events and increased family dysfunction would be associated with stress responsiveness and poorer overall diabetes control.

Methodology

Participants

Seventeen adolescents (nine male, eight female) with T1DM, followed in the diabetes clinic of a large paediatric hospital, participated in the study. The clinic provides routine diabetes care to 70% of the children and adolescents with T1DM in the Toronto area. English speaking participants aged 11-18 years were included in the study if they had a history of T1DM of at least one year. Clinic patients with co-morbid medical illnesses, (apart from treated hypothyroidism or mild asthma), developmental delay, or taking psychotropic medication at the...
time of the study were not eligible for study participation. Informed consent was obtained.

Approval for the study was granted by the Research Ethics Board at the Hospital for Sick Children.

**Experimental protocol**

All experimental sessions were run at the same time of day, in the afternoon, for all participants, who also refrained from eating, drinking, or teeth-brushing one-hour before saliva was sampled. Participants engaged in the TSST-C, which includes a social evaluative threat and an uncontrollability task. In the first part of the TSST-C the adolescents were escorted into an experimental room where two persons sat behind a table. Next, the adolescents received the beginning of a story. They were told that after a preparation period of 5 minutes in another room, they would finish telling the story to the committee and that their relay of the story would be videotaped. They were instructed to try to tell the story in the most exciting way possible and to try to perform better than all the other participants in the study. Immediately following the story completion task, participants were then asked to serially subtract the number 13 from 1023 as fast and as accurately as possible for a total duration of 5 minutes. On every failure, they were asked to restart at the number 1023. Following the completion of the TSST-C and the 60-minute recovery periods during which cortisol was collected, participants were debriefed about the stress procedure. Each participant was informed that the neutral behavior of the committee members was a pretense in order to induce stress and that he/she performed as well as the other participants. The family environment and early adversity measures were completed following the recovery period (described below).

**Cortisol**: Baseline saliva samples were collected at 20 and 10 minutes prior to the TSST-C task. Saliva samples were collected at 10-minute intervals for 60 minutes following TSST-C completion. Saliva was collected using salivettes and assayed using a salivary cortisol enzyme immunoassay kit (Salimetrics, State College, PA). Samples were stored at -20°C until assay. The inter- and intra-assay coefficients of variation were under 10%. Correlations between duplicates exceeded 0.95.

**Diabetes control**: The percentage of glycosylated hemoglobin, HbA1c (%), was used to determine diabetes control. HbA1c is measured at each clinic appointment as a part of routine clinical management of diabetes. Participants’ glucose levels were measured immediately prior to the TSST-C to ensure adequate baseline glucose levels for participation.

**Family functioning**: The Family Environment Scale (FES) assesses family members was a pretense in order to induce stress and that he/she performed as well as the other participants. The family environment and early adversity measures were completed following the recovery period (described below).

**Statistical analyses**

Cortisol response was calculated using area under the curve (AUC: nmol/L) using the six cortisol measures, at 10 minute intervals, from 0 to 60 minutes post TSST-C. Analysis of variance with repeated measures (with Greenhouse-Geisser correction) was used to compute cortisol changes in response to the stressor. Regression analyses were performed to determine predictors of HPA response. Data were analysed using SPSS, version 21.

**Results**

Sample and clinical characteristics of the nine male and eight female participants are presented in Table 1. Eight participants received insulin via insulin pump; nine participants used multiple daily injections of insulin. No other method of diabetes control (e.g. oral hypoglycemic medication) was used by any participant. The first objective was to evaluate the ability of the TSST-C to induce an adequate stress response among adolescents with T1DM. Figure 1 depicts the cortisol response prior to and following the TSST-C procedure. The TSST-C task was effective in inducing a cortisol stress response, F (7, 112)=7.50, p<0.01.

Our second objective was to examine predictors of stress responsiveness in adolescents with T1DM. Table 2 details the hierarchical model building steps taken, initially including only demographic factors as predictors of cortisol stress response, then adding diabetes-related factors, including HbA1c, age of T1DM diagnosis, and age of T1DM diagnosis. None of these factors were significant predictors of adrenal response. Lastly, we tested the role of early adversity and family dysfunction as predictors of adrenal response. Only early adversity emerged as a unique predictor of adrenal response to the psychosocial stressor (p=0.01; Table 2).

Lastly, on examination of the relationship between these factors and diabetes control, we similarly found that only early adversity was associated with poorer diabetes control, after accounting for age, years of diabetes, and family functioning (t=2.16, p=0.05).

**Discussion**

This study found the TSST-C to be effective in inducing a cortisol

| Mean (SD) | Range |
|-----------|-------|
| Age (yrs) | 15.7 (1.5) | 11-18 |
| Age at T1DM diagnosis (yrs) | 7.7 (4.8) | 1-16 |
| HbA1c (%) | 8.1 (1.6) | 5.8-11.5 |
| (mmol/mol) | 65 (6.0) | 40-102 |
| FES score | 4.7 (2.34) | 1-8 |
| CTQ score | 31.3 (5.9) | 25-49 |

**Table 1: Clinical characteristics of sample.**

![Figure 1: Mean salivary cortisol values at baselines and following psychosocial stress (n=17). The TSST-C was effective in inducing a cortisol stress response, F (7, 112)=7.50, p<0.01.](chart.png)
stress response among adolescents with T1DM. This is consistent with previous research demonstrating the association of childhood maltreatment with chronic HPA axis dysfunction [20,21]. Our findings suggest an extension of this association, as early adversity predicted both increased. HPA axis to a psychosocial stressor as well as poorer diabetes control among adolescents. Diabetes investigators with a psychological approach have demonstrated that family conflict, lack of parental involvement in diabetes management or chaotic home environment lead to poorly controlled diabetes among adolescents with increased adversity. While psychological factors are indeed important contributors, this novel study suggests that the association between increased stressful life events and poor glucose control may also, at least in part, be the result of biological dysfunction.

These findings must be considered in the context of the small study sample size, thus limiting the confidence with which conclusions can be drawn. In addition, relationships found in the adolescent population may not persist in to adulthood, as chronicity of illness and time from early adversity experiences increases. Despite these limitations, this study represents an important first step toward validating a measure of stress induction that may be reliable in an adolescent diabetes population, and contributing to current understanding of the mechanism of association between psychosocial stressors and poor diabetes control. These results require replication in a larger study sample in order to both confirm the presence of these associations and further evaluate potential mediating and moderating factors that may serve as key targets for intervention.

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Table 2: Demographic, diabetes-related, and psychological predictors of cortisol responsiveness to psychosocial stress.

| Predictor                  | Model 1: demographic factors | Model 2: diabetes factors | Model 3: psychological factors |
|----------------------------|-------------------------------|---------------------------|---------------------------------|
|                            | ΔR²  | DF  | Δp   | Std. B  | t    | p     | ΔR²  | DF  | Δp   | Std. B  | t    | p     | ΔR²  | DF  | Δp   | Std. B  | t    | p     |
| Age                       | 0.29 | 2.76| 0.10 |         |      |      |       | 0.31 | 0.38 | 0.27 |         |      |      | 0.65 | 5.21 | 0.04 |         |      |      |
| Sex                       | 0.09 | 0.31| 0.76 |         |      |      |       | 0.02 | 0.06 | 0.95 |         |      |      | 0.35 | 1.10 | 0.29 |         |      |      |
| Stressful life events     | 0.45 | 1.55| 0.14 |         |      |      |       | 0.46 | 1.50 | 0.16 |         |      |      | 0.57 | 1.81 | 0.09 |         |      |      |
| HbA1C                     | 0.04 | 0.19 | 0.86 |         |      |      |       | 0.04 | 0.19 | 0.86 |         |      |      | 0.40 | 1.76 | 0.11 |         |      |      |
| Age of diagnosis          | 0.23 | 0.86 | 0.41 |         |      |      |       | 0.23 | 0.86 | 0.41 |         |      |      | 0.31 | 0.96 | 0.36 |         |      |      |

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