Iran J Pediatr. 2022 April; 32(2):e113893. doi: 10.5812/ijp.113893.

Published online 2022 April 3. **Research Article**

Thiamine Deficiency in Children with Type I Diabetes Mellitus and Ketoacidosis Hospitalized in a Referral Pediatric Hospital in 2019 - 2020

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Received 2021 April 17; **Revised** 2022 February 05; **Accepted** 2022 February 08.

Abstract

Background: Thiamine is an essential coenzyme, reduced in type I and II diabetes. There has been little research on thiamine levels and their role in children with diabetic ketoacidosis (DKA).
Objectives: This study aimed to analyze thiamine deficiency in this patient group.
Methods: A cross-sectional study was done in 2019 - 2020 in Children's Medical Center, a pediatric referral hospital with 350 beds, on children with type I diabetes hospitalized in the PICU for DKA. A blood sample was taken on admission to obtain biochemical laboratory parameters and measure electrolytes and thiamine levels. Blood gases were taken regularly, and the first pH and first bicarbonate level were measured. The time required for pH normalization and recovery from acidosis was recorded. Hospital stay duration was also calculated. Plasma thiamine measurement was done with a Human Vitamin B1 (VB1) ELISA Kit from Bioassay Technology Laboratory. Data were analyzed with SPSS version 22 software.
Results: Of 62 patients, 56.5% were females with a mean age of 63 months. Thiamine level was 1.61 ± 1.17 μg/dL, and 66.1% of the patients were thiamine deficient. Hospitalization duration was 3.52 ± 0.41 days in the thiamine deficient group and 2.47 ± 0.32 days in the normal group (P value < 0.05). The white blood cell (WBC) count was higher in thiamine deficient patients. Thiamine levels were independently and inversely related to age.
Conclusions: Thiamine deficiency is common among children with DKA and could be a prognostic and therapeutic factor.

Keywords: Thiamine, Ketoacidosis, Diabetes

1. Background

Today, diabetes mellitus is considered a significant problem all over the world. Its prevalence is increasing among all age groups. Many children with diabetes suffer from diabetic ketoacidosis (DKA) as one of the significant reasons for emergency department admission. Resistance to insulin or lack of insulin can cause hyperglycemia in children with diabetes mellitus. Hyperglycemia then can lead to osmotic diuresis with subsequent dehydration, ketosis, and metabolic acidosis. The subsequent acidosis might be very severe and cause significant dysfunction in some organs, such as the central nervous system (CNS). One of the common presentations is altered mental status in children with severe DKA. Hyperglycemia leads to hyperosmolarity, which, combined with dehydration, can result in osmotic disequilibrium and cerebral edema. Cerebral edema in the early stages presents with headache, vomiting, agitation, and altered level of consciousness and is one of the most frightening complications for DKA patients because of its high mortality rates (1).

Thiamine (vitamin B1) is a water-soluble vitamin and an essential cofactor for metabolizing glucose in the body. Water-soluble vitamins have low tissue reserves. Therefore, unlike fat-soluble vitamins, thiamine is not stored in the body. Any state that causes less intake or more output can easily lead to thiamine deficiency, such as diseases leading to increased thiamine metabolism. In this situation, the thiamine-dependent enzymes cannot work correctly. Therefore, thiamine deficiency could result in hyperglycemia and pyruvate production. Pyru-

vate excess then converts to lactic acid (2). Alanine is increased, and glutamate, acetylcholine, and gamma-aminobutyric acid are decreased due to the dysfunction of alpha-ketoglutarate dehydrogenate, all linked to encephalopathy (3). This is why encephalopathy with hyperglycemia unresponsive to insulin is a sign of acute thiamine deficiency.

Diabetes is one of the reasons for thiamine deficiency because during hyperglycemic state and osmotic diuresis, thiamine absorption in the small intestine decreases, and thiamine excretion in kidneys increases (4-7). Moreover, insulin and glucose-containing solutions increase the use of thiamine during DKA in a short time, leading to acute thiamine deficiency in patients with low thiamine reserves. Thiamine deficiency has been studied in adults with diabetes mellitus, but there are a few studies on thiamine deficiency prevalence in children with DKA.

A significant proportion of healthy individuals with hyperglycemic statuses, such as high-carbohydrate diets, diabetes, and pregnancy, is thiamine deficient (4). Low plasma thiamine levels have been recorded in patients with type 1 diabetes mellitus (Type 1 diabetes mellitus (DM I) (5). Thiamine reserves were lowered in diabetic untreated mice disorders (6). Besides, DKA, lactic acidosis, and hyperglycemia can suggest acute thiamine deficiency in children (7, 8). Another study reported low levels of erythrocyte Tk and blood thiamine and high erythrocyte thiamine pyrophosphate (TPP) activity levels in diabetic patients (9). As known, Tk is a factor to measure tissue thiamine activity. In diabetic patients, low thiamine levels may be due to decreased apoenzyme levels, which relates more to the disease than the low thiamine levels (9). Moreover, thiamine levels in plasma are decreased by 76% in patients with type 1 diabetes and 75% in patients with type 2 diabetes and are associated with increased renal clearance and secretory thiamine fraction (10).

Genetic studies provide an excellent opportunity to examine the relationship between molecular changes and epidemiological data. Several biological effects are due to the alteration of DNA sequences, e.g., in polymorphisms. Thiamine-responsive megaloblastic anemia (TRMA) is an autosomal recessive disorder that is not very common. It is linked to non-autoimmune DM, megaloblastic anemia, and sensorineural disorders (11). Fibroblasts in patients with TRMA absorb 5% to 10% of thiamine absorbed by fibroblasts in people without the disease (12). Diabetes is inherited in patients with TRMA. The SLC19A2 gene on chromosome 1q23.3 is mutated in these patients. The final product of this gene is a thiamine transporter with great affinity. Due to this mutation, the thiamine transporter is corrupted, which results in thiamine deficiency in cells. Anemia is treated with high doses of thiamine. Moreover, high doses of thiamine can make the patients' condition better, reducing or eliminating the need for exogenous insulin (13). On the other hand, thiamine discontinuation may cause DKA in patients with TRMA (14). Nevertheless, changes in SLC19A2 did not lead to type 2 diabetes in Pima Indians (15). When proteins or lipids are exposed to sugars, they become glycated and form products called advanced glycation endproducts (AGEs). They can be used as biomarkers for aging and development and progression in degenerative diseases such as diabetes. In laboratory-induced diabetes, supplementation with thiamine and one of its synthetic derivatives, benfotiamine, could decrease the accumulation of additional compounds resulting from glycation, oxidation, and protein nitration in tissues and increase their excretion in urine (16). Karachalias et al. (17) reported that glyoxal, methylglyoxal, G-H1, and MG-H1-derived hydroimidazoleone AGE residues were increased by 115% and 68% in streptozotocin-induced diabetic rats. When they gave thiamine and benfotiamine to rats, these results were reversed. In contrast, N-carboxymethyl lysine and Ncarboxyethyl lysine residues in diabetic rats were increased by 74% and 118% and normalized only by thiamine.

2. Objectives

Given all the above and the fact that the effects of thiamine on type 1 diabetes and DKA have been evaluated in very few studies, and there are few studies on the relationship between thiamine and diabetes in children, we decided to evaluate thiamine deficiency in children with type 1 diabetes and DKA.

3. Methods

We conducted a cross-sectional study in children aged 1 to 18 years admitted to Children's Medical Center in Tehran for DKA treatment in 2019 - 2020. The study was approved by the Research Ethics Committee of Children's Medical Center with the code of IR.TUMS.CHMC.REC.1397.068. Children with DKA requiring admission, not undergoing IV insulin infusion, and having no underlying disease were eligible for enrollment. No extra blood or expenses were taken from the patients.

Demographic data of patients (age, sex, weight, and height) were recorded, and BMI was calculated. All patients were treated according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2018. According to the guideline, they were categorized into three groups of mild, moderate,

and severe DKA who were hospitalized in ER, endocrinology ward, and intensive care unit (ICU), respectively. Before DKA treatment, a blood sample was taken to determine thiamine levels, first pH, first HCO_3, and routine laboratory (hematologic and biochemical) parameters. Venous pH and serum HCO_3 concentration were monitored every two hours to ensure the steady improvement of biochemical parameters and record recovery from DKA. Electrolytes, calcium, magnesium, and phosphate were monitored every 2 - 4 hours. Before batch processing, initial blood samples were stored at -70°C for up to three months. Thiamine levels were checked with the human vitamin B1 (VB1) ELISA Kit from Bioassay Technology Laboratory. Based on the cutoff of 2.5 μg/dL for thiamine, patients were grouped into normal-thiamine and thiamine-deficient groups.

Data analysis was performed with IBM SPSS Statistics v21. Patients were grouped into "thiamine deficient" and "normal thiamine" categories and compared using the *t* test for continuous variables and the chi-square test for categorical variables. Bivariate correlation was used to identify correlations between different aspects. Finally, linear logistic regression analysis was used to eliminate correlation distortion factors and find independent factors affecting the outcomes.

4. Results

We enrolled 62 patients, including 35 (56.5%) females and 27 (43.5%) males with a mean age of 63 $\pm$ 8.13 months. Table 1 compares the parameters between the two groups. The mean thiamine level was 1.61 $\pm$ 1.17 μg/dL. Considering the cutoff of 2.5 μg/dL for thiamine deficiency, 42 (67.7%) patients were in the thiamine deficiency group and 20 (32.3%) in the normal thiamine group. The hospitalization duration was 3.52 $\pm$ 0.41 days in the group with thiamine deficiency and 2.47 $\pm$ 0.32 days in the group with normal thiamine (P = 0.046). Laboratory indices, including inflammatory, hematological, renal, metabolic, and electrolytic factors, were also compared between the two groups, four of which were meaningfully different between the two groups. The WBC count was 10696 $\pm$ 6342 in the thiamine deficient group and 7117 $\pm$ 5670 in the normal thiamine group (P = 0.037). Hemoglobin was 11.88 $\pm$ 2.18 gr/dL in the group with thiamine deficiency and 10.53 $\pm$ 2.36 in the other group (P = 0.031). Total protein was 4.93 $\pm$ 0.89 gr/dL in the thiamine deficient group and 6.21 $\pm$ 1.27 in the normal thiamine group (P = 0.023). The sodium concentration was 140.34 $\pm$ 9.71 mEq/L in the thiamine deficient group and 135.15 $\pm$ 6.69 in the other group (P = 0.036).

Then, the study parameters were analyzed regardless of the deficient/normal groups of thiamine. We measured the relationships between the study parameters and the main factors including vitamin level, length of hospital stay, time taken to reach normal blood pH, first blood pH, and first bicarbonate level. First, the correlations of these parameters were examined and the results are reported as follows. The hospitalization duration was correlated only with the time taken to reach normal blood pH (r = 0.346, P = 0.008). The first blood pH was correlated with the first bicarbonate level (r = 0.479, P = 0.000) and blood sugar (r = -0.361, P = 0.021). The first level of blood bicarbonate was correlated with the first level of pH (r = 0.479, P = 0.000), BUN (r = -0.283, P = 0.030), Cr (r = -0.369, P = 0.004), potassium (r = -0.282, P = 0.029), weight (r = 0.289, P = 0.046), and BMI (r = 0.457, P = 0.008). The hospitalization duration was the only variable correlated with the time taken to reach normal blood pH (r = 0.346, P = 0.008). Blood thiamine level was associated with CRP (r = 0.288, P = 0.037), WBC (r = -0.254, P = 0.048), Hb (r = -0.340, P = 0.007), sodium (r = -0.254, P = 0.048), and age (r = -0.321, P = 0.022). Logistic regression analysis was performed to investigate the effects of possible confounding factors. The hospital stay length was still related to the time required to reach normal blood pH in logistic regression (beta coefficient = 0.346, P = 0.008). Regarding the initial blood pH, only the first bicarbonate level remained related (beta coefficient = 0.449, P = 0.000). In the case of primary blood bicarbonate, the relationship between the initial pH level (beta coefficient = 0.548, P = 0.001) and BMI (beta coefficient = 0.714, P = 0.003) remained significant. Regarding blood vitamin levels only the age relationship remained significant (beta coefficient = -0.488, P = 0.021).

5. Discussion

This study evaluated thiamine deficiency in children with DKA admitted to the hospital. We found that 66.1% of the patients had thiamine deficiency. Different studies have shown thiamine deficiency in type 1 and type 2 diabetes people. In a study by Rosner et al. (18) on patients with ketoacidosis in the PICU, 23.8% were thiamine deficient. In a study by Moskowitz et al. (19), in 32 adult DKA patients, 25% were thiamine deficient. Van Snippenburg et al. (20) also reported thiamine deficiency in 39.7% of diabetic patients. These studies reported a lower prevalence of thiamine deficiency than our study. In general, the rate of thiamine deficiency has been reported in studies between 17% and 79% (21).

Altered erythrocyte transketolase activity indicates an increased risk of thiamine deficiency, which is significantly more prevalent in diabetic patients. Thiamine and thiamine esters reported in the blood, plasma, and serum have been different among different studies. In some studies, decreased thiamine levels in the plasma have been re-

Table 1. Characteristics of Patients with Low and Normal Thiamine Levels at Presentation [a]

Variables	Low Thiamine; 41 (66.1)	Normal Thiamine; 20 (32.3)	P Value
Gender			0.164
Male	20 (48.8)	6 (30)	
Female	21 (51.2)	14 (70)	
Age (mo)	75.83 ± 10.3	33.38 ± 8.69	0.056
Height (cm)	110.93 ± 5.2	93.85 ± 6.2	0.223
Weight (kg)	22.99 ± 3.1	12.69 ± 1.65	0.067
Body mass index (kg/m^2)	16.3 ± 0.95	14.04 ± 0.59	0.095
Time to get out of DKA (days)	3.52 ± 0.41	2.47 ± 0.32	0.046
Erythrocyte sedimentation rate (mm/h)	18.5 ± 5.22	31 ± 13.36	0.067
White blood cell (/mm^3)	10.69 ± 6.34	7.11± 5.67	0.037
Arterial blood gas			
pH	7.15 ± 0.10	7.18 0.05	0.340
HCO3 (mEq/L)	9.22 ± 5.99	9.49 ± 4.7	0.835
Blood urea nitrogen (mg/dL)	14.38 ± 12.5	12.5 ± 7.43	0.445
Creatinine (mg/dL)	0.61 ± 0.35	0.46 ± 0.22	0.094

[a] Values are expressed as No. (%) or mean ± SD.

ported in diabetic patients (5, 10). One study reported low blood cell thiamine levels in 15% of diabetic patients (22), which were normal in a different study. The difference in the values reported in the studies could be related to the method of measuring thiamine.

This study used some parameters to measure the relationship between the thiamine levels and the clinical course of the patients. Blood pH, bicarbonate level, and the time to reach normal pH were not different between the thiamine deficient and normal thiamine groups. However, the hospitalization duration was significantly different between the two groups. The hospitalization duration was 3.5 days in patients with thiamine deficiency and 2.4 days in the normal thiamine group. Although there are a few studies on thiamine status in children with ketoacidosis, no studies have reported this finding. The relationship between thiamine and hospital stay length seems to help determine the prognosis for hospitalization and thiamine administration for clinical improvement and hospital stay reduction. Some studies have shown the clinical benefits of thiamine. Clark et al. reported an immediate response to intravenous thiamine in a child who had recently developed diabetes and presented with neurological symptoms and ketoacidosis (7). Moskowitz et al. reported a negative correlation between lactic acid and plasma thiamine levels (19). In addition to helping with acidosis, oral thiamine has been shown to reduce glucose and leptin without altering other laboratory parameters significantly. Rosner et al. (18) also reported that thiamine deficiency should be considered in persistent metabolic acidosis despite appropriate treatment for ketoacidosis. Therefore, thiamine administration can improve the patient's clinical condition and speed up patient discharge. However, the recovery time from acidosis did not differ between the two groups in our study. We believe that more and larger studies are needed to investigate this issue.

We also measured and analyzed the relationship between laboratory parameters and thiamine. Blood sugar levels in our study did not differ between the two groups. Although thiamine deficiency is associated with hyperglycemia and diabetes mellitus, given that all patients in our study had diabetes and were in the ketoacidosis phase, this lack of difference in blood sugar levels could be reasonable. The WBC count was significantly higher in patients with thiamine deficiency than in the normal group; however, ESR and CRP levels did not reach statistical significance, although tending to be higher. These findings suggest that thiamine deficiency might cause an inflammatory condition in the body. Studies have shown that low plasma thiamine levels are associated with a range of diseases, primarily inflammatory diseases (23, 24), and decrease thiamine levels was reported during such disorders. Therefore, the interpretation of plasma thiamine levels in the presence of sepsis, surgery, or autoimmune disease should be performed with caution because of concomitant confounding factors (25).

Differences in hemoglobin and total protein levels were also observed, which requires further studies in this area. In further analysis to investigate the relationship between study parameters and clinical course, apart from thiamine status, it was found that the length of hospital stay was correlated with the time required to reach normal pH and recover from acidosis. It seems that taking actions to get the patient out of acidosis as soon as possible can shorten the hospital stay, and prescribing thiamine based on existing studies could be among such actions. Thiamine levels in our study were independently correlated with patient age; as the patient gets older, the thiamine level decreases. A few studies have studied the relationship between age and thiamine deficiency in children. In a study on children admitted to the ICU, the degree of thiamine deficiency did not differ significantly between children under one year and over one year (24), contrary to the findings of our study. It seems that since thiamine is not synthesizable in the human body, its oral intake is essential to meet the body's needs. The required daily amount of thiamine is related to some factors such as age, weight, physiological condition, and metabolism of the body in terms of the total energy content of the diet. Unlike adults, the optimal daily thiamine level is not yet agreed upon. It is generally said that the daily thiamine requirement is 0.2 mg before the age of six months, 0.3 mg between seven months and three years, 0.6 mg between four and eight years, and 0.9 to 1.2 mg at older ages. Breast milk contains thiamine and its derivatives amounting to about 0.21 mg/L, but it differs among different diets and countries. However, it is common for breast milk to contain low amounts of thiamine, which may seriously affect the thiamine status of breastfed infants (26). Overall, it seems that the probability of nutritional thiamine deficiency increases due to the increasing need of children for thiamine with age. This possibility, along with the findings of our study, should be considered and confirmed in future studies.

Our study had some limitations. The first limitation of our study was the lack of a non-diabetic control group. In the presence of a control group, the comparison and judgment of thiamine status in diabetes and the resulting ketoacidosis in our study would be much more comprehensive and more interpretable. The second limitation is that with this study design, we could just prove the prevalence of thiamine deficiency and the shorter hospitalization period, which only shows a correlation and is not enough for causality. Therefore, we recommend further prospective investigations to evaluate the potential benefits of thiamine supplementation as a therapeutic intervention.

5.1. Conclusions

According to the findings of our study, thiamine deficiency is a common problem in children with diabetic ketoacidosis admitted to the emergency department (66%). The hospital stay was significantly longer in patients with thiamine deficiency than in patients with normal thiamine. Inflammatory factors increase in patients with thiamine deficiency and provoke an inflammatory condition. Thiamine levels were independently and inversely correlated with patients' age.

Footnotes

Authors' Contribution: Study concept and design: Masoud Mohammadpour; drafting of the manuscript: Mahsa Mohammadpour; analysis and interpretation of data and statistical analysis: Mahsa Mohammadpour; critical revision of the manuscript for important intellectual content: Bahareh Yaghmaie, Fatemeh Sayarifard, Azadeh Sayarifard, Reihaneh Mohsenipour., and Meisam Sharifzadeh.

Conflict of Interests: The authors declare no conflict of interest.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after its publication. The data are not publicly available due to technical errors in the meantime. We will publish them as soon as possible or in the case of any researcher's request.

Ethical Approval: The study was approved by the Research Ethics Committee of Children's Medical Center with the code of IR.TUMS.CHMC.REC.1397.068 (ethics.research.ac.ir/ProposalCertificateEn.php?id=36102).

Funding/Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed Consent: As we did not take any further specimens for our study and no extra blood or expenses were taken from patients, informed consent was taken as general consent on admission.

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