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Evaluation Of Stress Hyperglycemia on the Admission and Follow-Up of Patients Admitted to The Pediatric Emergency Department

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Abstract

Background: This study aims to examine the demographic and clinical characteristics of patients with stress hyperglycemia (SH) at admission to the pediatric emergency department and investigate whether diabetes develops in the follow-up of patients with SH.

Methods: Data were collected retrospectively from the medical records of all children aged 1 month –18 years who visited the Pediatric Emergency Department during the years 2017–2022 and had a glucose level of >200 mg/dl. Patients with a final diagnosis or history of diabetes mellitus were excluded from the study. Data collected included age, gender, blood glucose level, treatment with medications affecting blood glucose levels, white blood cells (WBC), C-reactive protein (CRP), pH, lactate levels, hospitalization, and diagnosis in the Pediatric Emergency Department. The development of diabetes in the follow-up was determined by insulin, C-peptide, and HbA1c levels. A p-value below 0.05 was considered significant in all analyses.

Results: SH was observed in 818 patients who applied to the emergency department in the last five years. The median age of patients was 22 months (1-214 months). Age of 51.2% of the patients was between 1-23 months.57.2% of the patients were male, and 42.9% were female. The male/female ratio in the study was 1.3/1. The most common diagnoses of patients with SH in the emergency department were lower respiratory tract infection (59.5%), tonsillitis (11.1%), and acute gastroenteritis (10.5%), respectively. The median blood glucose level of the patients was 232 mg/dl (201-438 mg/dl). The blood glucose level of 9.3% of the patients was above 300 mg/dl. 15.7% of patients with SH were hospitalized. HbA1c level was lower than 5.5% in all patients who had an HbA1c test during their follow-up (n=45). Patients who received salbutamol (p=0.013) or corticosteroids (p=0.004) had higher blood glucose levels, and those who received fluid therapy (p=0.001) had lower blood glucose levels in the emergency department. Blood glucose levels were similar in hospitalized and non-hospitalized patients (233 mg/dl vs 227 mg/dl, p=0.536).

Conclusions: SH is a common finding among children evaluated in the Pediatric Emergency Department. Our findings regarding children with SH do not indicate an increased risk of diabetes.

Keywords
Children, Diabetes, Stress Hyperglycemia

Introduction

Stress hyperglycemia (SH), characterized by increased glycogenolysis and gluconeogenesis with insulin resistance, is a normal homeostatic response to acute stress. SH is frequently seen in children because of febrile convulsions, respiratory tract infections, and some commonly used medical treatments [1]. SH is not an underlying disease; it is defined as the plasma glucose level rising above 150 mg/dl due to an acute or critical illness and returning to normal when the underlying stress is eliminated [2, 3].

The frequency of SH in children is not known precisely. It has been reported that 3.8-5% of the children without diabetes who applied to the emergency department had a plasma glucose level above 150 mg/dL, and 20-35% of the children with critical illness or followed in the intensive care unit had a plasma glucose level above 200 mg/dl [4]. Evidence-based guidelines have been created using extensive data on Type 1 Diabetes Mellitus (DM) and its treatment in children. However, data on the pathogenesis of SH in children are limited and are often derived from adult studies. In addition, it is not precisely known when to treat SH, when to start the

treatment, and which agents to use. Moreover, SH is associated with poor prognostic outcomes such as prolonged hospital stay and increased mortality, especially in critically ill patients, indicating that SH encountered in the intensive care setting should be treated [5].

It was aimed to define the demographic and clinical characteristics of children who applied to the emergency department with a blood glucose level over 200 mg/dl and to determine whether they would develop diabetes in the future regarding their laboratory values at admission and HbA1c, insulin, and C-peptide levels in the controls. This study also aimed to determine SH patients' hospitalization rates and examine the differences between hospitalized patients and those who were not.

Materials and Methods

Study design and participants

This study was planned as a single center and retrospective study at Health Sciences University Ankara Atatürk Sanatorium Training and Research Hospital. Between January 1, 2017, and January 1, 2022, it was planned to retrospectively include patients who presented to the Pediatric Emergency Clinic of SBU Ankara Atatürk Sanatoryum Education and Research Hospital, who did not have a known diagnosis of diabetes or hypoglycemia, and whose blood sugar level was measured above 200 mg/dL.

During the study period, patients who presented to the emergency department for any reason and had no history or diagnosis of diabetes were screened from the hospital's digital archives. Data extracted from patient records included age, gender at presentation, presenting symptoms, diagnoses made in the emergency department, and treatments recommended at the time. While reviewing blood tests, results such as white blood cell (WBC) count, C-reactive protein (CRP), venous blood pH, lactate levels, as well as the presence of glucose and ketones in the urine, were recorded from the files. Additionally, the patients' current status in the emergency department, whether they were transferred to other centers, and whether they were admitted to inpatient wards were documented.

To assess whether these patients developed diabetes during subsequent visits, insulin, C-peptide, and HbA1c tests were evaluated. Insulin was requested in 50 patients, while C-peptide and HbA1c tests were requested in 45 patients. Normal insulin levels before puberty were considered up to 5-10 µU/L; after puberty normal levels were accepted as up to 10-17 µU/L in girls and 13-20 µU/L in boys. The normal reference range for C-peptide was 1.1–3.2 ng/mL, and for HbA1c, it was between 4% and 5.6%.

Patients' age, gender, symptoms in the admission to the emergency department, diagnosis in the emergency department, and recommended treatments were taken from the files. Laboratory values (HbA1c, insulin, and C-peptide) of the patients included in the study were taken from hospital records. HbA1C values were determined using the blood tubes anticoagulated with potassium-ethylenediamine tetra acetic acid (K3EDTA) in the Adams HA-8180V fully automatic HbA1c device in the Biochemistry Laboratory of the Ministry of Health Ankara Atatürk Sanatorium Training and Research Hospital. Insulin and C-peptide levels were determined in dry gel tubes and Abbott Architect I2000 branded device.

SH is defined by the "American Diabetes Association" as a fasting plasma glucose level above 126 mg/dl or a random glucose level above 200 mg/dl in patients who did not have diabetes before. As the study's design was retrospective and blood samples were taken in an emergency setting, values above 200 mg/dl were used to diagnose SH to exclude fasting and postprandial effects, in line with the "American Diabetes Association" recommendations.

Patients with blood glucose levels above 200 mg/dL were included in the study, and based on their blood glucose measurements, the patients were divided into two groups:

- Group 1: Blood glucose 200–299 mg/dL
- Group 2: Blood glucose exceeding 300 mg/dL

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 (Chicago, USA). The conformity of the variables to the normal distribution was checked using visual (histogram and probability graphs) and analytical methods (Kolmogorov Smirnov, Shapiro-Wilk test). Descriptive statistics were expressed as the mean and standard deviation in normally distributed data, median and minimum maximum in non-normally distributed data, and numbers and percentages in nominal data. "Independent groups t-test" was used to test the differences between two groups for normally distributed numerical variables, "Mann-Whitney U test" for non-normally distributed numerical variables, and "Chi-square analysis" and "Fisher Exact test" were used to compare nominal data. In all analyses, values below $p<0.05$ were considered statistically significant.

Ethics committee approval

The necessary permission was obtained from Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee with the decision numbered 2012-KAEK-15/2524 on 24.05.2022.

Results

A total of 547,638 patients were evaluated. Blood glucose levels were requested for 125,317 of these patients. Among them, 1,370 patients had blood glucose levels exceeding 200 mg/dL.

Of these 1,370 patients, 552 were excluded from the study and a total of 818 patients were included in the final analysis **(Figure-1).** The median age of 818 patients included in the study was 22 months (1-214 months). 51.2% of them were 1–23-month-old, 20% 24–47-month-old, 11.2% 48–71-month-old, and 17.5% 72-month-old and above. 57.2% of the patients were male, and 42.8% were female. The male/female ratio in the study was 1.3/1. The most common symptoms of patients who applied to the emergency department were cough (67.1%), throat ache (66.3%), and fever (65.2%). Regarding the diagnoses of the patients, 487 patients (59.5%) were diagnosed with lower respiratory tract infection (LRTI), 91 patients (11.1%) with tonsillitis, and 86 patients (10.5%) with acute gastroenteritis **(Table-1)**.

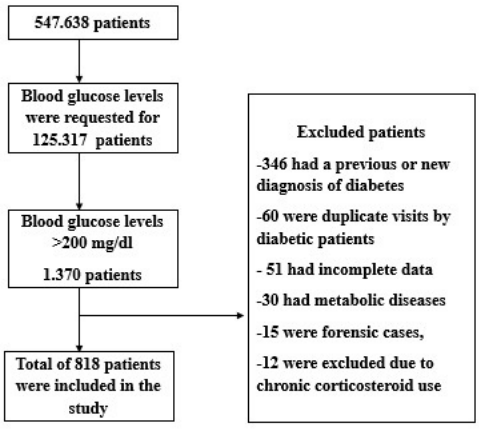

Figure 1: Flowchart showing number of patients of the study

The treatments applied to patients with SH in the emergency department were salbutamol (24.1%), salbutamol+ corticosteroid (CORT) + paracetamol (PCT) + (non-steroidal anti-inflammatory) NSAID (22.9%), PCT+NSAID (19.6%), and fluid (18.6%). The median blood glucose level of the patients was 232 mg/dl (201-438 mg/dl). The blood glucose level of 9.3% of the patients was above 300 mg/dl **(Figure 2).**

Table 1: Demographic Data of Patients (n=154)

Symptoms	**n**	**%**
Cough	549	67.1
Throat ache	542	66.3
Fewer	533	65.2
Malaise	399	48.8
Shortness of breath	205	25.1
Neck pain	125	15.3
Stomach ache	111	13.6
Diarrhea	101	12.3
Vomiting	89	10.9
Constipation	23	2.8
Dermatological complaints	19	2.3
Urinary burning	11	1.3
Patient's diagnosis	**n**	**%**
LRTI	487	59.5
Tonsillitis	91	11.1
Acute gastroenteritis	86	10.5
URTI	66	8.1
Convulsion	33	4.0
Sinusitis	17	2.1
Stomach ache	14	1.7
Urticaria	13	1.6
UTI	11	1.3
Other	35	4.2
Treatments	**n**	**%**
Salbutamol	197	24.1
Salbutamol+ CORT+PCT+ NSAID	187	22.9
PCT+ NSAID	160	19.6
Fluid	147	18
Salbutamol+ CORT	112	13.7
CORT	14	1.7
In admission to the ED	**n**	**Mean (Min-Max)**
Glucose (mg/dl)	818	232 (201-438)
WBC (10^3/µL)	818	10.5 (1.7-30.7)
CRP (mg/dL)	818	5.6 (0-120)
pH	586	7.37 (7.25-7.54)
Lactate (mmol/L)	585	3.1 (0.5-7.6)
In the control	**n**	**Mean (Min-Max)**
Insulin (µU/L)	50	10.7 (2.2-67.1)
C-peptide (ng/mL)	45	5.2 (0.6-21.1)
HbA1c (%)	45	5.3 (4.0-5.5)

LRTI: *Lower respiratory tract infection*, **URTI**: *Upper respiratory tract infection*, **UTI**: *Urinary tract infection*, **CORT**: *Corticosteroid*, **PCT**: *Paracetamol*, **NSAID**: *Non-steroid anti-inflammatory drug*, **ED**: *Emergency department*, **WBC**: *White blood cell*, **CRP**: *C reactive protein*, **HbA1c**: *Hemoglobin A1C*

Insulin levels ranged from 2.2 µU/L to 67.1 µU/L. The normal insulin level before puberty is 10 µU/L; after puberty, up to 17 µU/L is considered normal in girls and 13 µU/L in boys. C-peptide values of the patients ranged from 0.6 ng/mL to 21.1 ng/mL. C-peptide normal value range is 1.1-3.2 ng/ml. HbA1c level was lower than 5.5% in all patients whose HbA1c was tested. The mean HbA1c level was 5.3%. The normal range for HbA1c is between 4.0% and 5.6% **(Table 1).**

When the patients were compared according to their blood sugar levels, the most common symptom was

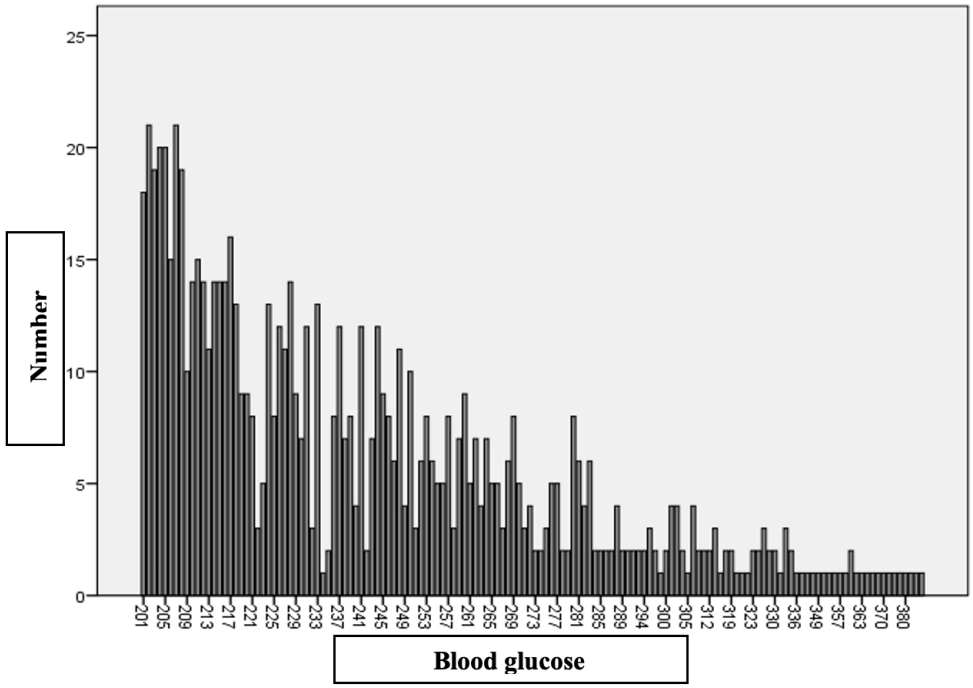

Figure 2: Blood glucose levels of patients in the emergency department

cough, and the most common diagnosis was LRTI, and there was no significant difference between the two groups (p>0.05). The use of CORT as treatment was found to be significantly higher in patients with blood glucose ≥300 mg/dl (p=0.028).

The mean insulin value was 9.6 in the group whose blood glucose level was between 200-299 and 21.7 in the group whose blood glucose level was above 300. However, this difference was not statistically significant (p=0.081). No significant difference was observed in HbA1c and other laboratory data **(Table 2).**

Table 2: Comparison of Laboratory Data of Patients According to Blood Glucose Levels

Mean, (Min-Max)	BGL 200-299 mg/dl (n=742)	BGL≥300 mg/dl (n=76)	p-value
WBC	10.6 (2.6-30.7)	10.1 (1.7-29.2)	0.14
CRP (mg/dL)	5.5 (0-120)	5.9 (0-92)	0.56
pH	7.37 (7.25-7.49)	7.37 (7.30-7.54)	0.81
Lactate (mmol/L)	3.1 (0.5-7.6)	3.0 (1.2-6.8)	0.99
Insulin (µU/L)	9.6 (2.2-67.1)	21.7 (4.4-61.1)	*0.08*
C-peptide(ng/mL)	4.9 (0.6-21.1)	6.1 (3.1-20.4)	0.15
HbA1c (%)	5.2(4.0-5.5)	5.3 (4.3-5.4)	0.91

BGL: *Blood Glucose Level*, **WBC**: *White blood cell*, **CRP**: *C reactive protein*, **HbA1c**: *Hemoglobin A1C*

The patients who received salbutamol during the treatment had higher blood glucose levels (p=0.013). The blood glucose levels of patients who used corticosteroids (CORT) in the emergency department were also higher (p=0.004).

Discussion

Hyperglycemia frequently occurs during a severe disease [6]. In hyperglycemia, glycogenolysis and gluconeogenesis are stimulated by the effects of cortisol, catecholamine, glucagon, and proinflammatory cytokines. This stimulus causes the emergence of peripheral insulin resistance. Although SH was thought to be a normal metabolic response to acute stress, it was reported to cause adverse clinical outcomes in pediatric and adult studies, including prolonged hospitalization, unnecessary drug use, and increased costs due to further tests [3]. It is especially wondered whether diabetes develops in the later stages in children with SH [7].

This study's plasma glucose threshold was set as 200 mg/dl while defining SH. However, in most studies, SH was defined as a plasma glucose level over 150 mg/dl in patients without known diabetes [3,5,8]. Some studies even accepted 126 mg/dl as the threshold [2]. On the other hand, the "American Diabetes Association" defined SH as a fasting plasma glucose level above 126 mg/dl in patients without diabetes mellitus, 140 mg/dl in hospitalized patients, and a random plasma glucose level above 200 mg/dl [9]. Since it was aimed to examine the SH frequency in patients admitted to the pediatric emergency department, those with a glucose level above 200 mg/dl were included in this study to eliminate the uncertainty about the fasting and postprandial status.

It is known that glucose levels rise temporarily during acute diseases. However, it is also suggested that SH may be the first sign of pancreatic beta cell damage and predisposes to the development of diabetes [10,11]. Saz et al. reported in their study conducted in Turkey that glucose metabolism disorder was not observed in the SH follow-ups of patients admitted to the emergency department with febrile disease [12]. Shehadeh et al. examined 36 patients with hyperglycemia after acute illness; the first phase of insulin response was low in 8 patients, and insulin autoantibodies were positive in 3 patients. However, they reported that none of the patients developed diabetes in their follow-ups 12-16 months later [13]. Therefore, it was thought that hyperglycemia developed during severe acute illness did not significantly affect the development of diabetes alone.

In this study, the HbA1c level of 818 patients diagnosed with SH at admission to the emergency department was below 5.5% in their subsequent controls. These patients' plasma glucose levels returned to normal in the follow-up and controls. It was observed that none of the patients diagnosed with SH in the emergency department developed diabetes in their controls. 9.3% of the patients had blood glucose levels above 300 mg/dl, but none developed diabetes in their follow-up, which is consistent with the literature.

Contrary to studies reporting that SH is a normal physiological response, there are also studies suggesting that SH facilitates the development of diabetes. The study of Oron et al. focused on the diagnosis of febrile infection in two patients who applied to the emergency department with a blood glucose level above 150 mg/dl. Patients' examination revealed that one patient's mother had gestational DM, the other patient had a family history of MODY, and heterozygous mutations in the glucokinase gene were observed in their genetic analysis. The study has suggested that SH with a family history may be associated with monogenic diabetes. However, only two cases were included in the study, which is a significant limitation [14].

Bae et al. reported that the frequency of 1-3-year-old patients was high in the SH population [14]. It has been attributed to the frequent monitoring of febrile diseases, which are an important cause of SH in this age group. On the other hand, regardless of SH, nearly half of the emergency department admissions were patients aged 5 years and younger [15]. In addition, the average age of patients with SH may vary depending on the characteristics of the emergency services. The average age of SH can be higher in pediatric emergency departments accepting trauma because traumas are mainly observed at the age of 5 and above. In our study, patients who underwent trauma and CPR were excluded, and the median age was 22 months; similar to the literature, approximately half of the patients were 1-24-month-old.

Valerio et al. Reported that the frequency of SH in children with febrile convulsions was higher than in children with only febrile disease [16]. In cases of hypoxic and ischemic damage such as febrile convulsions, hyperglycemia may not be harmful; on the contrary, it may be protective and increase cellular resistance against ischemia. SH between 140-220 mg/dl will keep cellular glucose uptake at the highest level without causing hyperosmolarity. In the current study, most of the patients with SH were patients diagnosed with LRTI; however, convulsions were observed in 4% of the patients. Many studies have reported that especially febrile convulsions are associated with SH. Unlike these findings, in the current study, the glucose level of patients diagnosed with convulsions was lower than those without a convulsion diagnosis. However, only patients with SH were included in the current study. This study's lower blood glucose level among febrile convulsion patients may be due to the immediate initiation of fluid treatment and making blood tests after the emergency intervention. Therefore, blood glucose levels may be lower.

Various pharmacological agents cause SH. Among them, the effect of corticosteroids on glucose metabolism is well known. Corticosteroids are preferred in many cases, such as asthma, rheumatological diseases, hematological diseases, and malignancies in pediatric patients. Corticosteroids cause hyperglycemia with insulin resistance, gluconeogenesis, and decreased insulin production [17,18]. In the study conducted by Donihi et al. in 2006, hyperglycemia was observed in a 1-month follow-up of 32 (64%) of 50 patients who took high-dose corticosteroids (over 40mg/day) for at least 2 days [19]. Although hyperglycemia is observed in all administration routes of corticosteroids (oral, intravenous, etc.), intravenous and high-dose administrations cause faster SH development [17]. In the current study, the blood glucose levels of patients treated with corticosteroids were higher, which supported this result. For the current study, it can be said that corticosteroids were frequently administered intravenously or orally to patients in the emergency department. Therefore, the blood glucose levels of the patients who took corticosteroid therapy in the emergency department may be higher.

Similar to corticosteroids, salbutamol is also known to be associated with hyperglycemia. β-2 agonists,

β-2 agonists, including salbutamol, are often preferred in asthma, cystic fibrosis, and chronic lung diseases. Activating β-2 receptors results in hyperglycemia with increased glycogenolysis and gluconeogenesis in the liver and muscles [20]. In the current study, patients most frequently received salbutamol treatment, and blood glucose levels were observed to be higher in these patients.

In the current study, insulin levels of 45 SH patients were measured in the controls. The median insulin level of these 45 patients was 10.7 μU/L. Since the patients in our study consisted of both pre-pubertal and pubertal children, it can be said that the median insulin level of 10.7 μU/L observed in this study is within the normal range.

It is known that disease severity affects admission to inpatient services [21]. In this study, the age of the patients admitted to the service was higher than non-hospitalized ones. However, approximately 42% of the patients admitted to the service were 1-23-month-old. In the current study, the diagnosis of LRTI was lower in patients admitted to the service than in non-admitted ones. The probable cause of this situation may be related to the comprehensive treatment of LRTI patients in the emergency department, or the severity of the disease is not high enough to require admission to the service. Similarly, the lower frequency of salbutamol treatment in patients admitted to the service supported that LRTI patients were primarily treated in emergency services.

Regarding the limitations of our study, the failure to obtain detailed anamnesis from the patients treated in the emergency department due to the lack of time caused us to be unable to conduct a more detailed analysis. Although 818 patients were included in the current study, only 45 patients had HbA1c levels in the controls, which masked the effect of SH on the development of diabetes. The limitations of our study are the retrospective design, the short follow-up periods of the patients, and not requesting HbA1c from every patient. Finally, more comprehensive data on SH could be obtained by comparing patients who applied to the emergency department but did not have SH with those diagnosed with SH.

Conclusion

As a result, it was thought that the impact of acute stress-induced SH in the development of diabetes in the future is low. We can help reduce families' anxiety levels by explaining to patients diagnosed with SH and their parents that this is likely to be a temporary condition associated with acute illness.

Author contribution statement

All authors (AAK, YY, ADB, UUI) participated in the planning, writing, editing, and review of this manuscript.

Conflicts of interest

None Declared.

Ethical approval

The necessary permission was obtained from Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee with the decision numbered 2012-KAEK-15/2524 on 24.05.2022.

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