Endocrine (2012) 42:653–657
DOI 10.1007/s12020-012-9707-y

ORIGINAL ARTICLE

Thyroid function and stress hormones in children with stress hyperglycemia

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Received: 12 March 2012 / Accepted: 15 May 2012 / Published online: 2 June 2012

Abstract The purpose of the study is to determine the prevalence of stress hyperglycemia and to investigate how thyroid and stress hormones alter during stress hyperglycemia in children admitted to pediatric emergency wards. A prospective cross-sectional study was conducted in children, less than 19 years old, who were admitted to pediatric emergency wards of Nemazee and Dastgheib Hospitals, Shiraz, Southern Iran. Those patients taking steroids, beta-agonists or intravenously administered glucose before venipuncture, and patients with diabetes mellitus (DM) or thyroid diseases were excluded. Children with blood glucose ≥150 mg/dL during admission were regarded as cases. The controls were age- and- sex- matched, euglycemic children. Stress hormones including cortisol, insulin, growth hormone, and prolactin were measured, and thyroid function was tested with a radioimmunoassay (RIA) method in all cases and controls. The resuts showed that among 1,054 screened children, 39 cases (3.7 %) had stress hyperglycemia and 89 controls were included in the study. The occurrence of hyperglycemia was independent of sex, but it occurred mostly in children under 6 years old. Hyperglycemia occurred more frequently in patients with a positive family history of DM (odds ratio = 3.2, 95 % CI = 1.3–7.9, and P = 0.009). There were no significant differences between cases and controls regarding any hormones except higher cortisol, and lower total T3 and T4 in cases compared with controls. Neither of cases developed diabetes in the 24-month follow-up period. These findings led us to the conclusion that stress hyperglycemia is occasionally seen in critically ill patients. Among the stress hormones measured, only cortisol increased during hyperglycemia. It seems that hyperglycemia is not an important risk factor for future diabetes.

Keywords Diabetes · Hyperglycemia · Stress hormones · Thyroid function

Abbreviations

BG	Blood glucose
CI	Confidence interval
DM	Diabetes mellitus
FT3	Free T3
FT4	Free T4
GH	Growth hormone
NTIS	Non thyroidal illness syndrome
OGT	Oral glucose tolerance test
RIA	Radioimmunoassay
SES	Sick euthyroid syndrome
SPSS	Statistical package for the social sciences
TRH	Thyrotropin-releasing hormone
TSH	Thyroid stimulating hormone

Introduction

Stress hyperglycemia is defined as a transient increase in blood glucose (BG) concentration during acute physiologic stress, such as trauma, acute stroke, acute myocardial infarction, burns, and surgical procedures [1–4]. It has been

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documented in children admitted with acute gastroenteritis, severe dehydration, and febrile seizure, with an incidence rate ranging from 3 to 9 % in different studies [1, 5–8]. The stress response in humans commonly involves elevations in the plasma concentration of glucocorticoids, catecholamines, glucagon, and growth hormone, an effect probably responsible for hyperglycemia and hypercatabolism in critically ill patients [9, 10]. Thyroid hormone metabolism is commonly affected by critical illness which results in characteristic abnormalities of thyroid function tests known as sick euthyroid syndrome (SES) [11, 12].

The aims of this study were (1) to determine the true prevalence of stress hyperglycemia in children admitted to emergency wards, and (2) to ascertain how thyroid function tests and stress hormones change during stress hyperglycemia.

Materials and methods

A prospective cross-sectional study was carried out at the pediatric emergency departments of Nemazee and Dastgheib Hospitals in Shiraz, Southern Iran. All children under 19 years old, who needed admission to the emergency departments from February 2008 through January 2010 were included.

We excluded children who were taking steroids, beta-agonists, or intravenously administered glucose before their venipuncture, and those with a history of diabetes mellitus (DM), thyroid disease or any other endocrine problems. Finally, 1,054 children were screened. Institutional ethical review board's approval was obtained. Informed written consent was also obtained from all participants to take part in the study. For all participants, we recorded data on age, gender, weight, family history of DM, and discharge diagnosis. Initial BG was measured with an Accucheck reflectance meter.

As the definition of hyperglycemia was somehow controversial, and many authors recommend the BG target of less than 150 mg/dL in their critically ill patients, we decided to define stress hyperglycemia as BG concentration equal to or greater than 150 mg/dL (8.3 mmol/L) based on the results of recent studies [1, 5, 13, 14]. Depending on admission BG levels, patients were classified as euglycemic (BG <150 mg/dL) or hyperglycemic (BG ≥150 mg/dL). Among patients who were evaluated, 39 patients were found to have hyperglycemia (the case group) and from the remained euglycemic patients, 89 sex- and age-matched children were randomly selected as the control group. We measured serum levels of stress hormones including cortisol, prolactin, insulin, growth hormone (GH) and also thyroid hormones (T3, T4, FT3, FT4, and TSH) with a radioimmunoassay (RIA) method (Immunotech kit, Czech Republic), in all patients with hyperglycemia and their control counterparts. We used Kolmogorov–Smirnov test to determine which variable was distributed normally. In order to compare continuous variables in different BG groups, we used an independent *t* test for normally distributed data. Otherwise, we used the Mann–Whitney test. In order to analyze the relationships between categorical variables, we used the Chi-squared test. A P value <0.05 was considered to be statistically significant. The statistical analysis was done with SPSS software version 15.0 for windows.

Results

The prevalence of hyperglycemia in children who were admitted in the emergency departments was determined as 3.7 % (39 out of 1,054 patients). The age range of the population was 1 month–18 years with a median of 18 months and interquartile range of 53 months. Mean age was 25.95 ± 24.93 months in the patient group and 41.02 ± 51.15 months in the control group ($P = 0.817$). The male/female ratio was 25:14 among patients and 44:45 among controls ($P = 0.126$). The discharge diagnoses in decreasing order of frequency were acute gastroenteritis, seizure disorders and febrile convulsions, pneumonia and hyperreactive airway disease, sepsis, poisoning, urinary tract infection, and others.

The incidence of hyperglycemia in various age groups differed significantly ($P = 0.014$) (Table 1). A positive family history of DM in the first- and the second-degree relatives of children with hyperglycemia was significantly higher compared to normoglycemic individuals ($P = 0.009$), with an odds ratio of 3.2 (95 % CI = 1.3–7.9).

The mean cortisol level was significantly higher in the hyperglycemic group compared to the controls ($P = 0.035$) (Table 2). Total T3 and T4 were significantly lower in children with stress hyperglycemia in comparison to euglycemic individuals ($P = 0.048$ and $P = 0.009$, respectively); (Table 2). However, TSH, FT3, and FT4 levels did not differ significantly between the two groups (Table 2). Similarly, there were no significant differences between the cases and controls regarding other stress hormones (Table 2).

Finally, we rechecked fasting blood glucose from the patients whose admission blood glucose was 150 mg/dL or higher due to stress hyperglycemia before discharge. All of them were euglycemic, and their fasting blood glucose were less than 120 mg/dL. In order to define if stress hyperglycemia is a risk factor for future diabetes, we followed these patients for a mean period of 20 months (range 15–24 months). The 39 patients with admission hyperglycemia were called back individually and their fasting blood glucose were checked with 6-month intervals. None of the

Table 1 Distribution of hyperglycemia among different age groups

Age (month)	Blood glucose <150 mg/dL N (%)	Blood glucose ≥150 mg/dL N (%)
1–12	41 (71.9)	16 (28.1)
13–72	31 (58.5)	22 (41.5)
73+	17 (94.5)	1 (5.5)

P value = 0.014

Chi-square = 8.478

Table 2 Comparison of thyroid and stress hormones in hyperglycemic and euglycemic children

	BG (mg/dL)	Mean ± SD	Median	*P* value
Cortisol (μg/dL)	<150	50.18 ± 27.13	51.70	0.035*
5–25	≥150	61.72 ± 30.43	65.10	
Insulin (mu/L)	<150	20.38 ± 51.08	6.55	0.546**
Children: up to 30	≥150	12.18 ± 15.75	5.60	
GH (ng/mL)	<150	9.38 ± 9.43	6.55	0.68**
Children: up to 12.5	≥150	9.61 ± 11.5	4.75	
Prolactin (ng/mL)	<150	888.43 ± 1262.18	311.25	0.811**
M: up to 448	≥150	723.11 ± 1042.12	283.95	
F: up to 700				
T3 (ng/dl)	<150	170.06 ± 71.08	162.00	0.018*
80–220	≥150	144.23 ± 57.61	131.00	
T4 (μg/dl)	<150	9.79 ± 2.77	9.40	0.009*
4.5–12.5	≥150	8.41 ± 2.61	8.70	
FT3 (Pg/ml)	<150	3.26 ± 1.00	3.30	0.467*
2.5–5.5	≥150	2.81 ± 1.58	2.90	
FT4 (ng/dl)	<150	15.25 ± 3.18	14.50	0.353*
10.5–23	≥150	13.26 ± 6.51	14.20	
TSH (μu/ml)	<150	2.37 ± 3.61	1.42	0.85*
0.3–5.2	≥150	2.52 ± 4.9	1.13	

Normal range of each hormone level is written in the related cell in the first column

SD standard deviation, *BG* blood glucose, *GH* growth hormone, *FT3* free T3, *FT4* free T4, *TSH* thyroid stimulating hormone

* Independent *t* test

** Mann–Whitney test

patients with stress hyperglycemia developed DM during the follow-up period.

Discussion

Critical illness triggers an acute phase response which is associated with several metabolic derangements including hyperglycemia. This has been attributed to peripheral and hepatic insulin resistance, excess dextrose administration via total parenteral nutrition, beta-cell dysfunction, glycogenolysis, increased hepatic gluconeogenesis due to cortisol, glucagon, and catecholamine release, and production of inflammatory mediators and cytokines [15–18]. Moreover, in the setting of acute stress without systemic inflammatory response such as healthy bungee jumpers, increased BG and stress hormones as well as insulin resistance were reported [19]. Although hyperglycemia was previously considered as an adaptive mechanism that would be beneficial by ensuring an adequate supply of fuel to stressed organs, more recent studies have suggested that this state of insulin resistance and hyperglycemia which is called stress diabetes is linked to increased mortality and morbidity, such as oxidative injury, abnormal vascular reactivity and clotting, and impaired immune response in critically ill patients [16–26].

We found here a prevalence of transient stress hyperglycemia of 3.7 %, a figure similar to the previous studies [1, 6–8]. The incidence could be as high as 25–60 % in critically ill patients admitted to intensive care units [21, 27]. But, our prevalence is much lower compared to other earlier studies such as the one by Karamifar et al. [28], who reported a prevalence of 12.7 %. The difference maybe explained in part by the differences in inclusion and exclusion criteria, the definition of stress hyperglycemia, and severity of the illness. We found that sex had no influence on the incidence of hyperglycemia. However, in contrast to most studies done before [1, 6], age was a risk factor, with most cases of hyperglycemia occurring in our 1–6 year old group followed by the 1–12 month old group, and only 2.6 % of cases were older than 6 years (Table 1). This is similar to what Karamifar et al. [28] noted in their research.

The hypothesis that stress hyperglycemia is a warning sign for future DM remains controversial. Although most researchers disagree with this hypothesis [1, 5, 6, 20, 29, 30], some believe that those who develop high BG in the hospital may have an inherent abnormality in glucose regulation that manifests with the stress of severe illness [4, 31]. As it is generally accepted, nondiabetic patients can compensate insulin resistance by increasing insulin secretion, it seems logical that stress hyperglycemia requires some degree of pancreatic β-cell dysfunction which could result in type I diabetes if specific immunologic and genetic markers, such as islet cell antibodies, insulin autoantibodies, and glutamic acid decarboxylase antibodies are present [15, 19, 32]. Although none of our hyperglycemic patients had high BG when discharged or during the 24-month follow-up period, it seems that longer follow-ups with oral glucose tolerance tests (OGT) and screening for the above-mentioned autoantibodies should be suggested especially for persons with a positive family history of DM.

Actually, a similar debate exists among different investigators regarding the correlation between glucose and mediators of stress. Vankooten et al. [33] found no association between glucose and catecholamine levels in stroke patients. Similarly, Heath analyzed patients with traumatic injury and found no correlation between glucose and cortisol or catecholamines [34]. In another study by Sam and colleagues [35], there was no correlation between mean glucose and cortisol level in severely septic individuals. In an animal study, there was no significant correlation between changes in mean glucose concentrations and changes in mean insulin, glucagon, cortisol, or epinephrine concentrations in struggling cats with elevated glucose and lactate levels [36]. However, some studies noted a significant correlation between stress hyperglycemia and increased concentration of stress hormones including beta-endorphin, cortisol, glucagon, growth hormone, prolactin, and insulin [4, 7, 9, 19].

In our study, only mean cortisol level was significantly higher in stressed hyperglycemic patients compared to euglycemic individuals, and serum concentrations of insulin, growth hormone, and prolactin did not differ significantly between the two groups. Another finding of our study was the low T3 and T4 levels in stressed hyperglycemic individuals despite normal TSH, FT3, and FT4 levels. These thyroid hormone abnormalities in critically ill patients could be a manifestation of decreased thyroid binding proteins, suppressed thyroidal secretion, reduced peripheral activation, increased inactivation by tissue deiodinases, as well as suppressed thyrotropin-releasing hormone (TRH) which is referred to as SES or non-thyroidal illness syndrome (NTIS) [37–40].

Although in severe illness, T3 and T4 decrease without evidence of clinical hypothyroidism, the effects of low T3 syndrome at the tissue level are similar to those seen in true hypothyroidism. It is believed that these effects which lead to conservation of energy and decreased protein breakdown, are actually a beneficial adaptive mechanism in stressful situations, in which the patient is endangered [41]. In contrast, mortality and morbidity of the critically ill patients depend on the severity and duration of the underlying NTIS [42]. The therapeutic role of exogenous thyroid hormones in the management of SES is still debated, and it should be generally avoided [41, 42].

On the other hand, some investigators reported higher frequencies of subclinical hyperthyroidism in patients with type 2 diabetes and concluded that the increase in thyroid hormone levels may correlate with insulin resistance [43, 44]. Moreover, T3 has been reported to mediate glucose transport in bone cells [45]. If the hormonal changes observed in NTIS are associated with the pathogenetic mechanisms involved in the stress hyperglycemia needs further elucidation.

It is not clear if these metabolic and hormonal changes are an appropriate response to stress or represent decompensation of the body's mechanisms for coping with stress. Although it was previously advised to intensify insulin therapy to control glycemia tightly (4.4–6.1 mmol/L), as suggested by the Leuven trial [46], the large multicenter NICE-SUGAR (The Normoglycemia In Intensive Care Evaluation- Survival Using Glucose Algorithm Regulation) study [47] showed high mortality and more episodes of hypoglycemia with tight glycemic control. Therefore, it seems logical to monitor the BG in patients admitted to emergency wards and keep their glycemia in the range of 8–10 mmol/L.

In conclusion, we detected hyperglycemia in about 4 % of our patients admitted to emergency wards. It was associated with some derangements in the levels of cortisol and thyroid hormones. Close follow-up of these patients, particularly those with a positive family history of DM, is advised.

Acknowledgments The authors would like to express their special thanks to Dr. H. Tabesh for carrying out the statistical analysis, Mrs. M. Farahmandi for typing the manuscript, and K. Shashok (Author AID in the Eastern Mediterranean) and Sh. Parand of the Hematology Research Center, for English editing the manuscript. This manuscript is relevant to the thesis of Reza Taj-aldini with project number 86-3714.

Conflict of interest None of the authors has financial disclosures or any conflict of interest to be declared.

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