Evaluation of Thyroid Functions in Patients with Diabetic Ketoacidosis

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ABSTRACT

Background: Diabetic ketoacidosis (DKA) is an acute life-threatening complication of diabetes. It is not only a sign of acute absolute insulin deficiency in type 1 diabetes mellitus (T1DM) but also increasingly seen in patients with type 2 diabetes mellitus. DKA can affect the function of the hypothalamus-pituitary- thyroid axis directly or indirectly due to various factors such as relatively insufficient insulin secretion and metabolic disorders.

Subjects and Methods: This study was performed in the ICU of Minia University Hospital and Beni-Suef University Hospital. It included 90 patients admitted in ICU of both Hospitals who had diabetic ketoacidosis and 30 normal individuals as control group. The thyroid function of patients group and control group, impact of Ketoacidosis on thyroid function of patients group and its correlation with the clinical features and laboratory findings at diagnosis were evaluated.

Results: As regard thyroid profile TSH, FT3 and FT4 were significantly lower in patients compared to control groups ($p < 0.001$). The mean reverse T3 was 780.1±55.6 in DKA patients, which was significantly higher than control group (325±62.5) with p value $p<0.001$. The mean TSH was (1.9±0.4) in DKA patients, which was significantly lower than control group (2.6±0.6) with p value $p<0.001$. The mean FT3 was (3±0.4) in DKA patients, which was significantly lower than control group (3±0.4) with p value $p<0.001$. The mean FT4 was (12.9±1.3) in DKA patients, which was significantly lower than control group (13.8±1.4) with p value $p<0.013$. There was significant negative association between rT3 and pH ($r= -0.610$, $p<0.001$).

Conclusions: Our study demonstrated that thyroid profile TSH, FT3 and FT4 were significantly lower in patients with DKA, while the mean reverse T3 was significantly higher in DKA patients. This dysfunction was correlated with severity of ketoacidosis. Findings of our study may have important therapeutic applications.

Keywords: Diabetic Ketoacidosis, FT3, FT4, rT3, Thyroid, TSH.

INTRODUCTION

Diabetes is chronic endocrine/metabolic disease with heterogeneous etiologies, clinical presentations and associated complications. Its biochemical hallmark is hyperglycemia caused mainly by insulin deficiency and/or insulin resistance [(1)]. Diabetic ketoacidosis (DKA) is the most common acute hyperglycemic emergency in people with diabetes mellitus. Usually resulting in the triad of hyperglycemia, metabolic acidosis and ketosis (elevated levels of ketones in the blood or urine; a serum ketone concentration of>3.0 mmol/l [(2)].

DKA shows a rapid onset, quick progression and severe conditions, with a mortality of 5%. Therefore, it is necessary to identify new and effective markers for the evaluation of DKA conditions, which is of prime importance to the screening of high risk patients and proper treatment [(3)].

The thyroid gland primarily produces two hormones: T4 (thyroxine) is the most abundant thyroid hormone but it has very little biological activity and must be converted into T3 to play out the roles normally associated with thyroid hormones, and T3 (triiodothyronine) is a thyroid hormone that plays many roles in the body, including metabolism, growth, and body temperature. The thyroid gland produces some T3, but most available T3 comes from the conversion of T4 [(4)].

The body sometimes converts T4 into rT3 (Reverse T3) instead. This rT3 has little biological activity and is considered an inactive compound [(5)]. The serum concentration of rT3 is typically 1/10 of that of T3 in elderly (10 to 24 ng/dL) but in some situations may exceed that of T3. The most common perturbation of serum rT3 concentration occurs in response to carbohydrate deprivation during starvation or severe illness (the no thyroidal illness syndrome or NTIS) [(6)].

In our study, we aimed to evaluate the impact of diabetic ketoacidosis on thyroid function of the patients (TSH, Free T3, FreeT4 and rT3) and its correlation with the clinical features and laboratory findings at diagnosis.

PATIENTS AND METHODS

The current study was conducted in the medical ICUs of both Minia University Hospital and Beni-Suef University Hospital during the period from May 2020 to February 2021.

All patients with diabetic ketoacidosis who were admitted to the ICU and aged more than 18 years old were eligible to be included in the study. Thirty age and gender-matched person were allocated as a control group.

Patients were excluded from the study if they: have any history of thyroid disorders, received any local and/or systemic treatment for hyper- or hypothyroidism,

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have any other causes of increased blood glucose level, severe liver or kidney impairment or received any hormonal treatment.

DKA was defined as a glucose concentration>300 mg/dL, pH≤7.25 or a serum bicarbonate concentration<15 mmol/L, and the presence of ketones acetoacetate (either in the blood or the urine) [7].

All participants were subjected to: careful history taking and thorough clinical examination, routine laboratory assessment included CBC, liver and renal function tests, ESR, CRP, FBS and PT, PC, INR and Urine analysis.

Arterial blood gases were done to all patients.

Thyroid profile included T3, T4, and TSH.

Specific laboratory investigation: Serum reverse tri-iodothyronine (RT3) was performed by (ELISA) (bioassay Technology laboratory, Yangpu Dist Shinghai, China).

Radiological Investigation: Chest X-ray and abdominal ultrasonography were done to all patients.

Ethical consent:

An approval of the study was obtained from Minia University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for the Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Numerical data were expressed as mean and standard deviation or median and interquartile range (IQR) and compared using t test or Mann-Whitney U test as appropriate. Categorical data were presented as number and percent and compared using chi-square test. $P < 0.05$ were considered to be statistically significant.

RESULTS

Table (1) illustrates that there was a statistically significant difference between both groups regarding pulse, temperature, and respiratory rate.

Table (1): Demographic and clinical data of studied groups

	Case (N=90)	Control (N=30)	p value
	Mean±SD or No. (%)	Mean±SD or No. (%)	
Age (years)	32±8 34 (19-43)	30±6 30 (21-41)	0.149
Sex Female Male	 47 (50.0%) 43 (50.0%)	 15 (50.0%) 15 (50.0%)	0.91
Pulse	93.2±8.3	80.9±8.1	<0.001*
SBP (mmHg)	118.4±14.3	116.4±11.5	0.397
DBP (mmHg)	78.2±10.8	75.6±7.7	0.173
Temp	38.7±0.8	37±0.2	<0.001*
Respiratory rate (RR)	24.7±5	13.1±1.1	<0.001*

Table (2) illustrates that there was a statistically significant difference between both groups regarding hemoglobin, WBCs, INR, RBS, urea, and creatinine were in DKA cases more than control group.

Table (2): Laboratory data of studied groups: DKA and healthy control groups

Lab	Case (N=90)	Control (N=30)	p value
	Mean±SD	Mean±SD	
Hb (gm/dl)	13.2±1.6	12.2±0.9	0.001*
WBC ($x10^3$)	11.87±2.22	7.57±1.37	0.003*
Plt ($x10^3$)	282±15	247±14	0.267
INR	1.2±0.27	1.06±0.07	0.044*
RBS (mg/dl)	368±17.9	149.8±28.3	<0.001*
Cr (mg/dl)	1.79±0.61	0.87±0.19	0.012*
Urea (mg/dl)	71.4±5.9	34.1±3.5	0.001*
Na (mmol/L)	138.9±5.9	140.4±3.7	0.118
K (mmol/L)	4±0.7	3.9±0.3	0.789

As regard ABG there was metabolic acidosis in patients of DKA as shown in table 3 in pH, PCO_2 and HCO_3.

Table (3): Blood gases in patients group

Lab	Case (N=90)
	Mean±SD
pH	7.18±0.11
PCO_2 (mm Hg)	28.6±12.5
HCO_3 (mEq/L)	9.8±2.4

As regard inflammatory markers, DKA patients had significantly higher level of CRP and ESR compared to control group (Table 4).

Table (4): Comparison in inflammatory markers between DKA patients and control group

Inflammatory markers	Case (N=90)	Control (N=30)	p value
	Mean±SD	Mean±SD	
CRP (mg/L)	75.8±18.9	3.9±0.2	<0.001*
Esr 1st (mm)	37.6±1.4	5.9±1.4	<0.001*
Esr 2nd (mm)	80.3±19.7	16.6±3.9	<0.001*

AS regard thyroid profile TSH, FT3 and FT4 were significantly lower in patients compared to control groups. The mean reverse T3 was significantly higher in DKA patients than control group (Table 5).

Table (5): Comparison in thyroid profile between the studied groups

Thyroid function tests	Case (N=90)	Control (N=30)	p value
	Mean±SD	Mean±SD	
TSH (mIU/L)	1.9±0.4	2.6±0.6	<0.001*
FT3 pmol/L	3±0.4	4.1±0.6	<0.001*
FT4 pmol/L	12.9±1.3	13.8±1.4	0.002*
rT3 pmol/L	780.1±55.6	325±62.5	<0.001*

There was significant negative association between rT3 with DBP and pH (Table 6).

Table (6): Correlation of reverse T3 with clinical, laboratory variables among the patients group

Variables	rT3	
	R	P
Age	-0.120	0.526
Pulse	-0.279	0.135
SBP (mmHg)	-0.350	0.058
DBP (mmHg)	**-0.543**	**0.002***
Temp	-0.091	0.633
RR	-0.069	0.718
Hb	-0.068	0.721
TLC	0.001	0.997
PLT	0.296	0.113
INR	-0.285	0.127
RBS	-0.296	0.112
Cr	0.100	0.599
Ur	-0.005	0.980
Na	0.135	0.476
K	0.142	0.454
ICA	0.077	0.685
pH	**-0.610**	**<0.001***
CO_2	-0.039	0.839
HCO_3	-0.194	0.305
CRP	0.277	0.138
Esr 1st	0.229	0.224
Esr 2nd	0.328	0.077
TSH	-0.126	0.505
FT3	-0.153	0.420
FT4	-0.183	0.332

DISCUSSION

The present study revealed that, there was a significant increase in hemoglobin and WBCs in the DKA patients than in the healthy control group. Our findings are in agreement with **Małachowska *et al.*** [8] who studied changes in hematological parameters during first days of diabetic ketoacidosis treatment in cases with type 1 diabetes mellitus, they found that the DKA group was characterized by significantly higher values of baseline RBC ($p = 0.0026$), hematocrit (Hct) ($p = 0.0019$), Hb ($p = 0.0235$), PLT ($p = 0.0427$) and WBC count ($p < 0.0001$) vs. patients without DKA.

Our study goes hand with **Kayashima *et al.*** [9] who found that there is direct relationship between blood pH and level of WBC where high level of WBC is correlated with increase of blood acidity.

Also, **Kayashima *et al.*** [9] found that the severity of DKA is related to the arterial pH value, and high H^+ values increase WBC production**.** Hyperketonemia increases systemic inflammatory activity processes and oxidative stress. It increases various cytokines, such as IL-6, IL-8, IL-10, so WBC production will increase too**.**

In our study we found renal function tests, urea and creatinine, were higher among DKA patients compared to control group (71.4 and 1.79 compared to 34.1 and 0.87 respectively) and this difference was statistically significant. And this goes with **Ying *et al.*** [3] who found elevation of plasma creatinine in patients presenting with diabetic ketoacidosis (DKA). This elevation may be due to three causes. First, diabetic patients may have an elevated plasma creatinine due to the presence of diabetic nephropathy. Second, dehydration may develop in the course of DKA because of osmotic diuresis of glucose and ketoacidosis. Finally, interference of ketoacidosis with the plasma creatinine assay can result in a falsely high plasma creatinine concentration.

As regard thyroid profile in the current study, TSH, FT3 and FT4 were significantly lower in patients compared to control groups. The mean reverse T3 was 780.1±55.6 in DKA patients, which was significantly higher than control group (325±62.5). The mean TSH was (1.9±0.4) in DKA patients, which was significantly lower than control group (2.6±0.6). The mean FT3 was (3±0.4) in DKA patients, which was significantly lower than control group (3±0.4). The mean FT4 was (12.9±1.3) in DKA patients which was significantly lower than control group (13.8±1.4).

Our results are in agreement with the results reported by **Naeije *et al.*** [10] on 19 patients with diabetic ketoacidosis with known previously to have normal TFT. They found thyroid dysfunction during ketoacidosis; T3 blood level decreased while rT3 increased. In this study also, a slight reduction in T4 serum level and normal TSH level were observed. These findings were consistent with low T3 syndrome in diabetic ketoacidosis.

Also our results are supported by the finding of **Miboluk *et al.*** [11] who evaluated thyroid function tests during and after treatment of ketoacidosis in 15 euthyroid patients, they found that T3 blood level was 0.36± 0.04 ng/dl (hypothyroid level) and rT3 was 0.4±0. 6 ng/ml (significantly increased) and T4 level 5.5± 0.7 mcg/dl (normal limit) were observed before ketoacidosis treatment. The results from above study were consistent with low T3 syndrome in which T3 blood level decreased and rt3 was increased**.**

Our finding is in line with a study of 17 adult patients with diabetes ketoacidosis, **Glinoer *et al.*** [12] found a significant reduction in TBG serum level and total T4 without any changes in T4 and TBG ratio and moderate increase in free T4 and blunted response of TSH to TRH. These changes were reversed to normal 5 days after appropriate diabetic metabolic control.

Moreover, the study of **Derkach *et al.*** [13] found that DKA can affect the function of the hypothalamus-pituitary-thyroid axis directly or indirectly due to various factors such as relatively insufficient insulin secretion and metabolic disorders, thus affecting thyroid function. Moreover, our study is in agreement with **Xing *et al.*** [14] who showed that the levels of T4, T3, FT3, FT4, and TSH were lower and the level of rT3 was higher in patients with DKA compared with patients with diabetes but not DKA. The levels of T4, T3, FT3, and FT4 were lower and the level of rT3 was higher compared with after treatment in patients with diabetes and DKA. They explained that the body's caloric intake is seriously insufficient in patients with DKA, leading to hypoxia in the cells, which reduced the biological activity of 5′-deiodinase, resulting in a significant reduction in the conversion of T4 to T3, and a significant reduction in the levels and activity of thyroid hormones.

Our results go hand in hand with **Tomer and Menconi** [15] who said that the presence of carbohydrate deprivation in DKA seemed to rapidly inhibit the de-iodination of T4 by type 1 iodothyronine-deiodinase in the liver, thereby inhibiting the production of T3 and preventing the metabolism of rT3. Carbohydrate deprivation will lead to a decrease in basal metabolic rate. The decrease in thyroid hormones is caused by the body's remaining adaptive response to calories and protein by inducing hypothyroidism theoretically. It was reported that the average level of rT3 was increased in patients with diabetic ketoacidosis and the average metabolic clearance rate of rT3 is decreased, on the other hand **Tomer and Menconi** [15] showed that T1DM and thyroid diseases have a common genetic basis**.**

Also, **Derkach *et al.*** [13] found that DKA can affect the function of the hypothalamus-pituitary-thyroid axis directly or indirectly due to various factors such as relatively insufficient insulin secretion and metabolic disorders, thus affecting thyroid function. Suggested mechanisms by **Piconi *et al.*** [16] **and Adler and Wartofsky** [17]**,** are high blood glucose trigger fluctuations in the production of nitro tyrosine and induce the expression of adhesion molecules and IL-6, the release of a large number of cytokines acted on the hypothalamus pituitary-thyroid axis through a variety of

ways, which can also affect the synthesis, secretion, metabolism, and feedback of thyroid hormones. An increase in cytokines such as IL-6 synchronizing with a low T3 level is often observed, which may cause hypothalamus involvement [14].

Interestingly, the present study recognized a moderate negative association between rT3 and PH (r= -0.610), which means that there is positive correlation between level of rT3 (as a marker of thyroid dysfunction) and severity of ketoacidosis expressed by lower PH.

Our results go hand in hand with **Xing *et al.*** [14] who demonstrated that because the aggravation of DKA, the levels of T4, T3, FT3, and FT4 would further decrease, but there was no statistical difference in the change of TSH. Thyroid function changed in diabetic patients with DKA. It is changed with the severity of DKA. This condition may be transient, preceding further recovery of DKA [14].

Studies also found that the severity of impaired hypothalamus-hypophyseal-thyroid regulation seems to be related to the degree of metabolic disorders regardless of the presence of anti-thyroid antibodies [18]. Previous studies have shown that the levels of serum T3 and T4 are related to the severity of the disease [19, 20].

Similarly, **Balsamo *et al.*** [18] showed that changes in hormone levels are usually related to the severity of metabolic disorders, among which thyroid function is one of the most serious disorders. The hypothalamus-pituitary-thyroid axis showed variable damage, which was defined as non-thyroid disease syndrome (NTIS). The relationship between the degree of NTIS and the severity of metabolic disorders has previously been reported in adults and children [6].NTIS is now more commonly used to describe a typical change in the serum levels of thyroid-related hormones that may occur after an acute or chronic disease not caused by intrinsic abnormalities in thyroid function. Changes in the hypothalamic-pituitary-thyroid axis also occur in diseases, usually associated with low levels of T3, which gave rise to the term "low T3 syndrome"[6].

It has been reported that acute disease can cause a variety of changes in the levels of thyroid hormones in patients who were not previously diagnosed with intrinsic thyroid disease. These changes are nonspecific and are related to the severity of the disease [21].

CONCLUSION

Thyroid profile TSH, FT3 and FT4 were significantly lower in patients with DKA, while the mean reverse T3 was significantly higher in DKA patients. There was positive correlation between increased level of rT3 (as a marker of thyroid dysfunction) and severity of diabetic ketoacidosis. Findings of our study may have important therapeutic applications. Use of thyroid hormones (THs) along with their metabolites and thyroid hormone receptor β (THR-β) agonists may be tried in management of DKA patients.

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