Determinants of deranged thyroid function parameters in children admitted for management of diabetic ketoacidosis/diabetic ketosis

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Abstract

Background: Sick euthyroid syndrome is frequent in children admitted with diabetic ketoacidosis/diabetic ketosis (DKA/DK). This study evaluates the interplay of various metabolic factors with occurrence of deranged thyroid function tests in children admitted for management of DKA/DK.

Methods: 98 DKA and 96 DK children patients were selected from hospital records, among which individuals on thyroxine replacement, with overt hypothyroidism or positive anti-thyroperoxidase (TPO) antibody were excluded. Tests for liver function, renal function, lipid profile, serum osmolarity, thyroid function, c-peptide levels, and glycosylated hemoglobin were done for all. Children were divided into euthyroid (n=88) and euthyroid sick syndrome（ESS）groups (n=106).

Results: The ESS group had a higher level of white blood cell count (WBC), plasma glucose (PG), beta-hydroxybutyric acid (β-HB), triglyceride (TG), anion gap (AG), glycosylated hemoglobin (HbA1c) and a lower level of HCO_3^-, prealbumin (PA), and albumin (ALB) compared with the euthyroid group (P<0.05). Free T3 (FT3) levels were significantly correlated to β-HB, HCO3-, AG, PA, and HbA1c (r=-0.642, 0.681, -0.377, 0.581, -0.309, respectively; P<0.01). Free T4 （FT4） levels were significantly correlated to β-HB, HCO_3^-, and ALB levels (r=-0.489, 0.338, 0.529, respectively; P<0.01). TSH levels were significantly affected by HCO_3^- only (r=-0.28; P<0.01). HCO_3^- level was the most important factor deciding euthyroid or ESS on logistic regression analysis (OR=0.844, P=0.004, 95%CI=0.751-0.948).

Conclusions: Lower levels of free thyroid hormones and occurrence of ESS were associated with a higher degree of acidosis in children with DKA/DK.

1. Background

Type 1 diabetes (T1DM) is a common autoimmune disorder associated with other autoimmune diseases like coeliac disease and autoimmune hypothyroidism. Although no age group is exempt, children under 18 are most likely affected.

Blood ketones would be higher than normal in children with T1DM for the insulin deficiency. The severe high level of ketones tends to trigger life-threating condition of diabetic ketoacidosis (DKA) manifested by nausea, vomiting, stomach pain, trouble breathing and loss of consciousness[1,2].The occurrence of DKA is most caused by infection, stress, inappropriate diet or medications，which has a higher incidence in younger children[3].

Euthyroid sick syndrome (ESS), also known as non-thyroidal illness syndrome, is a transient derangement in thyroid function tests characterized by low T3 levels. ESS is reportedly associated with a higher risk of fatality among critically ill patients admitted with myocardial infarction, sepsis, trauma, and chronic kidney disease[4-7]. Also, ICU patients with ESS tend to be more severer compared to those with normal thyroid function[8]. Thyroid dysfunction happens more in diabetic patients relative to general population while poor glycemic control coincides with a lower level of free T3 (FT3) in serum[9]. ESS in children with

T1DM connotes a poor metabolic control and ketoacidosis[10,11]. The potential mechanisms could be (but not limited to) deranged regulation of the hypothalamic-pituitary-thyroid axis, effect of inflammatory cytokines, or consequence of oxidative stress [12].

A study reported by Hu et al unveiled a higher level of HbA1c, anion gap, and plasma glucose, as well as a lower level of bicarbonate in T1DM children diagnosed with DKA and ESS than those without ESS [13]. However, it analyzed the association of just a few of parameters to ESS in DKA. So the relationship of DKA, ESS, and various metabolic parameters like hyperglycemia, hyperketosis, acidosis, and other acute phase reactants remains to be elucidated. In this study, we aim to evaluate the metabolic parameters like leukocyte count, blood biochemistry, liver function, kidney function, blood lipid, and C-peptide levels in relation to risk of ESS among children with T1DM admitted for management of DKA, diabetic ketoacidosis (DK) or acute hyperglycemia.

2. Methods

2.1. Patient recruitment and exclusion criteria: This is a retrospective case-control study undertaken in the Pediatric Department of Shandong Provincial Hospital affiliated to Shandong University in Shandong, China. We enrolled children with newly diagnosed (or already suffering from) T1DM admitted to the hospital for management of DKA or acute hyperglycemia between January 2014 and August 2019. Ethical approval was obtained from the Ethical Committee of Shandong Provincial Hospital. Study participants and parents of minors provided signed informed consent at the moment they admitted to the hospital.

T1DM was diagnosed based on the American Diabetes Association criteria and International Society for Pediatric and Adolescent Diabetes (ISPAD) clinical practice consensus guidelines 2018[14,15]. The criteria for diagnosing DKA was blood glucose (BG) >11 mmol/L, venous pH <7.3, or bicarbonate <15 mmol/L. A diagnosis of DK was made, if blood sugar was more than 11 mmol/L, urine ketones were positive, but venous pH ≥7.3 or serum bicarbonate level was normal (≥15mmol/L) [16]. Euthyroidism was defined when levels of thyroid function tests were within the reference ranges (FT3:3.1-6.8 pmol/L, FT4:12-22 pmol/L, TSH:0.27-4.2 μIU/mL). ESS was defined when FT3 and/or FT4 levels were decreased and TSH levels were normal or decreased[13,17,18] .

A total of 237 children patients were screened. All children under the age of 18 years admitted for management of DKA/DK (either newly diagnosed or already on insulin) were included in the trial. Children with overt hypothyroidism, on thyroid medications, or those with other types of diabetes like pancreatic diabetes or juvenile type 2 diabetes, morbid obesity, or on anti-hyperglycemic agents other than insulin were excluded from the trial. Children on steroids or any such medication that could significantly affect thyroid function tests were also excluded from the analyses. Children with other critical organ illnesses as rheumatic heart disease, heart failure, nephrotic syndrome, coeliac disease, or chronic kidney disease and those who were positive for anti-TPO antibody were also excluded.

A total of 194 children qualified for the final analysis. Among them, 88 were adjudicated to the euthyroid group including 19 cases of DKA and 69 cases of DK, and 106 to the ESS group including 79 cases of DKA and 27 cases of DK.

2.2. Laboratory assays: All samples for laboratory analysis were taken before commencing initial therapy. Serum biochemical analysis including electrolytes, renal function tests, lipid profile, and liver function tests were measured using an automatic biochemistry analyzer (AU5400, Beckman Coulter, Tokyo, Japan). Glycosylated hemoglobin (HbA1c) was measured by high-performance liquid chromatography (HLC-723G7, Tosoh Corporation, Tokyo, Japan). Thyroid function tests were measured using an automated chemi-luminescent immunoassay system (Advia Centaur, Siemens, Munich, Germany). The intra-assay and inter-assay coefficients of variation were <6% for all parameters. Serum C-peptide (C-p) level was measured by chemi-luminescent immunometric assay (Cobas E170, Roche Diagnostics, Mannheim, Germany).The corrected Na+ was derived from formula: [(Glucose (mmol/L) − 5.6] × 0.36 + Serum Na[19].

2.3. Statistical methods: Normally distributed data is represented as mean ± standard deviation (SD). Non parametric and skewed data is represented as median (interquartile range). Chi-squared test was used to compare rates and proportions. Two-tailed student t-tests was used to compare normally distributed data between two groups and Mann-Whitney Rank sum test was used to compare non parametric skewed data between the two groups. Pearson and Spearman correlation tests were applied to evaluate associations between parametric and nonparametric data, respectively. Multiple linear regression analysis was done to detect variables which had an independent effect on thyroid function tests. Logistic regression analysis was done using thyroid function status as a binary variable to determine which factors independently influenced the placement of a subject in a particular group. All analysis was performed on Statistical Package for Social Sciences version 25.0 (SPSS Inc. Chicago, IL, USA). A *p*-value <0.05 was considered statistically significant.

3. Results

3.1. Baseline clinical and laboratory characteristics: The baseline demographic and clinical characteristics of enrolled children are shown in Table 1. There was no statistically significant difference in mean age, gender ratio, and BMI between the euthyroid and EES groups. Levels of blood cell count (WBC), plasma glucose (PG), beta-hydroxybutyric acid (β-HB), triglyceride (TG), anion gap (AG), glycosylated hemoglobin (HbA1c) were significantly higher in the EES group than in the euthyroid group, whereas serum HCO_3^-, albumin (ALB) and prealbumin (PA) were significantly lower in the EES group than in the euthyroid group (p <0.05).

Table 1. Baseline clinical and laboratory characteristics in DKA/DK children

Variables	Thyroid function Euthyroidism	ESS	Z/T/χ^2	P
Gender (male/female)	50/38	59/47	0.03	0.871
Age (years)	7.16±4.24	7.42±4.27	0.416	0.678
BMI (kg/m^2)	16.93±3.19	15.80±3.07	-1.589	0.116
WBC (×10^9/L)	7.25 (6.15~9.82)	10.72 (7.82~16.9)	-5.316	<0.001*
PG (mmol/L)	19.13 (14.97~27.8)	21.77 (16.89~29.46)	-3.222	0.001*
BUN (mmol/L)	5.35 (4.48~6.35)	4.95 (3.93~6.75)	-0.372	0.71
Cr (umol/L)	31.3 (23.55~48.63)	34.05 (25.15~45.64)	-0.765	0.444
β-HB (mmol/L)	2.92 (1.61~5.22)	6.52 (4.28~8.46)	-7.375	<0.001*
K$^+$ (mmol/L)	4.25 (3.8~4.6)	4.2 (3.5~4.63)	-1.403	0.161
Na$^+$ (mmol/L)	133.42±4.72	131.02±5.28	3.309	0.001*
Corrected Na$^+$（mmol/L）	139（137.2~141.7）	138.6（134~140.6）	-1.405	0.16
Cl$^-$ (mmol/L)	99.3 (96~103)	101 (96~106.15)	-1.256	0.209
HCO3$^-$ (mmol/L)	19.15 (16.4~21.9)	9.55 (6.63~14.75)	-7.946	<0.001*
OSM (mOsm/L)	284.39 (279~289.03)	280.02 (272.05~286.49)	-0.978	0.328
AG (mmol/L)	19.2 (17.2~22.15)	22.97 (19.65~27.53)	-4.857	<0.001*
ALT (U/L)	14 (12~18.25)	14 (10~17.75)	-0.746	0.456
PA (mg/L)	123.93 (99.39~151)	93.88 (71.97~123.7)	-5.748	<0.001*
ALB (g/L)	39.76±4.58	37.58±5.53	2.809	0.006*
GLO (g/L)	23.1（20.08~26.78）	22.4 (19.3~25.95)	-1.594	0.111
TC (mmol/L)	4.4（3.77~5.06）	4.14（3.67~5.24）	-0.267	0.789
HDL (mmol/L)	1.15（0.96~1.44）	1.13（0.94~1.36）	-0.769	0.442
LDL (mmol/L)	2.51（2.06~2.99）	2.54（1.94~3.11）	-0.594	0.553
TG (mmol/L)	0.97（0.69~1.31）	1.34（0.91~2.19）	-3.724	<0.001*
HbA1c (%)	11.42±2.49	12.62±2.15	-3.593	<0.001*
C-p (ng/ml)	0.19（0.09~0.46）	0.19（0~0.34）	-1.294	0.196

Notes: β-HB, beta-hydroxybutyric acid; ALB, albumin; GLO, globulin; HbA1c, glycosylated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; OSM, osmolarity; AG, anion gap; PA, prealbumin; PG, plasma glucose; TC, total cholesterol; TG, triglyceride; WBC, white blood cell count; BMI, body mass index; BUN, serum urea nitrogen; Cr, creatinine; ALT, alanine aminotransferase; C-p, C-peptide

*P＜0.05 ESS vs. Euthyroidism

3.2 Correlation and multiple linear regression analysis:

3.2.1 Correlating and independent influencing factors of FT3: FT3 levels positively correlated with levels of serum corrected Na^+, HCO_3^-, PA, K^+, ALB, GLO, and HDL but negatively correlated with WBC, PG, β-HB, AG, TG, and HbA1c. There was no significant correlation between levels of FT3 and BUN, Cr, Cl^-, OSM, ALT, TC, LDL, and C-p (P>0.05, data not shown). Variables showing significant correlation were subjected to multivariate linear regression analysis, which showed that β-HB, HCO3$^-$, AG, PA, and HbA1c independently affected FT3 levels (Table 2). The correlations between these independent variables and FT3 were shown in the scatter plot on Figure 1 (r=-0.642, 0.681, -0.377, 0.581, -0.309, respectively; P＜0.01)

Table 2. Correlating factors of FT3 in DKA/DK children

Variables	B	SD	Beta	T	P
WBC	-0.016	0.011	-0.092	-1.417	0.159
PG	-0.001	0.01	-0.007	-0.122	0.903
β-HB	-0.151	0.048	-0.331	-3.116	0.002*
Corrected Na^+	-0.006	0.017	-0.02	-0.351	0.726
K^+	-0.013	0.102	-0.008	-0.128	0.898
$HCO3^-$	0.067	0.019	0.342	3.603	0.001*
AG	0.042	0.02	0.197	2.161	0.033*
PA	0.011	0.003	0.3	3.961	0.001*
ALB	0.02	0.02	0.076	1.04	0.3
GLO	-0.013	0.016	-0.049	-0.815	0.417
HDL	0.113	0.261	0.028	0.434	0.665
TG	-0.069	0.067	-0.064	-1.031	0.305
HbA1c	-0.07	0.034	-0.121	-2.082	0.039*

*P0.05

3.2.2 Correlating and independent influencing factors of FT4: FT4 levels positively correlated with serum levels of corrected Na^+, HCO_3^-, PA, ALB, GLO, and HDL but negatively correlated with WBC, PG, β-HB, AG, Cl^-, TG, and HbA1c. There was no significant correlation between FT4 levels and BUN, Cr, K^+, OSM, ALT, TC, LDL, and C-p (P>0.05, data not shown). Variables showing significant correlation were subjected to multivariate linear regression analysis, which showed that β-HB, $HCO3^-$, and ALB significantly affected FT4 levels (Table 3). The correlations between these variables and FT4 levels were shown in the scatter plot on Figure 2 (r=-0.489, 0.338, 0.529, respectively; P<0.01).

Table 3. Correlating factors of FT4 in DKA/DK children

Variables	B	SD	Beta	T	P
WBC	-0.009	0.045	-0.017	-0.199	0.843
PG	-0.003	0.039	0.007	0.086	0.931
β-HB	-0.434	0.196	-0.303	-2.216	0.028*
Corrected Na^+	0.095	0.077	0.103	1.237	0.218
$HCO3^-$	0.156	0.084	0.253	1.849	0.047*
AG	0.07	0.082	0.103	0.848	0.398
PA	0.013	0.011	0.119	1.219	0.225
TG	0.135	0.27	0.04	0.501	0.617
HbA1c	0.036	0.136	0.02	0.268	0.789
Cl^-	-0.07	0.039	-0.158	-1.782	0.077
ALB	0.164	0.078	0.193	2.093	0.038*
GLO	-0.026	0.064	-0.032	-0.413	0.681
HDL	1.338	1.053	0.107	1.271	0.206

*P0.05

3.2.3 Correlating and independent influencing factors of TSH: TSH showed positive correlation with levels of Corrected Na^+, HCO_3^-, OSM, TC, and LDL but negative correlation with WBC, β-HB, and BUN. There was no significant correlation between TSH and levels of PG, K^+, Cl^-, Cr, ALT, AG, PA, TG, HbA1c, ALB, GLO, HDL, and C-p (P>0.05), data not shown. Variables which showed significant correlation were subjected to multivariate linear regression analysis, which revealed that only serum HCO3- levels had an independent and significant effect on TSH levels (Table 4). The correlations between serum $HCO3^-$ and TSH levels are shown in the scatter plot on Figure 3 (r=-0.28, P<0.01).

Table 4. Correlating factors of TSH in DKA/DK children

Variables	B	SD	Beta	T	P
WBC	-0.009	0.018	-0.05	-0.495	0.621
β-HB	0.037	0.059	0.08	0.632	0.529
corrected Na^+	0.016	0.028	0.052	0.563	0.575
$HCO3^-$	0.071	0.025	0.362	2.834	0.005*
BUN	-0.025	0.052	-0.042	-0.493	0.623
OSM	0.005	0.005	0.079	0.876	0.383
TC	0.134	0.262	0.101	0.511	0.61
LDL	0.1	0.35	0.058	0.284	0.777

*P□0.05

3.3 Logistic regression of adjudicated thyroid function group with metabolic covariates□Logistic regression model analysis used the thyroid function subgroup (euthyroid or ESS group) as a non-parametric dependent variable and significantly correlated variables in Table 1 as parametric independent variables. As shown in Table 5, serum HCO_3^- levels were the only factor that independently and significantly associated with thyroid function group adjudication (OR=0.845, P=0.004, 95%CI=0.752-0.949).

Table 5. Logistic regression on the predictors of deranged thyroid function in DKA/DK patients

Variables	B	*p*-value	Wald	Adjusted p-value	OR	95% C.I. for OR	
						Inferior	Superior
WBC	0.127	0.062	4.227	0.050	1.136	1.006	1.283
PG	0	0.028	0	0.996	1	0.946	1.057
β-HB	0.14	0.145	0.937	0.333	1.15	0.866	1.558
$HCO3^-$	-0.168	0.059	8.072	0.004*	0.845	0.752	0.949
AG	-0.02	0.066	0.097	0.756	0.98	0.862	1.114
PA	-0.005	0.008	0.436	0.509	0.995	0.979	1.011
TG	0.227	0.267	0.723	0.395	1.255	0.743	2.119
HbA1c	0.179	0.115	2.401	0.121	1.196	0.954	1.499
ALB	-0.071	0.057	1.591	0.207	0.931	0.833	1.04

*P□0.05

4. Discussion

Few studies have focused on the interplay of metabolic disorders and deranged free thyroid hormone levels in DKA/DK children patients with ESS which was elucidated in the present work. The results unveiled a poorer glycemic control in those patients as evidenced by higher plasma glucose and glycosylated hemoglobin, who also showed a higher degree of acidosis indicated by higher levels of anion gap and β-HB, as well as a lower level of bicarbonate. Moreover, serum albumin and pre-albumin were reduced in ESS children patients.

Abnormal serum thyroid hormone levels have been well described in patients admitted with acute critical illness which are often associated with the severity of conditions[18,20-22]. The exact underlying causes had not yet been clarified although many hypothesis have been proposed[12,18,23,24]. In previous researches, FT3 and FT4 levels were positively correlated with bicarbonate levels and negatively correlated with HbA1c and AG levels [13]. In the present study, we apprised the role of more parameters including acute phase reactants and metabolic parameters in the specific situation. Linear regression analysis confirmed that β-HB and HCO_3^- levels had an independent influence on both FT4 and FT3 levels while serum pre-albumin and albumin levels related to only FT3 and only FT4 respectively. In addition, HCO_3^- was demonstrated as the only significantly independent influencing factor on TSH.

Previous studies have noticed the relationship between acidosis and free thyroid hormones levels [23,25]. Lower T4 and T3 and higher reverse T3 (rT3) serum concentrations were found in patients with metabolic acidosis[25]. Rashidi et al reported that the lower the pH in DKA patients, the lower the FT3 levels were [26]. pH may be the most important factor directly or indirectly affecting iodo-thyronine metabolism and its regulation *in vitro* and *in vivo*[25]. Our study results were consistent with these studies as we also found metabolic acidosis as reflected by serum bicarbonate levels being the most important factor correlated with parameters of thyroid function tests (i.e. FT3, FT4, and TSH). However, from the data obtained in the study, we still could not determine whether the ESS is a direct effect of pH or a more general effect of severity of DKA illness.

Many studies have suggested that blood β-HB can be used to rapidly and accurately diagnose DK/DKA in hyperglycemic patients[27,28]. Measurement of blood ketones has been recommended in national guidelines in UK for assessment of response to therapy and in tailoring insulin infusion rat{Dhatariya, 2017 #29}es[29]. {Dhatariya, 2017 #29}However, few studies have detected the relationship between β-HB and thyroid function. Boado et al found that β-HB may be capable of inducing a moderate depression of pituitary and plasma TSH in rats[30]. Our study showed a strong negative correlation between levels of β-HB and free thyroid hormone concentrations which may also be the consequence of TSH decline.

As to the underlying reasons for the low serum albumin or pre-albumin in DK/DKA with ESS patients, malnutrition might not be a key item, for there was no significant difference in BMI between ESS and euthyroidism groups in this study. The albumin synthesis in hepatocytes depends on the sufficient insulin secretion[31]. It has been demonstrated that the insulin deficiency led to diminished liver albumin

production while the insulin infusion in diabetic patients enhanced live albumin synthesis[32]. So the absolute lack of insulin in T1DM could account for the reduction of serum albumin and pre-albumin in the present study. Moreover, as the albumin deficiency arises with critical ill condition while the DKA/DK children patients tend to be in severe status, the diminished albumin in ESS as compared to euthyroidism might indicate the former are in an inferior situation and subject to more intensive treatment.

Children in the ESS group had a higher level of WBC and was negatively correlated with levels of FT3, FT4, and TSH in the current work. Elevated WBC has also been shown significantly correlated with severity of DKA and DK in other studies[33,34]. This phenomenon is most likely a leukemoid like reaction instead of a systemic inflammatory response as no fever or bacteria or virus infection evidence was present. Also, in both adult and pediatric DKA patients, the response to milieu interne changes including deranged hormones, cytokines and mediators actuates the elevation of white blood cell count[35].

We also found the lower serum sodium in ESS patients which when corrected by using blood glucose concentration showed no significant difference between the ESS and euthyroidism groups. So this could be a pseudohyponatremia due to the water being osmotically drawn into the vascular space in hyperglycemia. Although the low serum sodium concentration has been shown indicative of poor outcome or cerebral edema in DKA, the present study did not reveal the relationship of it with ESS.

Our study had several drawbacks as it was a retrospective study with a small number of participants. We did not measure the rT3 levels which are usually elevated in ESS patients and correlate ESS with recovery times and hospital stay duration as well as other parameters associated with DKA, such as venous thrombosis and cerebral edema.

Moreover, for the limitations on the detecting techniques, we did not apply equilibrium dialysis or ultrafiltration methods to measure the free thyroid hormones in serum of patients which might underestimate the concentration of FT3 or FT4. Although the setting of euthyroidism control compensated the weakness partly, the impact of methodology on the outcome might be inevitable.

5. Conclusions

Lower levels of free thyroid hormones were found to be associated with higher degree of acidosis and hence with the severity of DKA/DK.

Abbreviations

β-HB, beta-hydroxybutyric acid; ALB, albumin; DK, diabetic ketosis；DKA, diabetic ketoacidosis; ESS, euthyroid sick syndrome; GLO, globulin;HbA1c, glycosylated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; OSM, osmolarity; PA, prealbumin; PG, plasma glucose; TC, total cholesterol; TG, triglyceride; WBC, white blood cell count;

Declarations

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Authors' contributions: PS collected and analyzed the data, drafted the initial manuscript and reviewed the manuscript. GL conceptualized and designed the study, supervised the conduct of the study. SG helped to collect and analyzed the data, Daogang Qin, Sen Li and Ying Luan critically edited the manuscript. All authors gave their final approval of the version to be published.

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References

1. Weng J, Zhou Z, Guo L, Zhu D, Ji L, Luo X, Mu Y, Jia W (2018) Incidence of type 1 diabetes in China, 2010-13: population based study. Bmj 360:j5295. doi:10.1136/bmj.j5295
2. CDC (2017) National Diabetes Statistics Report. Centers for disease control and preventoin, U.S. Dept of Health and Human Services, Atlanta
3. Rodacki M, Pereira JR, Nabuco de Oliveira AM, Barone B, Mac Dowell R, Perricelli P, Bravo MT, de Oliveira MM, Brum JD, Belem LC, de Ornellas PG, Berardo RS, Luescher J, Campos L, Vangelotti Ade M, Kupfer R, Zajdenverg L, Milech A, Paulo de Oliveira JE (2007) Ethnicity and young age influence the frequency of diabetic ketoacidosis at the onset of type 1 diabetes. Diabetes Res Clin Pract 78 (2):259-262. doi:10.1016/j.diabres.2007.04.002
4. Meuwese CL, Carrero JJ, Cabezas-Rodríguez I, Heimburger O, Barany P, Lindholm B, Qureshi AR, Ripsweden J, Dekker FW, Stenvinkel P (2013) Nonthyroidal illness: a risk factor for coronary

calcification and arterial stiffness in patients undergoing peritoneal dialysis? J Intern Med 274 (6):584-593. doi:10.1111/joim.12107

5. Girvent M, Maestro S, Hernández R, Carajol I, Monné J, Sancho JJ, Gubern JM, Sitges-Serra A (1998) Euthyroid sick syndrome, associated endocrine abnormalities, and outcome in elderly patients undergoing emergency operation. Surgery 123 (5):560-567
6. Yildizdaş D, Onenli-Mungan N, Yapicioğlu H, Topaloğlu AK, Sertdemir Y, Yüksel B (2004) Thyroid hormone levels and their relationship to survival in children with bacterial sepsis and septic shock. J Pediatr Endocrinol Metab 17 (10):1435-1442
7. Su W, Zhao XQ, Wang M, Chen H, Li HW (2018) Low T3 syndrome improves risk prediction of in-hospital cardiovascular death in patients with acute myocardial infarction. J Cardiol 72 (3):215-219. doi:10.1016/j.jjcc.2018.02.013
8. Wang YF, Heng JF, Yan J, Dong L (2018) Relationship between disease severity and thyroid function in Chinese patients with euthyroid sick syndrome. Medicine (Baltimore) 97 (31):e11756. doi:10.1097/MD.0000000000011756
9. Ogbonna SU, Ezeani IU, Okafor CI, Chinenye S (2019) Association between glycemic status and thyroid dysfunction in patients with type 2 diabetes mellitus. Diabetes Metab Syndr Obes 12:1113-1122. doi:10.2147/DMSO.S204836
10. Tahirović H, Dućić V, Smajić A (1991) Euthyroid sick syndrome in type I diabetes mellitus in children and adolescents. Acta paediatrica Hungarica 31 (1):67-73
11. Joseph J, Saroha V, Payne H, Paul P, Didi M, Isherwood D, Blair J (2011) Thyroid function at diagnosis of type I diabetes. Archives of disease in childhood 96 (8):777-779. doi:10.1136/adc.2009.168799
12. Warner MH, Beckett GJ (2010) Mechanisms behind the non-thyroidal illness syndrome: an update. J Endocrinol 205 (1):1-13. doi:10.1677/joe-09-0412
13. Hu YY, Li GM, Wang W (2015) Euthyroid sick syndrome in children with diabetic ketoacidosis. Saudi Med J 36 (2):243-247. doi:10.15537/smj.2015.2.10304
14. American Diabetes A (2014) Diagnosis and classification of diabetes mellitus. Diabetes Care 37 Suppl 1:S81-90. doi:10.2337/dc14-S081
15. Mayer-Davis EJ, Kahkoska AR, Jefferies C, Dabelea D, Balde N, Gong CX, Aschner P, Craig ME (2018) ISPAD Clinical Practice Consensus Guidelines 2018: Definition, epidemiology, and classification of diabetes in children and adolescents. Pediatric Diabetes 19:7-19. doi:10.1111/pedi.12773
16. Basetty S, Yeshvanth Kumar GS, Shalini M, Angeline RP, David KV, Abraham S (2017) Management of diabetic ketosis and ketoacidosis with intramuscular regular insulin in a low-resource family medicine setting. J Family Med Prim Care 6 (1):25-28. doi:10.4103/2249-4863.214992
17. Vale C, Neves JS, von Hafe M, Borges-Canha M, Leite-Moreira A (2019) The Role of Thyroid Hormones in Heart Failure. Cardiovasc Drugs Ther 33 (2):179-188. doi:10.1007/s10557-019-06870-4
18. Lee S, Farwell AP (2016) Euthyroid Sick Syndrome. Compr Physiol 6 (2):1071-1080. doi:10.1002/cphy.c150017

19. Hursh BE, Ronsley R, Islam N, Mammen C, Panagiotopoulos C (2017) Acute Kidney Injury in Children With Type 1 Diabetes Hospitalized for Diabetic Ketoacidosis. JAMA Pediatr 171 (5):e170020. doi:10.1001/jamapediatrics.2017.0020
20. Fliers E, Bianco AC, Langouche L, Boelen A (2015) Thyroid function in critically ill patients. Lancet Diabetes Endocrinol 3 (10):816-825. doi:10.1016/s2213-8587(15)00225-9
21. Van den Berghe G (2014) Non-thyroidal illness in the ICU: a syndrome with different faces. Thyroid 24 (10):1456-1465. doi:10.1089/thy.2014.0201
22. von Saint Andre-von Arnim A, Farris R, Roberts JS, Yanay O, Brogan TV, Zimmerman JJ (2013) Common Endocrine Issues in the Pediatric Intensive Care Unit. Critical Care Clinics 29 (2):335-358. doi:10.1016/j.ccc.2012.11.006
23. Mirboluk AA, Rohani F, Asadi R, Eslamian MR (2017) Thyroid function test in diabetic ketoacidosis. Diabetes Metab Syndr 11 Suppl 2:S623-S625. doi:10.1016/j.dsx.2017.04.015
24. Maiden MJ, Torpy DJ (2019) Thyroid Hormones in Critical Illness. Crit Care Clin 35 (2):375-388. doi:10.1016/j.ccc.2018.11.012
25. Tahirovic HF (1991) Thyroid hormones changes in infants and children with metabolic acidosis. J Endocrinol Invest 14 (9):723-726. doi:10.1007/BF03347903
26. Rashidi H, Ghaderian SB, Latifi SM, Hoseini F (2017) Impact of diabetic ketoacidosis on thyroid function tests in type 1 diabetes mellitus patients. Diabetes Metab Syndr 11 Suppl 1:S57-S59. doi:10.1016/j.dsx.2016.12.001
27. Misra S, Oliver NS (2015) Utility of ketone measurement in the prevention, diagnosis and management of diabetic ketoacidosis. Diabetic medicine : a journal of the British Diabetic Association 32 (1):14-23. doi:10.1111/dme.12604
28. Dhatariya K (2016) Blood Ketones: Measurement, Interpretation, Limitations, and Utility in the Management of Diabetic Ketoacidosis. Rev Diabet Stud 13 (4):217-225. doi:10.1900/RDS.2016.13.217
29. Dhatariya KK, Umpierrez GE (2017) Guidelines for management of diabetic ketoacidosis: time to revise? Lancet Diabetes Endocrinol 5 (5):321-323. doi:10.1016/S2213-8587(17)30093-1
30. Boado R, Colombo O, Zaninovich AA (1985) Effects of diabetes, beta-hydroxybutyric acid and metabolic acidosis on the pituitary-thyroid axis in the rat. J Endocrinol Invest 8 (2):107-111. doi:10.1007/bf03350658
31. Cheng P-C, Hsu S-R, Cheng Y-C (2016) Association between Serum Albumin Concentration and Ketosis Risk in Hospitalized Individuals with Type 2 Diabetes Mellitus. Journal of Diabetes Research 2016:1-5. doi:10.1155/2016/1269706
32. De Feo P, Gaisano MG, Haymond MW (1991) Differential effects of insulin deficiency on albumin and fibrinogen synthesis in humans. J Clin Invest 88 (3):833-840
33. Xu W, Wu HF, Ma SG, Bai F, Hu W, Jin Y, Liu H (2013) Correlation between peripheral white blood cell counts and hyperglycemic emergencies. Int J Med Sci 10 (6):758-765. doi:10.7150/ijms.6155

34. Karavanaki K, Kakleas K, Georga S, Bartzeliotou A, Mavropoulos G, Tsouvalas M, Vogiatzi A, Papassotiriou I, Karayianni C (2012) Plasma high sensitivity C-reactive protein and its relationship with cytokine levels in children with newly diagnosed type 1 diabetes and ketoacidosis. Clin Biochem 45 (16-17):1383-1388. doi:10.1016/j.clinbiochem.2012.05.003
35. Gonzalez LK, Malhotra S, Levine M, Jacobson-Dickman E (2017) Leukemoid Reaction in a Pediatric Patient With Diabetic Ketoacidosis. Pediatr Emerg Care 33 (8):e27-e29. doi:10.1097/PEC.0000000000000558

Figures

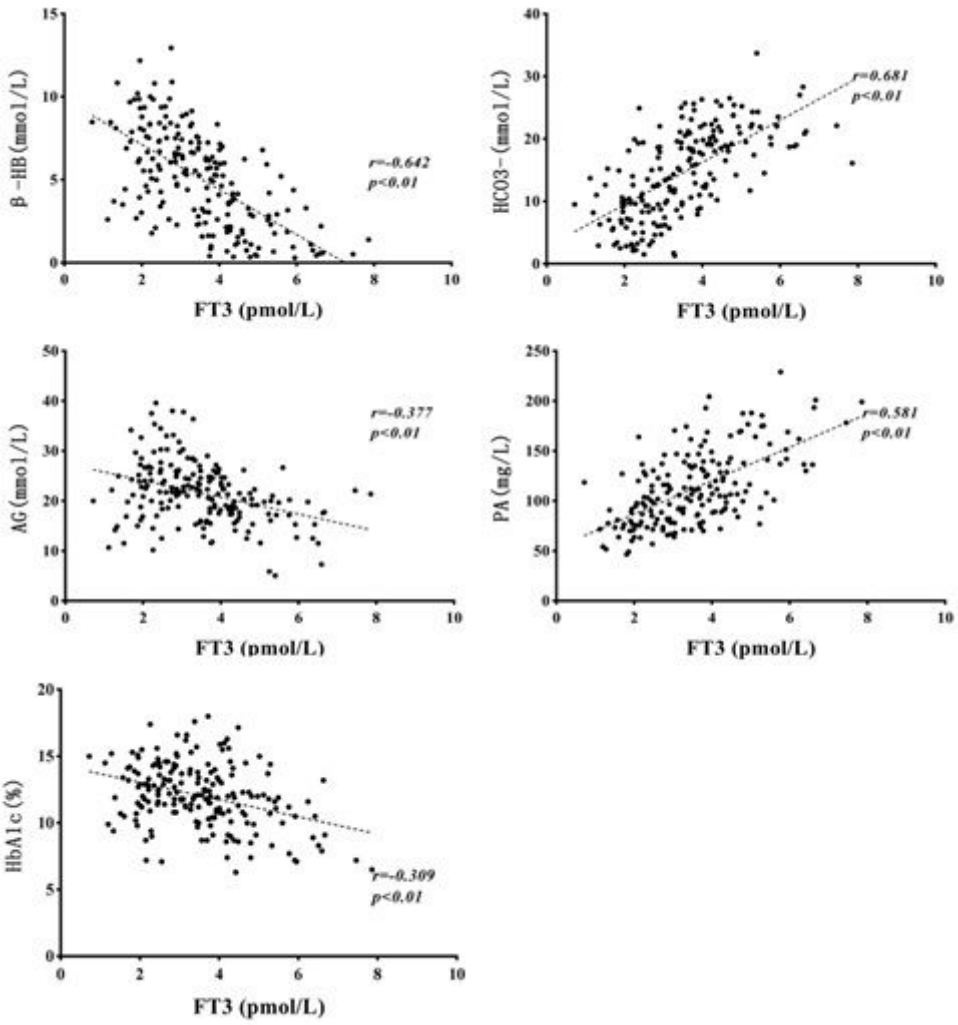

Figure 1

Correlations between FT3 and β-HB, HCO3-, AG, PA, HbA1c

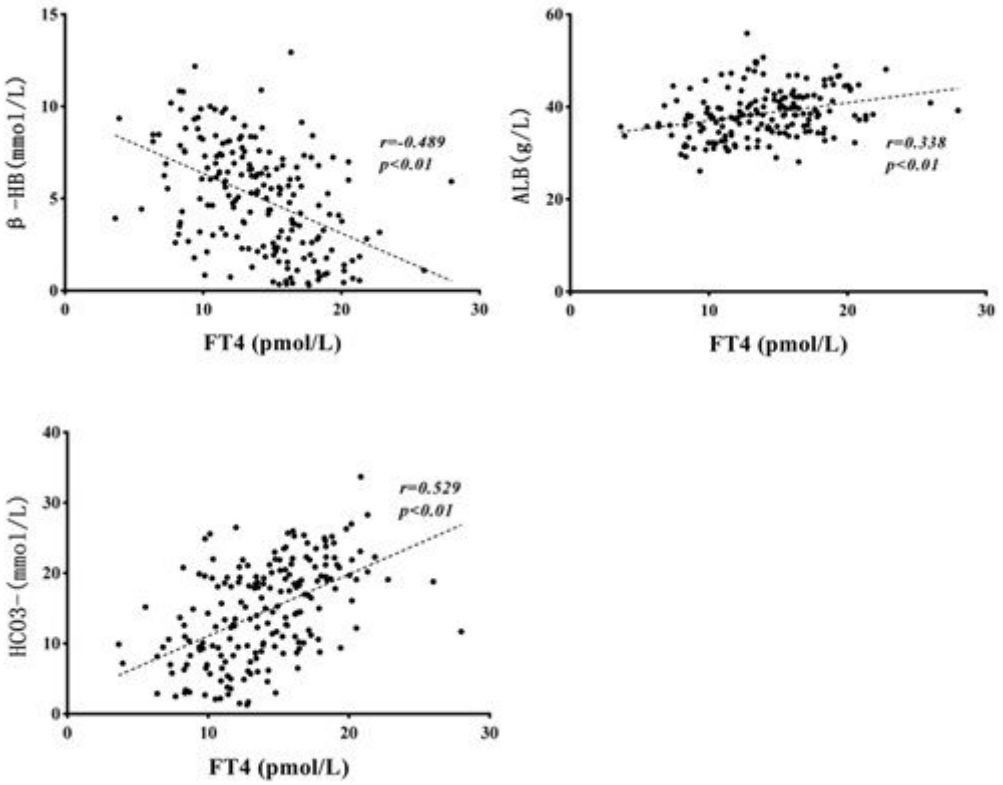

Figure 2

The correlations between FT4 and β-HB, HCO3-, ALB

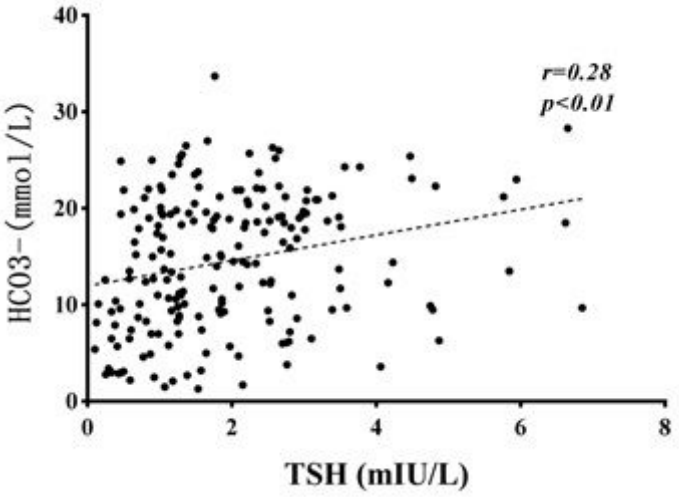

Figure 3

The correlations between TSH and HCO3-