# Stress Hyperglycemia in a Pediatric Emergency Department Setting and its Relationship to the Underlying Disease and Outcome

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**ABSTRACT** **Background:** Stress hyperglycemia (SH) is a common finding in patients in pediatric emergency departments (PED) and has been related to increased morbidity and mortality.

**Objectives:** To assess the incidence of SH among children visiting the PED. To identify which diseases predispose patients to SH and whether they indicate a worse outcome.

**Methods:** Data were collected retrospectively from the medical records of all children aged 0–18 years who visited the PED during the years 2010–2014 and who had a glucose level of ≥ 150 mg/dl. Data collected included age, gender, weight, blood glucose level, presence or absence of a pre-existing or a new diagnosis of diabetes mellitus, and previous treatment with medications affecting blood glucose levels or with intravenous fluids containing dextrose. Data were collected regarding hospitalization, duration of hospitalization, discharge diagnosis, and survival status.

**Results:** The study population included 1245 children with SH, which comprised 2.6% of all patients whose blood glucose level was measured in the PED during the study period. The mean age of children with SH was 49 months; 709 (56.9%) were male. The mean blood glucose level was 184 mg/dl. The rate of hospitalization was 57.8%. The mean duration of hospital stay was 5.6 days and mortality rate was 0.96%. The majority were diagnosed with a respiratory illness.

**Conclusions:** SH is a common phenomenon among children evaluated in the PED and is associated with a high incidence of hospitalization. It may serve as an additional clinical indicator of disease severity.

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**KEY WORDS:** stress hyperglycemia (SH), pediatric emergency department (PED), glucose, morbidity

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Stress hyperglycemia (SH) is defined as a transient increase in blood glucose concentrations (usually above 150 mg/dl), as a result of stress [1]. In most cases the blood glucose levels normalize when the stressful condition has surpassed [2,3]. The incidence of SH is reported to be as high as 5% in children visiting pediatric emergency departments (PED), in whom blood glucose is measured [4-7]. Stress hyperglycemia in adults has been related to adverse outcomes in a wide range of diseases [8-11]. In the pediatric population it has been found to positively correlate with the rate of hospitalization, duration of hospital stay and mortality, but large series from recent years are lacking [2,5].

In children visiting the emergency department, various conditions have been specifically related to stress hyperglycemia. In a study by Fattorusso et al. [3], febrile seizures and traumatic injuries were correlated to high levels of glucose, while Weiss and colleagues [2] found extreme stress hyperglycemia (glucose ≥ 300 mg/dl) in patients with respiratory illness, traumatic injury and seizures.

Research aimed to elucidate the mechanisms leading to SH has identified insulin resistance, β cell dysfunction, enhanced glycogenolysis, and increased gluconeogenesis as possible underlying factors. [12] Whether stress hyperglycemia represents the adaptation of the body to stress in order to provide glucose to suffering organs or is a pathologic phenomenon remains a matter of debate [13-15].

Some case reports suggested that SH may be the first sign of diabetes, but most studies that followed children with SH over the course of several years concluded that this is rarely the case [16].

In this study, we determined the incidence of SH in patients admitted to a PED of a tertiary referral center and characterized the underlying illnesses associated with the development of SH as well as its correlation with specific outcome measures.

## PATIENTS AND METHODS

### STUDY DESIGN

This retrospective review evaluated all cases of SH, defined as a blood glucose level ≥ 150 mg/dl, in children who visited the PED of Shaare Zedek Medical Center during the years 2010–2014. The institutional review board approved the study.

### STUDY SETTING AND POPULATION

The PED of Shaare Zedek Medical Center treats all children aged 0–18 years, with the exclusion of patients with major trauma. The average yearly census was approximately 19,300 visits per year during the study period (range 15,334–24,337). Patients with a final diagnosis of diabetes mellitus or those who received intravenous fluids containing glucose prior to the detection of hyperglycemia were excluded from the study.

A detailed review of patient medical records was conducted. Information obtained included age; gender; laboratory blood glucose levels; recent or chronic administration of medications known to affect the metabolism of glucose such as steroids, beta-agonists, and adrenalin; hospital admission; pediatric intensive care unit (PICU) admission; length of hospital stay; primary discharge diagnosis; and survival status. In cases where patient data were missing, the patient visit was excluded from the study.

The blood glucose level was assessed in the clinical chemistry laboratory of our medical center by the standard glucose oxidase method, using Vitros 5.1 equipment (Ortho Clinical Diagnostics Company, USA). According to the principal discharge diagnosis recorded in the medical summary, cases of SH were divided into the following groups: respiratory, neurologic, gastrointestinal, infectious, otolaryngeal, urinary tract infection, surgical, cardiac, and miscellaneous.

The respiratory group included mostly pneumonia of different causes, bronchiolitis, asthma, and reactive airway disease. Neurologic illnesses included mainly febrile and non-febrile seizures. The gastrointestinal illness group included mostly gastroenteritis and abdominal pain. Since there was a preponderance of cases with diagnoses specific to either otolaryngology infections or urinary tract infections, we separated these two groups from the remainder of cases with infectious diseases diagnoses. The infectious diseases group was heterogeneous and included the full range of infections seen in children. The cardiac illness group included chest pain, brief resolved unexplained event, dehydration and hypovolemic shock, fainting, arrhythmias, and hypoplastic left heart syndrome. The miscellaneous group was comprised of less common diagnoses and included hemato-oncological diseases, various kidney diseases, allergic reactions, autoimmune diseases, burns, and trauma.

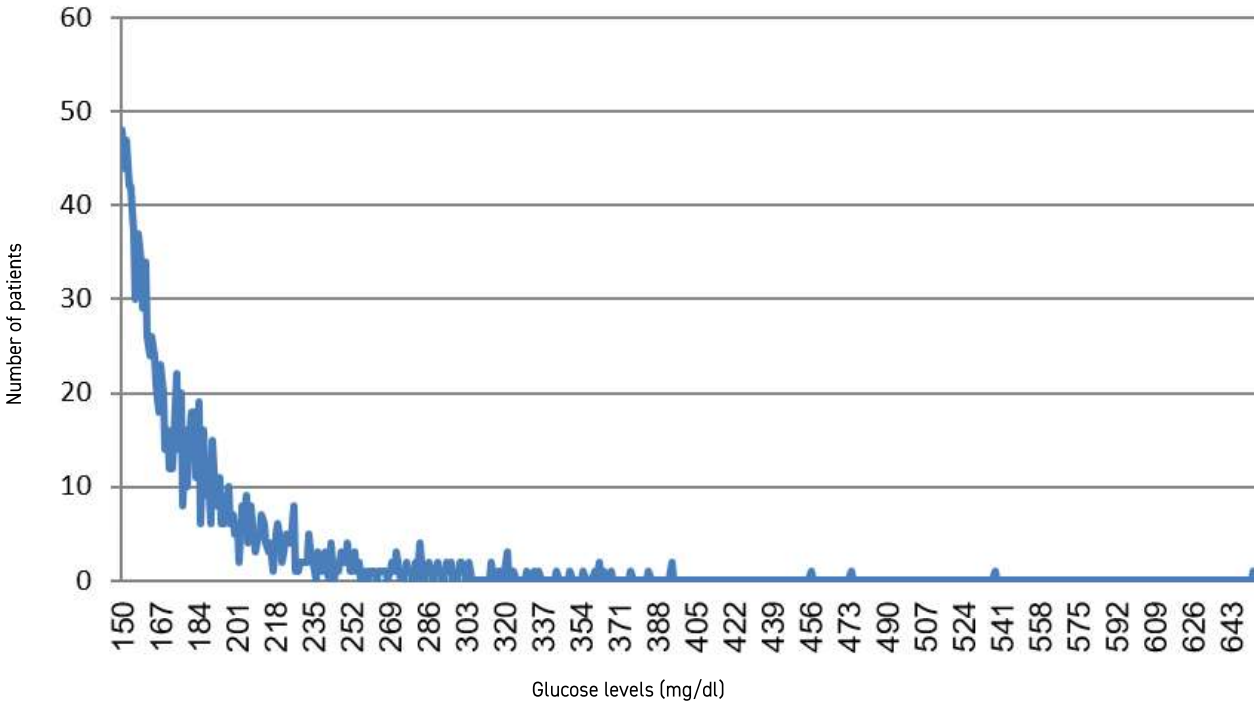
### THE RELATIONSHIP BETWEEN MEDICATION AND STRESS HYPERGLYCEMIA IN WHEEZING CHILDREN

Within the respiratory disease group, the average blood glucose level was compared between children with wheezing who received corticosteroids (inhaled or systemic), beta-agonists (inhaled), or adrenalin (inhaled or systemic) prior to the blood test, and children with wheezing who received none of these medications.

### DATA ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA). We used the *t*-test to detect the difference between averages of two groups. A logistic regression model was applied to examine the effect of external variables on the binary dependent variable. To evaluate the effect of continuous external variables on the continuous dependent variable, a linear regression model was applied. To analyze variance between the years of the study, we used the one way ANOVA test. $P < 0.05$ was considered significant.

**Figure 1.** Distribution of blood glucose levels among all children with stress hyperglycemia



## RESULTS

During the study period there were 96,510 visits to the PED. Of the 47,626 (49%) patients who had their blood glucose level measured, 1557 (3.3%) had a glucose level of ≥ 150 mg/dl, and 301 of these patients were excluded from this study (5 patients were over the age of 18 years, 2 arrived at the PED at the end of 2009 and the blood test was taken in 2010, 31 had the first blood glucose level in the PED below 150 mg/dl, 198 had diabetes mellitus, and 65 received intravenous fluids containing glucose prior to the blood glucose measurement). In addition, medical records of 11 cases were not found and therefore these were excluded as well. The remaining 1245 cases, 2.6% of all patients whose blood glucose level was measured, comprised the study group.

The mean age was 49 months (range 7 days–17 years and 11 months) and 56.9% were male. The mean blood glucose level was 184 (range 150–653) mg/dl [Figure 1]. The rate of hospitalization in patients with SH was 57.8%, compared to 23% in those without SH. The mean duration of hospital stay was 5.6 days (range 1–73 days). The mortality rate was 0.96%. Only four patients had blood glucose levels ≥ 400 mg/dl, two of whom were admitted to the PICU. One was admitted to the pediatric ward and one was returned to his chronic care facility after undergoing resuscitation. None of these four children died.

The discharge diagnoses among children with SH appear in Table 1. The most common diagnosis was a respiratory illness, accounting for 37.8 % of the cases, followed by Neurologic illnesses (14.8%).

In our regression logistics analysis, higher Blood glucose levels was a predictor of increased rates of hospitalization (by 0.6%, $P < 0.01$), PICU admission (by 1.3%, $P < 0.01$), and mortality (by 1.3%, $P < 0.01$) compared to all patients enrolled in this study. Length of hospital stay increased by two days for every 100 mg/dl increase in blood glucose. There was no significant difference between the blood glucose levels among children who received any medication for wheezing and wheezing children who did not ($P = 0.72$). However, wheezing children treated with adrenalin (either systemic or inhalation) had higher blood glucose levels than children whose wheezing was not treated with medication (233 mg/dl vs. 196 mg/dl, $P = 0.02$).

We also found a significant effect of age on blood glucose levels, with younger children having higher blood glucose levels ($P < 0.01$). We did not find a significant difference between boys and girls.

The incidence of SH during the years 2010–2014 did not follow a constant trend, with an average incidence of 2.6% (range 2.1–3.3) [Figure 2].

## DISCUSSION

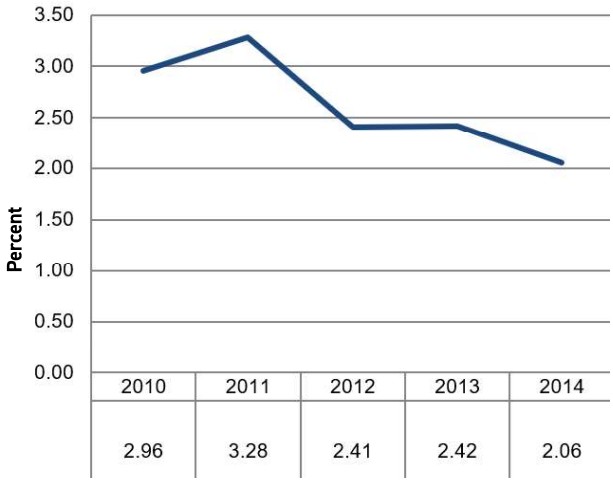
The incidence of SH in children visiting our PED was less than what has been previously reported [3-5]. This finding may be attributable to the fact that our PED does not treat major trauma. In previous studies the vast majority of cases of SH in children were found with major trauma [3]. The general practice in our PED favors avoiding blood testing whenever possible, and this too may explain the lower rate of SH in our study.

The major diagnoses associated with SH in the current study were respiratory, neurologic, and gastrointestinal diseases. Interestingly, the highest mean glucose level (202 mg/dl) was in cardiac diseases, but this group was small. In previous studies, respiratory and neurologic diseases, seizures, and trauma were the most common diagnoses associated with SH, while cardiac diseases compromised only a small percentage of the cases [2,3].

**Table 1.** Blood glucose levels in different disease groups with stress hyperglycemia

| Illness category | Percent of the total | Mean glucose levels (mg/dl) | Standard deviation | Maximun glucose levels (mg/dl) |
|---|---|---|---|---|
| Respiratory | 37.8 | 192.3 | 50.8 | 653 |
| Neurologic | 14.8 | 180 | 32.1 | 384 |
| Gastrointestinal | 14.1 | 181.4 | 51 | 538 |
| Infectious | 10.4 | 171.9 | 25.7 | 294 |
| Otolaryngeal | 6.5 | 172.1 | 28.6 | 304 |
| Miscellaneous | 6.5 | 187.7 | 44.2 | 335 |
| Urinary tract infections | 4.3 | 177 | 27.5 | 296 |
| Surgical | 4.2 | 175.5 | 33.3 | 320 |
| Cardiac | 1.4 | 201.8 | 56.8 | 376 |
| Total | 100 | 184 | 43.8 | 653 |

**Figure 2.** Percent of stress hyperglycemia from all the glucose blood tests in the pediatric emergency departments by year




PED = pediatric emergency departments, SH = stress hyperglycemia

Among children with wheezing, we found a correlation between SH and treatment with adrenalin. Dawson and co-authors [17] found that in children with acute asthma a strong correlation was demonstrated between hyperglycemia and treatment with nebulized salbutamol [17].

Despite the global increase in the incidence of childhood-onset diabetes, the rate of hyperglycemia in our study did not rise during the 5-year study period. It is possible that a longer study period would reflect this global trend.

A significant finding of our study was the correlation between higher blood glucose levels and the severity of illness as reflected by the need for hospitalization, length of hospitalization, PICU admission, and death. This finding is consistent with the results of other studies that evaluated adverse outcomes with SH [18-20].

Although these outcome measures are largely interdependent, overall, the degree of hyperglycemia on presentation to the PED may serve as a clinical marker of severity of illness.

A particular strength of our study is that it included all children who were evaluated in the PED during the research period, thus eliminating selection bias. However, it is possible that a rare patient whose only blood test was a bedside glucose level without a sample tested in the laboratory was not included in the study. Its retrospective design and the absence of patients with major trauma and a control group are the study's major limitations. Another possible limitation is the absence of data regarding the time elapsed since the patient's last meal until the blood glucose were tested. However, in a healthy child, even an immediate postprandial blood glucose level should not exceed 150 mg/dl. Therefore all of our cases of hyperglycemia can be attributable to SH.

## CONCLUSIONS

SH among children who are evaluated in a PED may represent a clinical indicator of disease severity. Whether or not SH is a sign of early β cell dysfunction and future diabetes is a critical question which future prospective studies should aim to answer.

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