

Frequency of Hyperglycemic Stress in Patients Referred to Emergency Department of Akbar Hospital in Mashhad Depending on the Type of Disease

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Abstract

Background: Hyperglycemic stress is a transient increase in blood glucose during an acute physiological stress in the absence of diabetes. In children, a blood glucose level of >150 mg/dl is considered as hyperglycemia. The purpose of this study was determining the frequency of hyperglycemic stress based on the underlying diseases in patients referred to the emergency department of a pediatric hospital in Mashhad-Iran.

Methods: This cross-sectional study enjoyed census sampling method. Participants of the study were 201 patients including 120 boys (59.7%) and 81 girls (40.3%) with mean age of 3.01 ± 3.03 years (age range: 2 months to 15 years). Both qualitative and quantitative data were collected and analyzed using descriptive statistics and SPSS software version 21. Chi-square test was used to compare the qualitative variables. For quantitative statistical analysis, normality of data was evaluated by Smirnov Kolmogorov tests. Afterwards, Pearson correlation test and independent T test were used for analyzing the quantitative data.

Results: Findings revealed that there is not any significant correlation between the type of disease and hyperglycemia, while temperature and dehydration are directly associated with hyperglycemia. Furthermore, no connection was found between convulsion and the risk of increased glucose level, but status seizure had an important role in hyperglycemia. In fact, the degree of hyperglycemia increased with worsening the disease.

Conclusion: The severity of disease, high body temperature and dehydration rate are important risk factors in the rate and severity of hyperglycemia.

Key Words: Children, Hyperglycemia, Stress.

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1- INTRODUCTION

Hyperglycemic stress is defined as a transient increase in blood glucose during an acute physiological stress in the absence of diathesis (1). It is actually a protective function and physiological adaptation, which results in the suppression of glucose uptake in the peripheral tissues by increasing glucose delivery to the brain during a period when cerebral blood flow is reduced due to the underlying disease (burns, trauma, and infections) and the resulting shock (2). These processes are mainly led by insulin-controlling hormones including glucagon, growth hormone, catecholamines, and glucocorticoids (3). These hormones and cytokines such as interleukin-2 and tumor necrosis factor (TNF α), which increase during stress, act both on the surface of the pancreatic islet cells and in the target tissues to provide the brain with greater access to glucose (4-6).

In children, blood glucose levels of >150 mg/dl are typically considered as hyperglycemia (7). Hyperglycemic stress in children has been reported frequently in cases such as fever and severe gastroenteritis (8, 9). It also occurs in certain clinical conditions such as trauma, burns, septicemia, and stroke in adults (10). Various studies have shown that hyperglycemia and insulin resistance have been observed in many serious diseases. Hyperglycemic stress has also been observed in patients with no previous history of hyperglycemia. Epidemiological data shows that hyperglycemic stress may not always be a transient clinical event, and patients who develop this condition during an acute clinical event may develop diabetes in the future; hence, follow-up of these patients is of particular importance (11). Since previous studies have reported contradictory results on the association between the varieties of diseases with this condition, determining the frequency of hyperglycemic stress in children and its

relation to the type of disease can be effective in improving the treatment process for physicians. Also, familiarity of physicians with this phenomenon can help avoiding the use of unnecessary and in some cases dangerous therapeutic approaches.

Positive family history of diabetes mellitus increases the risk of stress hyperglycemia in critically ill patients (12).

The risk of progression to type 1 diabetes is low in patients with stress hyperglycemia, however these subjects have an increased prevalence of insulin resistance and metabolic syndrome (13).

The aim of this study was, then, to determine the frequency of hyperglycemic stress in hospitalized children based on their type of disease.

2- MATERIALS AND METHODS

2-1. Patients' enrollment and inclusion criteria

This cross-sectional study was performed on all pediatric patients admitted to the Emergency department of Akbar Hospital from April to September 2019 and met the inclusion criteria. Due to the fact that hyperglycemic stress has a prevalence of 2 to 5%, the selection of 2.1 patients with hyperglycemic stress was considered in the study. The sampling method of the study was census.

Prior to implementation, the research plan was approved by the Ethics Committee of Mashhad University of Medical Sciences (Code:

IR.MUMS.MEDICAL.REC.1397.696), and then a written consent was obtained from the parents of the patients who participated in the study. General information of patients were also recorded and evaluated; they included previous history of diabetes, body temperature, complete blood tests, blood glucose level, HbA1c (blood samples were taken after at least 2 hours of fasting), dehydration status

investigated in three levels of dehydration criterion: mild (only feels thirsty), moderate (the child is restless, has no tears, tachycardia, the eyes are sunken, and very thirsty) and severe (Decreased level of consciousness, decreased urine volume, greatly sunken eyes, and increased skin turgor), and Other information including age, weight, vital signs (blood pressure, heart rate respiratory rate, and leukocytosis), specific illness history, family history of diabetes, duration of vomiting or diarrhea, and intravenous fluid injections. Vital signs of patients were evaluated according to systemic inflammatory response syndrome (SIRS) criteria.

2-2. Systemic inflammatory response syndrome (SIRS criteria):

An overstated defense response of the body to a noxious stressor (infection, trauma, surgery, acute inflammation, ischemia or reperfusion, or malignancy, to name a few) causes Systemic inflammatory response syndrome (SIRS). The criteria SIRS is defined by Body temperature over 38 or under 36 degrees Celsius, Heart rate greater than 90 beats/minute, Respiratory rate greater than 20 breaths/minute or partial pressure of CO₂ less than 32 mmHg, Leucocyte count greater than 12000 or less than 4000 /microliters or over 10% immature forms or bands (14).

2-3. Stress hyperglycemia

Stress hyperglycemia also called stress diabetes or diabetes of injury is common in critically ill patients and appears to be a marker of disease severity (15). Stress hyperglycemia is especially common in patients with hypertonic dehydration and those with elevated catecholamine levels (e.g., after emergency department treatment of acute asthma with epinephrine) (16).

In the present study, patients with any types of malignancy, history of diabetes,

isovaleric acidemia, and those taking adrenergic agents such as dopamine were excluded from the participants. Therefore, inclusion criteria for being enrolled in the study were as follows:

- a. Pediatric patients admitted to the emergency department because of acute illnesses
- b. Being in the age range of 2 months to 15 years
- c. Having no history of diabetes in patients and in her/his family
- d. Hospital stay longer than 24 hours
- e. Not taking certain medications, such as corticosteroids, adrenergic drugs and adrenalin
- f. Not consuming Sugar containing beverages during the last 24 hours

2-4. Treatment procedure

Treatment of patients enrolled in this study was performed based on the underlying disease, firstly by relieving the stress factors such as fever, convulsion and dehydration, and then by administration of normal saline (10 cc/kg) to lower the blood glucose. In the absence of response to the earlier therapies, regular insulin administration was initiated based on the blood glucose level. Blood glucose was monitored every hour to correct hyperglycemia until the stressor was resolved within the first 24 to 48 hours of patient admission, otherwise insulin administration continued until controlling the blood glucose level.

2-5. Statistical analysis

Data were analyzed using descriptive statistics and SPSS software version 21. Significance level was considered less than 0.05 in all experiments. Chi-square test was used to compare the qualitative variables.

For quantitative statistical analysis, normality of data was evaluated by

Smirnov Kolmogorov tests. Afterwards, Pearson correlation test and independent T test were used for quantitative data, respectively.

2-6. Ethical considerations

The study was approved by the Ethics Committee of Mashhad University of Medical Sciences (code: IR.MUMS.MEDICAL.REC.1397.696).

Written consent was obtained from the parents of the patients who participated in the study.

3- RESULTS

3-1. Demographic information

Of all 10042 hospitalized patients, 241 had hyperglycemic stress, among whom 15 patients were excluded due to malignancies such as brain tumors and leukemia, etc., and 8 due to receiving corticosterone and glucose-containing serum prior to admission. Moreover, 13 patients were excluded due to non-cooperation, leaving the hospital or death before 48 hours of admission and 4 patients due to isovaleric acidemia. Among patients hospitalized with hyperglycemic stress, children under two months were excluded from the study and only the age group of 2 months to 15 years were included. Thus, the study was performed on 201 patients, 120 (59.7%) of whom were boy and 81 (40.3%) were girls. The highest prevalence of patients with hyperglycemic stress was in the age group of one to two years, indicating that the prevalence of hyperglycemic stress-inducing diseases is higher at this age group (43.2%) among children.

Mean and median serum glucose levels in patients at the time of admission were 181.75 mg/dl, and 168 mg/dl with standard deviation of 31.48, respectively. According to their serum glucose levels, patients with hyperglycemic stress were classified into three categories of mild (150-159 mg/dl), moderate (160 to 199

mg/dl), and severe hyperglycemia (≥ 200 mg/dl). Patients with hyperglycemia included 57 mild cases (28.4%), 120 moderate cases (59.7%) and 24 severe hyperglycemia cases (11.9%).

3-2. Frequency of hyperglycemia based on the type of disease

Of the 201 patients with hyperglycemia admitted in the emergency department of Akbar Hospital, the most frequent disease was gastroenteritis with 63 patients (31.3%). After gastroenteritis, pneumonia was the second most commonly diagnosed disease with 54 (26.9%) hospitalized patients followed by febrile seizure with 33 (16.4%) patients. Due to the limitations of Akbar Hospital for referring patients with other diseases such as neurological, cardiovascular, trauma, and poisoning, these diseases were not possible to be evaluated in this study. No association was found between the types of diseases and the category of hyperglycemia ($p > 0.05$). Frequency of diseases and results of chi square tests are listed in **Table 1**.

3-3. Relationship between hyperglycemia and the measured variables

Evaluation of body temperature before and after admission showed that among the children with hyperglycemic stress, 186 patients (92.5%) did not have fever (body temperatures below 37.3 °C) after 48 hours, and only 15 cases (7.5%) had fever. Evaluation of relationship between body temperature and serum glucose in hospitalized patients showed that blood sugar levels increased with increasing body temperature (Pearson correlation, p value= 0.0002). In other word, blood glucose level decreases by controlling fever. Therefore, temperature is considered as an important risk factor in critically ill children with hyperglycemia. Also, in the study of patients 48 hours after hospitalization, dehydration was controlled in 90% of patients. The results showed that

with the management of dehydration, blood glucose levels were also decreased to less than 150 mg/dl in 92.5% of patients. The analysis showed that there was significant association between the rate of hyperglycemia and dehydration (p

value= 0.0001), indicating the importance of dehydration in hyperglycemia. Therefore, the rate of dehydration and the severity of the disease can affect the rate of hyperglycemia.

Table-1: Frequency of the diseases and their association with hyperglycemia.

No	Disease	Frequency No (%)	Significance (p value)
1	Gastroenteritis	63 (31.3 %)	0.981
2	Pneumonia	54 (26.9 %)	0.242
3	Febrile convulsion	33 (16.4%)	0.217
4	Asthma	9 (4.5 %)	0.616
5	Head trauma	6 (3 %)	0.413
6	Anaphylaxis	6 (3 %)	0.761
7	Appendicitis	18 (9 %)	0.284
8	Poisoning	3 (1.5 %)	0.451
9	Steven Johnson Syndrome	3 (1.5 %)	0.678
10	Invagination	6 (3 %)	0.481

In this study, 76 (37.8%) of patients had different types of seizures. These patients included 13 children (17.1%) with static seizures, 43 (56.5%) with short seizures and 20 (26.3%) with frequent seizures. Evaluation of the relationship between hyperglycemia and seizure in the hospitalized patients showed that seizure has no effect on hyperglycemia (p value: 0.43) and may not be a risk factor for it; however, statistical analysis showed that there is a significant relationship between hyperglycemia and status seizure. The longer the seizure, the higher the rate of hyperglycemia. In other words, longer duration of seizure may lead to severe hyperglycemia (p value = 0.0015).

The evaluation of systolic blood pressure showed that the majority of patients were critically ill which was significantly associated with hyperglycemia (p = 0.0001). The heart rate of hyperglycemic stress patients was directly related to hyperglycemic rate (p value = 0.05), respiratory rate (p = 0.001) and blood leukocyte levels (p < 0.05). All data were summarized in **Table 2**.

4- DISCUSSION

Hyperglycemic stress has been frequently reported in children with febrile diseases and severe gastroenteritis. Previous research Findings have shown that patients who develop hyperglycemic stress during an acute clinical condition may develop diabetes in the future. Therefore, follow-up of these patients and elucidating the association between the underlying disease and hyperglycemic stress, especially in pediatric patients is of particular importance. Mohammadzede et al. in 2003 reported that the prevalence of hyperglycemic stress in pediatric emergencies was 3.2%, indicating that the disease is rare among children with acute illness. This finding was in close agreement with our results. In their study, hyperglycemia was more prevalent among patients with asphyxia, infection and cerebral hemorrhage (17). On the other hand, the prevalence of hyperglycemic stress in the study of Mousavi and colleagues was 14% among neonates admitted to the neonatal intensive care unit (18). Another descriptive cross-sectional

study in 1998 on 291 patients showed that the relative frequency of hyperglycemic stress was 25.42%. In that study, any clinical intervention including surgery was considered as stress (19). In a study by Weiss et al, on 55120 patients referred to a pediatric emergency department, 72 patients had glucose levels above 300 mg/dl that were classified as severe

hyperglycemic stress. The prevalence of hyperglycemic stress was 0.13%, and the most prevalent diseases in their study were respiratory disease, gastroenteritis, and seizures, respectively (20). In the present study, the most frequent diseases among children with hyperglycemic stress were gastroenteritis, followed by pneumonia and febrile seizure, respectively.

Table-2: Relationship between vital signs and SIRS criteria with hyperglycemia.

SIRS criteria		Frequency No (%)	P value *
Blood leukocyte levels	Leukocytosis	147(73.1%)	0.014
	Leukopenia	8(4%)	
	Normal	46(22.9%)	
Heart rate	Tachycardia	169(84.01%)	0.05
	Normal	39(15.0%)	
	Bradycardia	0(0)	
Respiratory rate	Tachypnea	146(72.6%)	0.0001
	Bradypnea	4(2%)	
	Normal	51(25.4%)	
Systolic blood pressure	Hypotension	147(73.1%)	0.001
	Normal	54(26.9%)	
	Hypertension	0(0)	

* Chi square test

In the same line, the results of a study on 170 pediatric patients admitted to NICU had revealed that blood glucose levels above 180 mg/dl had a significant correlation with mortality and length of ICU stay (21). In our study, hyperglycemic stress was more common in patients with ICU conditions.

Moreover, consistent with other findings, no significant correlation was found between any types of diseases with hyperglycemic stress, indicating that the type of disease had no effect on hyperglycemia, but the severity of clinical conditions, such as fever and dehydration, could increase blood glucose levels (7, 22). On the contrary, Hashemipour reported that there is no association between the stress and blood sugar levels, but the type of illness can be effective (19). In addition,

consistent with other findings, we found that, regardless of the type of disease that causes dehydration, fever (≥ 38.5 °C), and/or seizure, these clinical conditions could be indicative of the severity of disease in patients, which was significantly correlated with the rate of hyperglycemia (7, 22). But, we found that long-term or static seizures positively correlated with the rate of hyperglycemia. In a study by Lee et al. on the prevalence of hyperglycemic stress in children with febrile seizure, a 10% prevalence of hyperglycemic stress was reported; and it was shown that hyperglycemic stress not only was associated with febrile convulsion, but also this relationship was more prominent in long-term seizures (23). Besides, in agreement with other reports (7, 22), it was found in this study that the

risk of hyperglycemic stress increases with worsening the patient's clinical condition, indicated by symptoms such as high body temperature, or severe dehydration. This study has some limitations, including the restrictions of Akbar Hospital in admission of patients with some types of diseases such as neurology, intoxication, cardiology, and hematology, which definitely influenced the reported frequency of diseases and their association with hyperglycemic stress. Due to the existence of contradictory results in different studies, it is suggested to evaluate the association of different diseases and the risk of hyperglycemic stress, particularly in pediatric patients in a large population-based study.

Another limitation in our study was the absence of control group, though it would not be possible to more validly determine the correlation between hyperglycemia and the types of diseases in an experimental design.

5- CONCLUSION

Although the type of disease may not affect hyperglycemia, unstable vital signs and severity of disease can have an influential effect on it.

6- CONFLICT OF INTEREST: None.

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9- CONTRIBUTIONS

A.S. carried out the data collection and drafted the manuscript. A.Kh. & N.G. undertook the literature searches. All authors conceived the study idea, participated in its design, and performed

the statistical analyses. All authors have read and approved the final version to be published.

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