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Impact of Thiamine Deficiency on Diabetic Ketoacidosis in Egyptian Type 1 Diabetic Children

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ABSTRACT

Objectives: To assess the level of thiamine among diabetic children presented with DKA, and its correlation with the degree of acidosis and encephalopathy.

Methods: A cross-sectional study was done at the Suez Canal University hospital, Ismailia, Egypt. A convenient sample of 40 diabetic children aged below 18 years, and presented with DKA were submitted to full history taking, examination and laboratory investigations including the thiamine level prior to fluids and Insulin administration.

Results: The studied children had their diabetes of 1.85 ± 2.6 years duration, and their HbA1C mean was 9.96 ± 2.27% while receiving 1.08 ± 0.27 IU/kg of insulin. DKA triggers were medication non-adherence, and infection ((32.5% &17.5% respectively), while newly diagnosed diabetes was the cause in 50% of new cases. 42.5% had encephalopathy while more than 50% had moderate to severe acidosis (37.5% and 20 % respectively) at the time of presentation. The mean thiamine level of the studied group was 47.37±28.52 ng/ml; among them 45% were found to have absolute thiamine deficiency with levels less than 40 ng/ml PH and HCO3 level had statistically significant strong positive correlation with level of thiamine (r=0.96, p>0.01) and (r=0.92, p>0.01) respectively. While Glasgow Coma Scale had positive but moderate significant correlation with level of thiamine (r=0.57, p>0.01). Thiamine level was the most significant best-fitting predictor of level of acidosis in stepwise backward regression analysis model among DKA patients (t=9.94, p>0.01).

Conclusions: Thiamine deficiency is not uncommon finding among children with diabetic ketoacidosis. It can be predicted by the severity of acidosis and to a lesser extend the degree of encephalopathy. Thiamine can be introduced as a line in the management of the DKA.

KEYWORDS

Thiamine, Vit B1, Diabetic ketoacidosis (DKA), T1D, Encephalopathy

INTRODUCTION

DKA is one of the acute complications of T1D, it is a complex disordered metabolic state characterized by hyperglycemia, ketoacidosis, and ketonuria [1]. Patients with DKA had a high prevalence of thiamine deficiency where thiamine levels are inversely related to lactate levels [2].

Thiamine (vitamin B1) is a water soluble vitamin. It has an important role in carbohydrates and fat metabolism [3]. Since very little thiamine is actually stored in the body, depletion can take place in 14 days to one month [4]. Thiamine deficiency leads to a marked impairment in insulin synthesis and secretion [5]. In diabetic children, acute thiamine deficiency can be manifested by Diabetic Ketoacidosis (DKA), lactic acidosis and hyperglycemia [6]. Thiamine deficiency has been documented in adults with diabetes and has been clearly linked with acute encephalopathy; unfortunately there is a little data about thiamine status in children with DKA, in whom one of the most serious complications is cerebral edema of which the primary symptom may be encephalopathy [7].

SUBJECTS & METHODS

A descriptive cross sectional study, including 40 children admitted with DKA during the period from May / 2016 to April / 2017.

Any child with T1D presented with DKA, aged 2-12 years old was enrolled. Children with vitamin B supplementation or vitamin B deficiency, children with chronic diseases, and children receiving insulin immediately before sampling were excluded. Hemolyzed samples were excluded.

Measurements

Full history was taken for each child. Clinical examination including height, weight, body mass index (according to the Egyptian growth curves [8] were obtained. Neurological examination was done including assessment of level of consciousness by GCS. GSC is a clinical scoring system for the rapid evaluation of encephalopathy in children. General and local examinations were performed.

Laboratory parameters included: Random blood sugar, Arterial blood gases, Serum creatinine, Sodium and Potassium. Complete blood count, Urinary Ketones, Glycated haemoglobin (HbA1c) [9] and Lipid profile [10]. Thiamine level was measured by Human Vitamin B1 (VB1) ELISA kit, for determination of the level of VB1 in undiluted original human serum. The normal thiamine level is 40-80 ng/dl.

The procedures were approved by the Ethics Committee of Human Experimentation in Suez Canal University Hospital, in accordance with the Declaration of Helsinki.

Data Analysis

Statistical analysis was performed according to standard methods using Statistical Package of Social Science (SPSS) version 18.

The data was presented as numbers and percentages for the qualitative data, mean, standard deviations and ranges for the quantitative data with parametric distribution. Chi-square test was used in the comparison between two groups with qualitative data and Fisher exact test was used when the expected count in any cell found less than 5.

Independent t-test was used in the comparison between two groups with quantitative data and parametric distribution and Mann. Whitney test was used in the comparison between two groups with quantitative data and non-parametric distribution.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant if <0.05.

RESULTS

This study was performed on 40 children with T1D presenting with DKA to the Pediatric intensive Care unit, Suez Canal University hospital, Ismailia, Egypt.

The mean age of patients was 8.6 ± 3.4 years, the majority of them were females 72.5%. Residence was urban in 57.5% of them and there was a positive family history of DM in 37.5 % of them. The mean BMI (Z score) of patients was 0.4 ± 1.45 and it ranges from (-3 to +3). The study showed that 52% of our patients were diagnosed as diabetics for the first time. Children with diabetes had mean disease duration 2.6 ± 1.85 years with mean dose of insulin 1.08 IU/kg ranging from 0.7 - 2.0 IU/kg. The mean HbA1C level in those patients was 10 ± 2.3% ranging from 7.5 to 15.9%. A trigger for diabetic ketoacidosis was not identified among 5% of T1D patients presented with DKA. In connection with the rest of examination, assessment of level of consciousness by GCS score revealed that mean GCS was 14 ± 1.4 with range from 11 to 15. Encephalopathy was considered when GCS was <14 (Elizabeth et al; 2015) (12). Accordingly 42.5% were considered to have encephalopathy.

There was no clinical evidence of cerebral edema in any of the patients. Considering their laboratory results, data were as follows: The mean thiamine level was 46.2±26.9 ng/dl with range (2.3 - 80 ng/dl). The reference range of plasma thiamine level in our study is (40 - 80 ng/dl). The majority of our patients (55%) were hyponatremic, while 22.5% had hypokalemia. One fifth of the patients presenting with DKA suffered severe acidosis while Thiamine deficiency was found in 40% of the children Table 1 show that pH and HCO3 levels had statistically significant strong positive correlation with level of thiamine (r=0.96, p>0.01) and (r=0.92, p>0.01) respectively. Glasgow Coma Scale had positive but moderate significant correlation with level of thiamine (r=0.57, p>0.01).

On logistic regression analysis for various factors affecting serum thiamine level in the studied population; PH, dehydration were significant factors as shown in Table 2. There is no statistical significant difference between thiamine deficient and normal thiamine patients regarding socio-demographic data.

There is no statistical significant difference between thiamine deficient and normal thiamine patients in relation to consanguinity, family history and duration of diabetes. There is no statistical significant difference between thiamine deficient and normal thiamine patients regarding triggering factors for DKA. Other than abdominal pain, all presenting symptoms of DKA were less prominent in thiamine deficient patients. However, the difference was not statistically significant between the two groups regarding abdominal pain. Group Comparison between Thiamine deficient and normal thiamine patients regarding laboratory parameters revealed that the levels were significantly lower among thiamine deficient children for all indices indicating more severe conditions Table 3. GCS scores were

Table 1: Correlations between thiamine level and different studied variables

Variables	Thiamine level	
	Correlation coefficient (r)	p-value
PH	0.96	> 0.01**
HCO_3	0.92	> 0.01**
GCS	0.57	> 0.01**

Table 2: Multiple Stepwise regression analysis of level of acidosis in Diabetic patients presented with DKA

Model	Unstandardized Coefficients		Standardized Coefficients	T	P-value
	B	Std. Error	Beta		
Age	0.006	0.004	0.144	1.51	0.14
BMI	0.001	0.003	0.019	0.22	0.82
Thiamine	0.005	0.001	0.873	9.94	> 0.01**
Serum Creatinine	- 0.084	0.051	- 0.136	-1.661	0.11
Cholesterol	-0.001	0.001	-0.141	-1.49	0.14
Hb	0.004	0.013	0.024	0.28	0.77
TLC	-0.003	0.003	- 0.065	- 0.82	0.42

Table 3: Group comparison between newly diagnosed diabetics and those who are known to have Diabetes

Variables	Newly diagnosed with DM (N= 21)	Known to have DM (N= 19)	P-value
Thiamine level]	19.64	21.45	NS
Initial RBS	20.83	20.13	NS
HbA1c	15.90	25.58	> 0.01**
ABG			
PH	19.21	21.92	NS
HCO3	19.29	21.84	NS
Serum Creatinine	17.71	23.58	NS
Electrolytes			
Na+	17.79	23.50	NS
K+	24.21	16.39	0.03*
Lipid profile			
Cholesterol	13.31	28.45	> 0.01**
Triglyceride	17.31	24.03	NS
LDL	19.29	21.84	NS
HDL	21.69	19.18	NS
CBC			
Hb	17.93	23.34	NS
TLC	21.07	19.87	NS
Examination			
Initial GCS	18.29	22.95	NS
BMI	17.69	23.61	NS
Weight	13.83	27.87	> 0.01**
Height	13.88	27.82	> 0.01**

*Significant p-value at <0.05, **highly significant p-value at <0.01.

significantly lower among thiamine deficient children indicating more severe conditions. Regarding PH, the level was significantly lower among thiamine deficient children indicating more severe conditions. Lower measures of HbA1c level, serum potassium and cholesterol, weight and height show statistically significant difference among newly diagnosed diabetics than those who are known to have diabetes. Table 2 shows that Stepwise backward regression analysis model of significance best-fitting predictor of level of acidosis in diabetic patients presented with DKA was their level of thiamine (t=9.94, p>0.01).

DISCUSSION

Diabetic ketoacidosis is an acute, major, life-threatening complication of diabetes that mainly occurs in patients with T1D [1]. Patients with diabetic ketoacidosis had a high prevalence of thiamine deficiency [2]. Early recognition of thiamine deficiency is difficult in critically ill patients because clinical signs are non-specific [13]. Because children with diabetes are at risk for thiamine deficiency and encephalopathy is a common presenting symptom in DKA, we sought to determine the prevalence of thiamine deficiency in those children and its relation to the degree of acidosis and encephalopathy. Moskowitz, et al [2] stated that DKA triggers were; unknown in (46.3%), medication non-adherence (34.3%), newly diagnosed (16%), infection (12.5%) and insulin pump malfunction (3%). Hanas, et al (16) conducted a study in which, reported factors were missed insulin doses (48.6%), gastroenteritis (14.1%), pump problems (12.7%), infection (13.4%), social problems causing insulin omission (1.4%), unknown (5.6%), and not stated (4.2%). This is concordant with our study as the missed insulin dose was the most common triggering factor in patients already known to have T1D presented with DKA; taking into consideration the minimal use of insulin pumps here. Xin et al., [15] found that polyuria with polydipsia were the most common presenting symptoms (98%) followed by weight loss (81%), fatigue (62%), dyspnea (57%), vomiting (46%), preceding febrile illness (40%), abdominal pain (32%) and polyphagia (23%) while Razavi [16] found that presenting symptoms were as following polydipsia (85.4) polyuria (83.3%), weakness (68.8%) and abdominal pain (52.1%). In the previously mentioned studies, polyuria and polydipsia were the most common presenting symptoms while in our study vomiting was the most common one which may be due to that polyuria and polydipsia are not a serious alarming symptom in our culture and great number of our patients presented in a stage of moderate and severe dehydration not in early stage. In continuity with our results, the mean serum thiamine level in our study was 120 nmol/l. Elizabeth et al [12] found that the mean thiamine level was 97.5 nmol/l.

In the current study we measured thiamine levels before starting insulin, as administration of insulin and glucose-containing solutions during treatment of DKA rapidly increases thiamine utilization and may precipitate acute thiamine deficiency [12]. The current study showed that 40% of the studied population had thiamine deficiency which was higher than the results reported by Elizabeth et al [12] who conducted a study to assess thiamine level in children with T1D presented with DKA in which 24% of patients had low serum thiamine levels on presentation, in contrary to our study, Moskowitz et al [2] conducted a study on the relationship between lactate and thiamine levels in DKA patients in which (25%) were thiamine deficient.

This may be due to the worse glycemic control that was observed in our study indicated by the relatively high mean level of HbA1c. It may be also due to increased number of anemic diabetic patients, or due to having higher number of patients with dehydration and severe acidosis because these were the most common variables that affect the serum thiamine level. The prevalence of encephalopathy at admission as defined by GCS less than 14 [12] appeared relatively high (42.5%) and there was no clinical evidence of cerebral edema in our patients.

In line with Elizabeth et al [13] we found a clinically significant correlation between thiamine deficiency and GCS. Clark et al [6] published a case report on acute thiamine deficiency in DKA, they concluded that thiamine deficiency should be considered in children with DKA whose encephalopathy does not improve with improvement

of biochemical status. In this study we found that thiamine deficient patients had a statistically significant lower GCS compared to those with normal thiamine level. In contrary to our findings, Elizabeth et al [12] found that the relationship between low serum levels of thiamine and encephalopathy is not well described, they explained that what was reported by McCandless and Schenker [17] that brain thiamine levels in an animal model have to be less than 20% of normal before neurologic signs, such as difficulty walking, imbalance, and drowsiness, are present. Our study with low serum thiamine levels were within 73% of normal, and this may explain the absence of a relationship between thiamine level and encephalopathy. We found that thiamine deficient patients had low HCO_3 level and this is consistent with Moskowitz, et al (2014) [2] who reported the same findings.

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