“Adolescents With Type 1 Diabetes Mellitus Experience Psychosensorial Symptoms During Hypoglycemia”

Running Head: Hypoglycemia Symptoms in Adolescents

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Word Count: 2,371

The project described was supported in part by the following funding sources:
T32DK007129 from the National Institute Of Diabetes And Digestive And Kidney Diseases.
6-6323 from the University of North Carolina Children's Promise Funds
Novelty Statement

There are multiple cases of people reportedly feeling “high” during hypoglycemia, which may be explained by psychosensorial symptoms (alterations in how one’s environment and subjective self are perceived).

- This is the first study of psychosensorial symptoms during hypoglycemia in adolescents with type 1 diabetes.

- Psychosensorial symptoms are common and are often reported as positive experiences during hypoglycemia.

- There were no differences in how hypoglycemia symptoms were reported in adolescents from two different cultures.
Abstract

Aim

Describe mood and psychosensorial symptoms of hypoglycemia in adolescents with type 1 diabetes mellitus (type 1 DM) in two different cultures.

Methods

We developed a 68-item questionnaire assessing physical, behavioral, mood, and psychosensorial symptom frequency and ratings ["good," “bad,” or “both” (sometimes good, sometimes bad)]. Adolescents with type 1 DM were recruited from pediatric diabetes clinics at the University of North Carolina at Chapel Hill in the USA (UNC) and Kocaeli University in Turkey (KU). Percent of participants who endorsed individual symptoms, symptom categories, and symptom ratings were calculated and compared.

Results

Cronbach’s alphas were greater than 0.7 for each real symptom category. No symptom items were excluded from the questionnaire analysis based on item-total correlation results which were all greater than 0.2.

Data were collected from 132 participants (69 from UNC, 63 from KU, 54% male). Mean age was 14.9 years (± 1.9), HbA1c 8.7% (± 1.8) and duration of type 1 DM 5.8 years (± 3.7). On average, each physical symptom was experienced by 65.2% of participants, each behavioral symptom by 46.5%, each mood symptom by 42.8%, and each psychosensorial symptom by 48.9%. On average, each physical, behavioral, mood, and psychosensorial symptom was rated as “good” or “both” by 23.0%, 29.1%,...
36.9%, and 37.2% of participants, respectively. There were no symptom differences by study location.

**Conclusions**

In addition to classical physical symptoms, adolescents with type 1 DM report psychosensorial, mood and behavioral symptoms during hypoglycemia and some describe them as positive experiences. Symptom experiences were similar between these 2 cultures.
Introduction

Hypoglycemia is a well-known complication of type 1 diabetes mellitus (type 1 DM) treatment that can lead to seizure, coma, long-term neurocognitive sequelae, and even death. Individuals with type 1 DM experience about two episodes of symptomatic hypoglycemia per week [1]. Severe hypoglycemia (requiring help for recovery) has an annual prevalence of 30–40% among people with type 1 DM and an annual incidence of 1.0 – 1.7 episodes per patient per year for all people with type 1 DM. Since hypoglycemia is so commonly experienced, early recognition of symptoms is paramount to prevent severe complications.

Aside from the traditionally recognized symptoms of hypoglycemia (e.g., neuroglycopenic, autonomic, and malaise symptoms) [2], some adults with type 1 DM report both negative and positive mood changes [3-6], and children may manifest hypoglycemia in behavioral changes [7,8]. There are cases of adults and adolescents reporting symptoms of being “high” [9-14], however these symptoms have never been scientifically studied before. Feelings of being “high” may be explained by the psychosensorial experiences of derealization (distortion in how the immediate environment is perceived) and depersonalization (distortion in how one’s own body and subjective self feel). Few pediatric studies have described physical, mood, and behavioral symptoms associated with hypoglycemia and none have described psychosensorial experiences. Some people with type 1 DM have reported pleasurable symptoms and experiences during hypoglycemia, which may contribute to episodes being perceived as positive, even desirable, rather than negative and potentially dangerous.
Our study aimed to broaden the understanding of hypoglycemic symptoms in adolescents with type 1 DM by describing self-reported psychosensorial as well as physical, behavioral, and mood symptoms of hypoglycemia. We further sought to examine whether these symptoms were rated as “good” (ie, positive), “bad” (ie, negative), or “both: sometimes good and sometimes bad” by the participants. Taking advantage of an investigator’s relationship with pediatric endocrinology clinics at both the University of North Carolina at Chapel Hill (UNC), Chapel Hill, North Carolina, United States and with Kocaeli University (KU), Kocaeli, Turkey, we decided to also examine if the reported symptoms were consistent in these two different cultures.

Patients and Methods

Questionnaire Development

A 68-item questionnaire was developed to assess previous experiences with hypoglycemia. The first item asked participants to report at what blood glucose level they typically “begin to feel low” and the remaining 67 items were possible symptoms divided into 5 different categories: physical (19 items), behavioral (5 items), mood (17 items), psychosensorial (19 items), and dummy items (7 items). The physical and behavioral symptoms were assembled from those described previously in the pediatric literature (7, 8) and mood symptoms consisted of a compiled list of conventionally perceived negative (e.g. mean) and positive (e.g. silly) emotions. Psychosensorial items were based upon studies on panic disorders and substance abuse [15, 16]. Dummy items were symptoms that are not thought to be associated with hypoglycemia (e.g. rash), and were used to assess the integrity of each participant’s responses.
Dummy items were used to exclude any participant who endorsed all dummy items due to concern for credibility of participant answers.

A 5-point Likert scale was used to assess the frequency that each symptom had ever been experienced (0=never, 1=rarely, 2=sometimes, 3=often, 4=always). That is, participants would indicate that during hypoglycemic events they never, rarely, sometimes, often, or always experience a particular symptom. Participants who ever experienced a symptom (Likert score 1, 2, 3, or 4) were then asked to rate the symptom experience as “good,” “bad,” or “both: sometimes good, sometimes bad.” At the completion of data collection, the Likert scale was condensed into two categories to improve statistical power: ever experienced a symptom versus never experienced a symptom (Likert score 0 versus 1, 2, 3, or 4).

Face and content validity for the questionnaire was examined by a panel of experts including pediatric endocrinologists, child psychologists, and a survey methodologist who reviewed the questionnaire content and construct. Item-total correlation was calculated further examine survey construct. Item-total correlation greater than 0.2 was considered acceptable. Cronbach’s alphas for each symptom category were calculated to validate the questionnaire and assess whether the symptoms in each category measured similar concepts. An alpha greater than 0.7 was considered acceptable.

The survey was first developed in English and then translated into Turkish by a pediatric endocrinologist and child psychologist fluent in both English and Turkish. Forward and backward translations were used to assess accuracy of the language translation. During the first 2 weeks of the study, participants were asked if they had
any difficulty understanding or answering the questionnaire after completing it in order to assess the appropriateness of the language used as well as the ease of questionnaire completion; no difficulties were reported.

Participants

Participants were eligible if they: 1) had type 1 DM for at least 6 months (to increase the likelihood that they had experienced hypoglycemia); 2) were 12-18 years old (children under 12 may not be able to independently describe their hypoglycemia symptoms as well as older children); and 3) received care from diabetes clinics at UNC or KU. We invited 134 consecutive patients who met eligibility criteria to participate during routine visits from February 2010 through June 2010; 133 participants and their parent/guardian provided written informed consent and assent and completed the questionnaire anonymously and privately without parents in the room. The study was approved by the Institutional Review Boards of UNC and KU.

Medical Record Review

The medical record was reviewed to obtain demographic information including age, gender, duration of diabetes, and the Hemoglobin A1c (HbA1c) level at the time of study participation.

Data Analysis

Demographic and clinical data from the time of study participation was assessed by percent or mean values ± 1 SD for gender, age, HbA1c at the study visit, duration of
diabetes, and reported blood sugar at which the patients begin to feel they are becoming hypoglycemic. T-tests were used to compare continuous variables and chi-square tests were used to compare proportions for categorical variables.

Next, the percentage of participants who experienced each symptom was calculated, and then a mean percentage of participants reporting symptoms was calculated for each symptom category. Similarly, the percentage of participants who rated a symptom (having had reportedly experienced the symptom) as “good,” “bad,” or “both” was calculated, and a mean percentage of participants was calculated for each category rating. To determine what percentage of participants endorsed the symptoms as ever being a positive experience, the percentage of participants that described symptoms as “good” or “both” was also calculated. To compare the ratings between symptom categories, a mixed-effects logistic regression model was used in order to avoid over-dispersion of a sequence of binary outcomes within the same symptom category by a participant. The odds ratio and its 0.95 confidence interval were calculated based on the coefficient estimation and its Wald-type coverage in the logistic model.

Results by site were analyzed for differences via t-tests for continuous variables and chi-square tests for categorical variables, and then the results of the sites were combined after determining that there were no differences between sites for symptom category endorsements or ratings.

All statistical tests were 2-tailed with an alpha of 0.05 significance level. R (R Development Core Team, Vienna, Austria) and IBM SPSS Statistics 19 (SPSS Inc., Chicago, IL) were the statistical packages used for analyses.
Results

Cronbach’s alphas were greater than 0.7 for each symptom category except the dummy items, demonstrating the reliability that each real symptom category measured similar concepts (physical 0.81, behavioral 0.78, mood 0.82, psychosensorial 0.89, dummy 0.60). No symptom items were excluded from the questionnaire analysis based on item-total correlation results which were all greater than 0.2.

Of 133 eligible and consenting participants, one participant survey was excluded from analysis due to endorsing all dummy items, leaving a total sample size of 132 participants, 69 from UNC and 63 from KU. There were slightly more males (54%) than females, and the average age was 14.9 years (±1.9)(Table 1). The sites differed in regard to duration of diabetes, average HbA1c, and blood glucose level at which symptoms begin such that participants at UNC had a higher average HbA1c, higher average reported blood glucose level at which symptoms begin, and longer duration of diabetes at the time of study participation.

In examining the percentage of participants who ever experienced the symptoms presented in the questionnaire (ie, reported a Likert score indicating “rarely” to “always”), we found that the most commonly reported symptom category was physical, with an average of 65.2% of participants reporting each symptom(Table 2). The physical symptoms experienced by the most participants were trembling, weakness, feeling run down, headache, and feeling awful. Psychosensorial symptoms (depersonalization and derealization) were experienced on average by 48.9% of participants, and the most experienced symptoms were difficulty concentrating,
lightheadedness, confusion, feeling spaced out, and feeling like you don’t care.

Behavioral symptoms were reported on average by 46.5% of participants. The most frequently experienced behavioral symptoms were odd behavior, argumentativeness, and aggressiveness. Mood symptoms were experienced on average by 42.8% of participants. The most experienced mood symptoms were jitteriness, unhappiness, edginess, uneasiness, and moody/emotional roller coaster.

Generally, symptoms were reported as “good” or “both” by 1/4-1/3 of the participants. Of participants who ever experienced physical symptoms, 23.1% reported them as “good” or “both.” The physical symptoms most commonly reported as “good” or “both” were yawning, sleepiness, warmness, tiredness, and restlessness. Of participants who ever experienced behavioral symptoms, 29.2% reported them as “good” or “both.” The behavioral symptoms most commonly reported as “good” or “both” were naughtiness, meanness, and odd behavior. Of participants who ever experienced mood symptoms, 36.9% reported them as “good” or “both.” The mood symptoms most commonly reported as “good” or “both” were feeling jolly/silly, cheerful, revved up, full/rush of energy, and excited. The psychosensorial symptom category had the most positive responses, with 37.2% of participants reporting the symptoms as “good” or “both.” The psychosensorial symptoms most commonly reported as “good” or “both” were dreaming, feeling free/let go of self, mellow/chilled out, alert, and floating/moving through the world differently. The psychosensorial and mood categories had the highest odds of positive endorsement compared to other symptom categories [psychosensorial compared to physical OR 2.8 (95% CI 2.3, 3.4), psychosensorial compared to behavioral 1.7(1.2, 2.3), and psychosensorial compared to mood 1.1 (0.9,
mood compared to physical 2.5 (2.1, 3.1) and mood compared to behavioral 1.5 (1.1, 2.1)]. The symptoms by frequency and ratings for mood and psychosensorial categories are displayed in figures 1 and 2, respectively.

There was no statistically significant relationship for any symptom category endorsement frequency or ratings with study location, age, gender, HbA1c, reported blood glucose level at which hypoglycemia symptoms begin, or duration of type 1 DM at the time of study participation.

Discussion

As anticipated, adolescents commonly experience physical and behavior symptoms during hypoglycemia. This is the first study to report that many adolescents with type 1 DM also experience psychosensorial symptoms of depersonalization and derealization and mood changes during hypoglycemia. Surprisingly, hypoglycemia symptoms are also sometimes described as positive experiences, particularly the psychosensorial and mood symptoms. The reported symptom experiences were similar in both the UNC and KU samples, suggesting no difference between these two cultures.

Our findings are supported by adult studies evaluating mood symptoms of hypoglycemia which have shown that low blood glucose is often associated with negative mood states, but also occasionally with positive mood states [1, 17-19]. There have also been case reports of adults and adolescents who misuse insulin to achieve a euphoric or “high” effect [7,8, 14, 20-22]. Shober et al further reports that 35% of adolescents who overdose insulin reported feeling “high” during hypoglycemia as one of the reasons for their actions in addition to suicidal intentions or attention seeking [14].
Therefore, we feel our findings of mood changes and psychosensorial symptoms in addition to the well-known physical and behavioral symptoms of hypoglycemia and that these symptoms are sometimes positively experienced are real.

Limitations of our study include a relatively small sample size and a reliance on recall of previous hypoglycemia experiences. We also do not know the frequency with which participants experience hypoglycemia. However, based on the work presented here, further studies can now be designed with knowledge that some adolescents endorse psychosensorial symptoms and hypoglycemia symptoms are sometimes reported as good. In addition, while our questionnaire categories demonstrated excellent internal consistency as evidenced by high Cronbach’s alphas, further validation techniques would be needed before application to other populations.

Hypoglycemia is known to cause a considerable burden to the family through increased anxiety, poor sleep, and increased hospitalizations, while also leading to excessive lowering of insulin doses and worsening glycemic control [21]. Prompt hypoglycemia symptom recognition is important for reducing diabetes-associated morbidity and mortality such as the hypoglycemia-associated decrease in neurocognitive function and structural brain changes found in some studies of young children with type 1 DM [17-20, 23-24]. Understanding the array of hypoglycemia symptoms presented in this study may help providers educate patients and their families regarding the variety of possible hypoglycemia symptoms, including the potential for positive experiences. In turn, patients and families may improve their recognition of hypoglycemia, which could lead to faster treatment and prevention of complications.
Author Contributions:
Jennifer R. Law, MD, and Gül Yeşiltepe-Mutlu, MD, were primary investigators for this project at each location. Dr. Law also participated in study design and data interpretation. Sarah Helms, PhD, and Echo Meyer, PhD, aided in English questionnaire development and implementation. Elif Özsu, MD, and Filiz Çizmecioğlu, MD aided in Turkish questionnaire development and implementation. Feng-Chang Lin, PhD, performed statistical analysis of the data. Şükrü Hatun, MD, and Ali S. Calikoglu, MD, provided mentorship for research design, implementation, and data interpretation at each research site. Each author actively contributed to manuscript preparation.

Acknowledgements:
As guarantor of this work, Dr. Law had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors do not have any conflicts of interest to disclose.

The project described was supported in part by the following awards:
T32DK007129 from the National Institute Of Diabetes And Digestive And Kidney Diseases.
6-6323 from the University of North Carolina Children's Promise Funds
UL1RR025747 from the National Center for Research Resources
The project described was accepted in abstract form and presented at the Pediatric Academic Societies/Asian Society for Pediatric Research conference in April 2011.
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Tables

Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 132)</th>
<th>UNC (n = 69)</th>
<th>Turkey (n = 63)</th>
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<tbody>
<tr>
<td>Male (%)</td>
<td>53.8</td>
<td>53.6</td>
<td>54.0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>14.9 (±1.9)</td>
<td>15.0 (±1.9)</td>
<td>14.7 (±1.9)</td>
</tr>
<tr>
<td>HbA1c (%; mmol/mol)*</td>
<td>8.7 (±1.8); 72 (±19)</td>
<td>9.4 (±1.7); 80 (±18)</td>
<td>7.9 (±1.5); 63 (±17)</td>
</tr>
<tr>
<td>Blood glucose at which hypoglycemia symptoms begin (mmol/L)*</td>
<td>3.7 (±0.9)</td>
<td>4.2 (±0.7)</td>
<td>3.21 (±0.8)</td>
</tr>
<tr>
<td>Duration of type 1 diabetes &lt;5 years (%)†</td>
<td>48.7</td>
<td>39.4</td>
<td>58.8</td>
</tr>
</tbody>
</table>

Categorical measures are presented as percentages and continuous measures are presented as mean values ± SD

*p < .001, †p = .022