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ORIGINAL ARTICLE

Factors associated with thyroid dysfunction in children with newly diagnosed type 1 diabetes mellitus

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ABSTRACT

BACKGROUND: This study aimed to investigate the possible factors associated with thyroid dysfunction (TD) in children with type 1 diabetes mellitus (T1DM).

METHODS: Eighty-seven children with T1DM were evaluated in terms of their clinical profile as well as tested for pancreatic and thyroid antibodies. Thyroid function was tested at baseline and 10 days after treatment onset.

RESULTS: Thyroid dysfunction was present in 13 (14.9%) patients after correction of acute metabolic disorders. The prevalence of subclinical hypothyroidism (10.3%) was found to be higher than that of clinical hypothyroidism (3.4%) and clinical hyperthyroidism (1.2%). Both pancreatic and thyroid antibody were detected positive in TD patients, which was significantly different from that with euthyroidism ($P<0.01$, $P<0.05$). The frequency of TD family history was significantly higher in subjects with TD rather than with euthyroidism ($P<0.01$). The levels of free and total triiodothyronine, free and total thyroxine were in the hypothyroid range at the time of admission, all of which increased to normal range after 10 days of therapy in 32 DKA children ($P=0.02$ and $P<0.01$). There was a significant correlation between pH and free triiodothyronine levels ($P<0.05$).

CONCLUSIONS: TD is related to family factors, autoimmunity, and acute metabolic stress in the T1DM and regular thyroid screening should be performed.

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KEY WORDS: Child; Diabetes mellitus; Autoimmunity.

A high prevalence of thyroid dysfunction (TD), ranging from 6.6% to 14.7% among different populations, has been reported in patients with type 1 diabetes mellitus (T1DM).[1] Findings from the population-based cohort study on Taiwanese children and adolescents showed that the incidence of simple and unspecified goiter, thyrotoxicosis, unspecified hypothyroidism, and thyroiditis were significantly higher in the type 1 diabetes group compared with the control group – with incidence rate ratios of 2.74, 6.95, 6.54, 16.07, respectively.[2] TD includes clinical hypothyroidism (C-Hypo), subclinical hypothyroidism (SC-Hypo), clinical hyperthyroidism (C-Hyper), and subclinical hyperthyroidism (SC-Hyper).[3] Although a few independent factors impacting thyroid function such as autoimmune thyroid disease, severe stress conditions, and hyperlipidemia have been reported in diabetic patients, the most prevalent change in thyroid function has been found in diabetic patients with autoimmune thyroid disease or dyslipidemia.[4-6] It is inferred that T1DM and autoimmune lymphocytic thyroiditis are based on a common genetic origin with similar pathogenicity, which are the results of T lymphocyte infiltration into target or-

gans leading to organ dysfunction.[7] TD has been associated with growth and puberty disorders in children ranging from short stature, precocious puberty, and hypogonadism to anemia.[8-10] Previous studies have described the prevalence and characteristics of TD in European and Indian with T1DM, however, little is known about thyroid conditions in Chinese children and adolescents with T1DM. The aim of this study was to investigate the frequency of TD and its possible independent risk factors in Han Chinese children and adolescents with T1DM.

Materials and methods

Subjects

This is a retrospective analysis to evaluate the prevalence and possible risk factors of TD in T1DM children attending the pediatric endocrine clinic from January 2011 to June 2017 at the Affiliated Hospital of Nantong University in Nantong, China. 87 subjects with a diagnosis of T1DM according to the International Society for Pediatric and Adolescents Diabetes definitions were enrolled into the study.[11] Children with diabetes classified as other than T1DM and those who did not have available clinical data or laboratory tests for thyroid function and antibody measurements were excluded. Subjects who had systemic illnesses or were receiving any drugs that could interfere with thyroid function or autoantibody tests were excluded. The research has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the Affiliated Hospital of Nantong University Ethics Board. Informed consent was obtained from all individuals included in this study.

Clinical and biochemical information that was collected included demographics, family history of thyroid disease and diabetes, and laboratory test results. TD was classified as follows according to the levels of thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), total triiodothyronine (TT3), and total thyroxine (TT4): C-hypo (increased TSH with decreased FT4 or TT4), C-Hyper (decreased TSH with increased FT4, FT3, TT3, or TT4), SC-Hypo (increased TSH without decreased FT4 or TT4), SC-Hyper (decreased TSH without increased FT4, FT3, TT3, or TT4). Diabetic ketoacidosis (DKA) was defined as blood glucose >11.1 mmol/L, pH<7.3 or HCO_3<15mmol/L with ketonemia or ketonuria.

Laboratory tests

Laboratory tests included those for arterial pH, HbA1c, blood and urine ketones, and serum glutamic acid decarboxylase antibodies (GADA), insulin autoantibodies (IAA), islet cell autoantibodies (ICA), thyroglobulin (TG) antibodies, thyroid peroxidase (TPO) antibodies, thyroid stimulating hormone receptor (TSHR) antibodies, FT4, FT3, TT3, TT4, and TSH. Blood samples were obtained within 1 week of onset of diabetes for IAA, GADA, and ICA and thyroid antibodies. Thyroid function was tested at baseline and 10 days after treatment onset. All blood samples were obtained and sent to the laboratory for subsequent processing within 2 hours. FT4, FT3, TT3, and TT4 were measured by chemiluminescence (Abbott AxSYM, Abbott Laboratories; Abbott Park, IL, USA). The reference values were as follows based on the standard of children and adolescents in the east of China: (1-5 years): TSH 0.63-6.20 μIU/mL, FT3 3.54-6.90 pmol/L, FT4 9.32-18.40 pmol/L, TT3 1.33-3.49 nmol/L, TT4 66.88-156.4 nmol/L; (5-10 years): TSH 0.58-5.39 μIU/mL, FT3 3.97-7.83 pmol/L, FT4 10.65-19.23 pmol/L, TT3 1.04-3.24 nmol/L, TT4 66.88-156.4 nmol/L; (10-14 yr):TSH 0.39-5.36 μIU/mL, FT3 4.27-8.55 pmol/L, FT4 9.80-19.64 pmol/L, TT3 1.04-3.24 nmol/L, TT4 66.88-156.4 nmol/L; (14-17 yr):TSH 0.48-5.06 μIU/mL, FT3 3.14-6.15 pmol/L, FT4 9.57-18.27 pmol/L, TT3 1.54-2.74 nmol/L, TT4 78.38-157.4 nmol/L. TPO antibody, TG antibody, and TSHR antibody were measured using a chemiluminescence immunoassay (DPC Immulite, Siemens Healthineers; Erlangen, Germany). GADA, IAA, and ICA were assessed by a radioimmunoassay kit (RSR Ltd., Cardiff, UK).

Statistical analysis

SPSS v. 20.0 (IBM; Armonk, NY, USA) was used for data analysis. For continuous variables, the independent-samples *t*-test and paired- samples *t*-test were used. Fisher's Exact test and χ^2

test were used for proportions. To evaluate the relationship of pH and HbA1C on thyroid hormone levels, Pearson correlation analysis was conducted. Data are expressed as mean±standard deviation or proportion (%). P value <0.05 was considered statistically significant.

Results

Clinical features and frequency of TD in children with T1DM

Overall 87 patients (M:F, 47:40) with T1DM were included in the study. All patients were Han Chinese. The age at onset of diabetes was 8.52±3.58 years and Body Mass Index (kg/m^2) was 16.58±2.01. The percent of DKA and hemoglobin A1C at diagnosis were 36.8% and 12.52±2.71, respectively. In the total study population (N.=87), after the correction of acute metabolic disorders, the prevalence of C-Hypo was 3 (3.4%), C-Hyper was 1 (1.2%), and that of SC-Hypo was 9 (10.3%) (Table I).

Autoimmune and genetic characteristics

For euthyroidism group with T1DM, 35 (47.3%) subjects had positive thyroid antibodies, and 52 (70.3%) tested positive for pancreatic antibodies; however, thirteen (14.9%) patients were diagnosed with TD during the clinical evaluation with both positive thyroid and pancreatic antibodies, which was significantly different from the euthyroidism group (P<0.01, P<0.05). Moreover, of the 13 TD subjects, nine patients had TD family history, which was significantly different from those with euthyroidism (P<0.01) (Table II).

TABLE I.—*The clinical features and frequency of thyroid dysfunction in T1DM children.*

Clinical features and thyroid function	T1DM (N.=87)
Age at onset (yr)	8.52±3.58
Gender(male/female)	47/40
BMI (kg/m^2)	16.58±2.01
DKA at diagnosis	32 (36.8%)
HbA1c	12.52±2.71
C-Hypo	3 (3.4%)
SC-Hypo	9 (10.3%)
C-Hyper	1 (1.2%)
SC-Hyper	0
Euthyrodism	74 (85.1%)

Age at onset is described as mean±standard deviation: the other data are present as N. (%). The prevalence of TD in the table were the data after correction of acute metabolic disorders.
T1DM: type 1 diabetes mellitus; C-Hypo: clinical hypothyroidism; SC-Hypo: subclinical hypothyroidism; C-Hyper: clinical hyperthyroidism; SC-hyper: subclinical hyperthyroidism.

TABLE II.—*The autoimmunity and genetic characteristic in T1DM: (N.=87).*

Parameters		Euthyroidism	TD	P value
Thyroid antibody	++	35	13	<0.01
	-_	39	0	
Pancreatic antibody	++	52	13	0.03
	-_	22	0	
TD family history	++	2	9	<0.01
	-_	72	4	

Data are presented as n. P<0.05 was statistic significant.
+: at least one antibody positive; -: all the antibodies are negative.
TD: Thyroid disfunction.

Prevalence of thyroid and pancreatic antibodies in T1DM

Positive IAA antibodies were detected in 8 (9.2%) subjects, while ICA was present in 9 (10.3%) subjects, 36 (41.4%) patients showed positivity of both IAA and ICA antibodies, and 2 (2.3%) patients presented positivity of both GADA and ICA antibodies. The presence of all three antibodies (IAA, ICA and GAD) was found in 10 (11.5%) subjects. In the T1DM group, TPO antibodies were positive in 14 (16.1%) subjects, and TG antibodies were detected in 22 (25.3%) patients. Twelve (13.8%) patients showed positivity of both TPO and TG antibodies. The prevalence of antibodies is shown in Table III.

Changes in thyroid function in T1DM children with DKA

The prevalence of TD in all DKA patients was 14 (43.8%). The levels of FT3 (3.51±0.89 pmol/L), TT3 (0.89±0.53 nmol/L), FT4 (9.60±2.41 pmol/L), and TT4 (59.49±17.50nmol/L) were in the hypothyroid range at the time of admission and increased to the normal range after 10 days of therapy in 32 DKA children (P<0.05). The levels of TSH were in the normal range at the time of admission and after treatment (P=0.88) (Table IV). Moreover, there was a significant relationship between pH and FT3 levels (P<0.05) (Table V). However, there was no relationship between FT3, FT4, TSH levels and HbA1c (P>0.05).

TABLE III.—*Prevalence of thyroid and pancreatic antibody in T1DM children.*

Pancreatic antibody	T1DM (N.=87)	Thyroid antibody	T1DM (N.=87)
GADA	0	TPO	14 (16.1%)
IAA	8 (9.2%)	TG	22 (25.3%)
ICA	9 (10.3%)	TSHR	0
GADA+IAA	0	TPO+TG	12 (13.8%)
IAA+ICA	36 (41.4%)	TPO+TSHR	0
GADA+ICA	2 (2.3%)	TG+TSHR	0
GADA+IAA+ICA	10 (11.5%)	TPO+TG+TSHR	0
Negative	22 (25.3%)	Negative	39 (44.8%)

Data are presented as N. (%).
GADA: glutamic acid decarboxylase antibody; IAA: insulin autoantibody; ICA: islet cell autoantibody; TG: thyroglobulin; TPO: thyroid peroxidase; TSHR: thyroid stimulating hormone receptor antibody.

TABLE IV.—*The change of thyroid function in T1DM with DKA: (N.=32) (x±S).*

Parameters	FT3 (pmol/L)	FT4 (pmol/L)	TT3 (nmol/L)	TT4 (nmol/L)	TSH (mIU/L)
DKA onset	3.51±0.89	9.60±2.41	0.89±0.53	59.49±17.50	1.88±1.12
10 days after treatment	4.71±0.60	10.83±2.85	1.93±0.46	91.76±10.62	1.91±0.92
t value	6.92	2.45	9.88	7.54	0.15
P value	<0.01	0.02	<0.01	<0.01	0.88

P<0.05 was statistically significant.
TSH: thyroid-stimulating hormone; FT3: free triiodothyronine; FT4: free thyroxine; TT4: total thyroxine; TT3: total triiodothyronine.

TABLE V.—*Relationship of thyroid hormone with pH and HbA1c in T1DM with DKA: (N.=32).*

Parameters		FT3	FT4	TSH
pH	*r*	0.56	0.29	-0.15
	P value	0.001	0.09	0.42
HbA1c	*r*	-0.34	0.05	0.19
	P value	0.06	0.77	0.28

P<0.05 was statistically significant.

Discussion

The incidence of T1DM in children and adolescents is rising in many countries.[12] In China, the quoted prevalence of T1DM in children reached mean annual increase of 14.2% per year during 1997-2011.[13] T1DM is an autoimmune disease that is frequently associated with other autoimmune disorders,[14] and TD is commonly reported in patients with T1DM.[1, 15] Our study demonstrated that TD has a prevalence of 14.9% among T1DM patients after the correction of acute metabolic disorders. The most frequent dysfunction was SC-Hypo, with a prevalence of 10.3% in T1DM patients. At the same time, we observed a frequency of 3.4% for C-Hypo and 1.2% for C-Hyper, observations which are similar to previous studies.[1]

T1DM as a component of Poly glandular Autoimmune Syndrome can also result in thyroiditis. Epidemiological evidence suggests a common genetic background for both thyroid disease and T1DM. There is evidence suggesting that autoimmune thyroid disease and T1DM, both organ specific T-cell-mediated diseases, share a strong genetic susceptibility as they frequently occur in the same individuals and in the same families.[16-19] In our study, we observed both pancreas and thyroid antibodies in TD patients with T1DM. The prevalence of pancreatic antibodies in children with T1DM was 9.2% for IAA, 10.3% for ICA, 41.4% for IAA/ICA, 2.3% for GADA/ICA, and 11.5% for GADA/IAA/ICA at onset. A study from Korea showed that 87.7% of T1DM patients had at least one pancreatic antibody (GADA, 4.0%; ICA, 20.5%; IAA, 24.7%).[15]

TD and autoimmunity seem to be common not only in patients with T1DM but also in their first-degree relatives.[20] In the analysis of T1DM patients, 12.6% of patients were found to harbor a positive TD family history.

Thyroid function disorders are also associated with acute diabetes complications including DKA and hypoglycemia. At onset, thyroid hormone is not influenced by thyroid autoimmunity but by metabolic derangement.[21, 22] Previous research reported that girls had a higher frequency of DKA

as compared with boys.[23] A recent study reported that hypothyroidism was detected in 9.6% of children with T1DM and was associated with higher rates of DKA and younger age at initial diagnosis.[24] During DKA, TT3 and FT3 decreased more than the other parameters that were assessed. We observed the levels of FT3, TT3, FT4 and TT4 were in the hypothyroid range at the time of admission, and all rose to the normal range just after treatment in DKA children. Serum thyroid hormone level is influenced by the degree of metabolic control and the severity of acidosis which is the main factor to decrease the level of thyroid hormones such as FT3 and T3.[25, 26]

Limitations of the study

The limitation of the present study is that ZnT8 and IA-2 antibodies were not tested.

The prevalence of TD increases with the presence of thyroid autoantibodies. Thyroid function disorders are characterized by the presence of antibodies such as TPO, TG, and TSHR. TPO antibodies are the most common antibodies associated with TD. The prevalence of thyroid autoantibodies in children with T1DM varies widely, from 3% to 50% in different studies.[27, 28] In our study, TG, TPO, and TPO/TG antibodies were identified in 25.3%, 16.1% and 13.8% of T1DM patients, respectively. TPO and TG antibodies can be detected before changes in thyroid hormone levels occur; consequently, detection of these antibodies might be useful for early diagnosis of thyroid disease before clinical TD happens.

Conclusions

In conclusion, the results of this study show a high prevalence of TD in the T1DM population. TD is related to family factors, autoimmunity, and acute metabolic stress. Thus, regular thyroid screening among children and adolescents with diabetes should be routinely performed.

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