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Original Article

Association of Pediatric Stress Hyperglycemia with Insulin Metabolism Disorders

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Abstract

Introduction:
Transient hyperglycemia is a condition that happens during acute physiologic stress in children. The aim of this study is to determine if there is any relation between stress hyperglycemia and diabetes mellitus and metabolic syndrome in pediatric patients.

Materials and Methods:
The study was performed on children hospitalized in Amirkola pediatric hospital, North of Iran, between February 2011 to January 2013. Children with a history of stress hyperglycemia were studied for the presence of metabolic syndrome or Anti GAD65 Autoantibodies. A total of 50 patients were studied.

***Results*:**
None of our patients had developed type 1 diabetes. OGTT was normal in all patients. Metabolic syndrome was present in 2 cases (4%). The prevalence of insulin resistance was 16%. The most common metabolic abnormality noted was hypertriglyciredemia and one patient was positive for GAD 65 autoantibody. *Conclusion*: According to our data children with stress hyperglycemia do not appear to be at increased risk of developing type 1 diabetes but insulin resistance is relatively common in these patients.

Key words:
Diabetes mellitus, Hyperglycemia, Insulin resistance, Metabolic Syndrome X.

Introduction

Stress hyperglycemia is defined as transient increase in blood glucose level (more than 200 mg/dl) during an acute physiologic stress (1-3). In pediatric population, stress hyperglycemia develops in circumstances such as fever, seizures, gastroenteritis and dehydration. Its relative incidence is between 0.46 - 51.9% (3-5). Stress hyperglycemia is not always a transient clinical phenomenon. It sometimes may indicate a reduced insulin secretion capacity or a reduced sensitivity and is sometimes the first clue to incipient diabetes (6-8). With the availability of sensitive assays for measuring auto antibodies such as islet cell antibodies (ICA), insulin auto antibodies (IAAs), anti

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GAD65antibodies and anti tyrosine phosphatase like protein auto antibodies (IA -2As), it is now possible to predict the disease in first -degree relatives of type 1 diabetic patients (9). Among children who are not first degree relatives of patients with type 1 diabetes, presence of these immunologic markers puts them at increased risk for the development of type 1 diabetes (7). Anti GAD65 is one of the best screening tests of type 1 diabetes (10,11).

Metabolic syndrome is a combination of medical disorders that increases the risk of developing cardiovascular disease and diabetes (12). The real pathogenesis of this syndrome is not yet fully understood but the most important risk factors for this syndrome are: genetic predisposition, overweight, aging, life style and insulin resistance (13).

In this study we tried to determine the presence of type 1 diabetes, insulin resistance, and metabolic syndrome and GAD65 auto antibodies in patients with a history of stress hyperglycemia, identified retrospectively.

Materials and Methods

This study was performed on children hospitalized in Amirkola pediatric hospital, North of Iran between February2011-January 2013. The study was approved by the medical ethics committee of Babol University of Medical sciences prior to performance.

Blood glucose greater than 200 mg/dl was considered as hyperglycemia. Exclusion criteria were as follows:

1. Patients with diabetes.
2. Patients receiving β agonist drugs or those who had received glucocorticoids or dextrose solution on admission.
3. Chronic renal or hepatic disease.
4. Cystic fibrosis.
5. Patients with protein energy malnutrition.

A total of 78 patients met our criteria and 50 subjects signed informed consent and enrolled in the trial.

Patient's heights and weights were measured and recorded with standard scales. Scales were controlled prior to study. BMI was calculated and compared with NCHS (National Center for Health Statistics) growth charts.

Right arm blood pressure measurements were obtained using ALPK2 sphygmo-manometers and were compared with standard tables.

Fasting blood sugar, triglyceride and cholesterol levels were measured after 12 hours of fasting and insulin level was also measured with enzyme linked immuno-sorbent assay (ELISA) method.

2 ml of patient's serum was freezed in-21^0c and sent to Mashhad for evaluating GAD 65 antibodies.

OGTT was performed using a single dose of 1.75 gram/kg of glucose and blood glucose was determined 2 hours after glucose administration.

Insulin resistance was determined with the use of HOMA_IR index:

HOMA _IR = FBS (nmol/l) ×ins/22.5 or FBS (mg/dl) × ins/404

Good sensitivity = HOMA-IR<3

Anti GAD 65 antibodies were measured by Elisa assay. The threshold for positivity was >= 5 IU/ml. This test gives a 92.3% sensitivity and 98.6% specificity (14).

Metabolic syndrome was defined as presence of 3 of the followings:

1. BMI > 2SDS
2. TG > 2 SDS
3. HDL < 2 SDS
4. blood pressure > 2SDS
5. FBS > 100

SDS = Standard Deviation Score

According to American Diabetes Association guidelines, diabetes was defined as FBS>126 mg/dl or BS > 200 mg /dl after 2 hours in glucose tolerance test. FBS 100-125 and BS 2 hour after OGTT 140 -199 were considered as pre diabetes state.

Statistical analysis was carried out using Spss 16 statistical package. The student's t test and chi square test were performed on quantitative and qualitative variables.

Results

A total of 50 patients were evaluated in this study. 27 (54%) were boys and 23 (46%) were girls. Mean age of patients was 9.812 ± 1.452 years (Table1).

None of our patients had developed type 1diabetes. One patient was in pre diabetic category and had impaired glucose tolerance test. 8 patients (16 %) had impaired HOMA -IR.

2 of our patients (4%) had 3 or more criteria of metabolic syndrome (Table 2).

Table 1: Clinical characteristics

	mean±SD
Age (years)	9.81 ± 1.45
Weight (Kg)	29.3 ± 11.4
Height (m)	1.35 ± 0.15
Body-mass index	21.7 ± 3.7
Systolic pressure (mmHg)	104.1 ± 12.5

Table 2: Metabolic profile and metabolic syndrome criteria.

	N(%)
Impairment of glucose tolerance	1 (2)
BMI > 95th percentile	4 (8)
Systolic blood Pressure > 95th Percentile	2(4)
HDL < 5th percentile	4 (8)
Triglycerides > 95th percentile	8 (16)
Insulin resistance (HOMA)	8 (16)

High triglyceride, systolic blood pressure, diastolic blood pressure and BMI were seen in 16%, 4%, 2% and 8% of our patients respectively.

Low HDL levels were reported in 8% of patients.

One patient (2%) was positive for GAD65 antibody.

Discussion

Because stress hyperglycemia is not always a transient clinical phenomenon and may be an indicator of glucose intolerance or propensity to future diabetes development (6-8), we decided to perform a series of tests on pediatric patients with a history of stress hyperglycemia to evaluate the possibility of diabetes development, glucose intolerance and insulin resistance. And because insulin resistance is known as the main pathophysiology of metabolic syndrome (7), we also evaluated the prevalence of this syndrome.

The prevalence of diabetes type 1 in patients with stress hyperglycemia is reported between 0-30% in previous studies (4,7). Type 1 diabetes is one of the most serious and prevalent chronic diseases of children, so screening of individuals at risk for this condition is undeniably significant to public health. None of our patients had developed diabetes and did not meet the ADA criteria for diabetes and only one (2%) was positive for anti GAD65.

In a study by Razavi on patients with stress hyperglycemia none had developed diabetes after one year follow up (15). Another study by Valerio on 41 patients with stress hyperglycemia did not show development of diabetes after 3.5 years follow up and they concluded that hyperglycemia is probably due to non adapted insulin response and this is not a prediabetic condition (4). In a study by Saz Eu, patient's glucose tolerance tests were normal on follow up and they did not show any signs of diabetes and they all had normal immunologic markers (16). In another study by Bhisitkul, on patients with stress hyperglycemia none had positive anti GAD65 antibody (17). In our study one patient's (2%) FBS was in prediabetic range but all our patients had normal OGTT. In a study by Gered fasting plasma glucose after burn was significantly elevated but returned to normal after 6 months and glucose tolerance test was also normal after 9 months (18).

It seems that stress hyperglycemia is a hyperglycemic response due to changes in carbohydrate metabolism but this is not a persistent phenomenon.

We used HOMA-IR index to evaluate for insulin resistance. 8 of our patients (16%) had HOMA-IR more than 3.

In a study by Margoth on obese children, using HOMA-IR index, prevalence of insulin resistance was 39.4% (19). In another study by Hsiao 16% of patients had elevated HOMA_IR and he concluded that children with BMI>85thpercentile have elevated HOMA_IR and increased serum insulin levels (20). Our study's result on insulin resistance prevalence is lower than Margoth's which seems to be due to their study on obese children.

In Gred's study children with burns had elevated HOMA_IR and this remained elevated after 3 years of follow up (18). It seems that insulin resistance unlike blood glucose remains elevated for longer periods.

Insulin resistance is closely related to metabolic syndrome and we evaluated the frequency of this syndrome in our study. 2(4%) of our patients had 3 or more of this syndrome's criteria.

In a study by Azizi on children 3-9 years old, the overall prevalence of this syndrome was 0.9% and he reported that its prevalence is higher among obese children (21). The higher incidence of metabolic syndrome in our study may be because we performed the study on patients with stress hyperglycemia that 16% of them had insulin resistance which a plays a role in metabolic syndrome and also Azizi's study had a greater sample size.

In another study by Cruz prevalence of metabolic syndrome was reported to be 3-4% (22) which is similar to our results. Chaoyang Li states in his study that prevalence of metabolic syndrome differs according to country, ethnicity and sex and is especially high in north and South America (23).

The most prevalent component of metabolic syndrome in our study was dyslipidemia. 12 patients (24%) had dyslipidemia. 8 (16%) of them had hypertriglyceridemia (>2SDS) and 4 (8%) had low HDL levels (<2SDS). Dyslipidemia was the most prevalent component of metabolic syndrome in Margoth's study too (19). Azizi reported the prevalence of hypertriglyceridemia as 14.4% in his study (21).

Prevalence of obesity was 8% in our study which is similar to previous studies in Iran (24,25).

The results of this study might have been influenced with its relatively small sample size. Studies with larger patient population using other auto antibodies may be needed.

Conclusion

The risk of progression to type 1 diabetes is low in patients with stress hyperiglycemia but these subjects have an increased prevalence of insulin resistance and metabolic syndrome according to our findings. So, education on a healthy life style seems important for this population.

One of our patients was positive for antiGAD 65 antibody and there is the possibility of developing type 1 diabetes in this patient. We can't prevent its development however, but with more serious follow up and early diagnosis, complications of diabetes can be reduced. His/her first degree relatives should also be screened for this antibody.

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Conflict of interest: None Declared

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