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Original article

Prevalence of β-cell antibodies and associated autoimmune diseases in children and adolescents with type 1 diabetes (T1DM) versus type 2 diabetes (T2DM) in Qatar

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Summary. *Introduction:* Type 1 diabetes mellitus (T1DM) is an autoimmune disease with the development of abnormal immune responses to specific β-cell autoantigens in addition to other organ-specific autoimmunity. The most frequent associated disorders are thyroid dysfunctions and celiac disease. There are limited studies in the current literature on the prevalence of associated autoimmunity, especially multiple, in children and adolescents with T1DM and Type 2 diabetes mellitus (T2DM). *Objectives:* The aim of the present study was to determine the prevalence of autoantibodies and thyroid dysfunctions in a cohort of children and adolescents (aged 0.5-16 years) with T1DM living in Qatar. *Research design and methods:* The records of all children and adolescents attending the Pediatric Diabetes Center of Hamad Medical Center, for the past 5 years (from January 2012 to December 2016), were reviewed and all clinical and biochemical data, including β-cell autoimmunity [anti-glutamic acid decarboxylase (GAD) antibodies, anti-islet cell and anti-insulin antibodies (IAA)], thyroid function (Free thyroxine: FT4 and thyroid-stimulating hormone: TSH), anti-thyroid peroxidase antibodies (TPO) and anti-tissue transglutaminase (ATT) were collected at their first presentation (cross-sectional study). Data for patients with T1DM (n=431) and T2DM (n=59) were recorded analyzed and the prevalence calculated and compared with other studies. *Results:* The prevalence of anti-GAD antibodies was 75.5 % in T1DM and 29.3% in T2DM. Anti β-islet antibodies (Ab) were detected in 53.4% of T1DM and 29.4% of T2DM. Anti-insulin Ab were detected in 40.4% of T1DM and 58.3% of T2DM. The three antibodies together were detected in 18.4 % of T1DM and none of T2DM. At presentation, hypothyroidism (FT4 <11.5 pmol/L) was detected in 10.6% of T1DM and 10% of T2DM. Subclinical hypothyroidism was diagnosed in 3.5% of T1DM and 8% of T2DM. High anti TPO was detected in 27.2% of T1DM and 34.6% of T2DM. High TPO with normal thyroid function were found in 22.7% of T1DM and 23.1% of T2DM. ATT IgA was high in 5% of T1DM and 8.7% of T2DM whereas ATT IgG was high in 4.4 % of T1DM and not detected in any patient with T2DM. Mucosal biopsy proved celiac disease in 9 out of 12 patients (75%) with positive ATT IgA and IgG antibodies. *Conclusions:* Qatar has a relatively high incidence of T1DM compared to incidences reported worldwide. We report a high prevalence of associated autoimmune abnormalities in our patients with T1DM and T2DM. These data strengthen the argument for routine screening of all children and adolescents with T1DM and T2DM for other autoimmune disorders, particularly the thyroid gland. (www.actabiomedica.it)

Key words: type 1 diabetes mellitus, type 2 diabetes, children, adolescents, autoimmune diseases, Qatar

Introduction

Diabetes is the most common chronic metabolic disease diagnosed in children and adolescents. Type 1 diabetes mellitus (T1DM) is associated with the autoimmune process of pancreatic β-cell destruction, which leads to absolute insulin deficiency and organ damage. Complex interactions between environmental and genetic factors contribute to the development of T1DM in genetically predisposed patients. The T1DM-inducing autoimmune process can also affect other organs, resulting in development of additional autoimmune diseases in the patient. The most common T1DM comorbidities include autoimmune thyroid diseases and celiac disease (1-6). Autoimmune thyroid disease is well recognized in children and adolescents with T1DM with difference prevalence rates and leading to subclinical hypothyroidism and overt hypothyroidism. However, the prevalence of thyroid autoimmunity differs considerably between 3 and 50% in different countries (1-7).

In adults, thyroid diseases occur more common in type 2 diabetes mellitus (T2DM) than expected. In a large cohort study, 27.3% of T2DM patients had a thyroid disorder with more women being affected. However, the prevalence of thyroid disorders in children and adolescents with T2DM has not fully evaluated (8-10).

The incidence of T1DM and T2DM has shown a rise in Qatar and worldwide. Generally, most cases of diabetes mellitus (DM) are classified as either type 1 DM or type 2 DM based on their pathophysiologic features. However, there is a notable increase in the incidence of a new expression of the disease in children and adolescents, with the characteristics of a mixture of the two types of diabetes and referred to as 'double diabetes'. Insulin resistance and obesity, together with the presence of markers of pancreatic autoimmunity - namely, autoantibodies to islet cell antigens - typically define this condition (5). This hybrid form of diabetes appears to be increasing and thus there has been keen attention among researchers about this unclear condition (11-14). In Qatar, the prevalence of this form of diabetes has not yet been assessed.

Aim of the Study

The aim of this study was to determine the prevalence of autoantibodies and thyroid

dysfunctions in a large cohort of children with T1DM and T2DM attending the Diabetes Centre of Hamad General Hospital (HMC), Doha (Qatar).

Research design and methods

We determined in a retrospective cross-sectional study the prevalence of β-cell autoimmunity [anti-glutamic acid decarboxylase (GAD) antibodies (Ab), anti-islet cell Ab (ICA) and anti-insulin Ab (IAA)], thyroid function (Free thyroxine: FT4 and thyroid-stimulating hormone: TSH), anti-thyroid peroxidase Ab (TPO) and anti-tissue transglutaminase (ATT) in a cohort of children and adolescent (aged 6 months-16 years) with T1DM (n: 431) and T2DM (n: 59) checked at their first presentation at Pediatric Diabetes Center of HMC, Doha, (Qatar) from January 2012 to December 2016. All sera were analyzed in HMC Central Lab.

Children and adolescents with T2DM were all obese or overweight, had acanthosis nigricans, family history of T2DM and fasting serum C-peptide levels of >2 nmol/l (0.7 ng/ml).

Results

Table 1 summarizes the prevalence of autoimmune markers and thyroid status in our cohort of diabetic children and adolescents. Anti-GAD antibodies were detected in 75.5% of T1DM patients and 29.2% of T2DM patients. Anti-islet Ab were detected in 53.4% of T1DM and 29.4% of T2DM patients. Anti-insulin Ab were detected in 40.4% of T1DM and 29.2% of T2DM patients. The three antibodies together were detected in 18.4% of T1DM but none of T2DM patients.

Anti TPO were high in 27.2% of T1DM and 34.6% of T2DM patients. At presentation, hypothyroidism (FT4 <11.5) was detected in 10.6% of T1DM and 10% of T2DM. Subclinical hypothyroidism was

Table 1. Prevalence of autoimmune markers and thyroid dysfunctionin diabetic children and adolescents

	T1DM Positive/total screened → %	T2DM Positive/total screened → %
Prevalence of β- cell autoimmunity		
1-GAD	211/280 → 75.5%	14/48 → 29.3%
2-islet cell AB	86/161 → 53.4%	5/17 → 29.4%
3-insulin AB	38/94 → 40.4%	7/24 → 29.2%
4-GAD +ICA2	56/127 → 44.1%	4/48 → 8.3%
1+2+3	12/65 → 18.4%	0%
Prevalence of thyroid disease and antibodies		
1-T4 (<11.5 pmol/L	42/396 → 10.6%	5/50 → 10 %
2-TSH (5.6-10 mIU/L)	15/395 → 3.5%	4/50 → 8%
3-TSH (>10 mIU/L)	10/395 → 6.6%	3/50 → 6%
4-TPO (>100)	96/352 → 27.2%	14/48 → 29.3%
5-TPO (>100) + normal thyroid function tests	78/344 → 22.7%	12/52 → 23.1%
6-TPO (>100) + hypothyroid (T4 <11.5 pmol/L or TSH >10 mIU/L)	13/344 → 3.4%	4/52 → 7.7%
7-TPO (>100) + subclinical (TSH 5.6-10 mIU/L)	14/192 → 7.2%	2/52 → 3.8%
TPO (<100) +hypothyroid (T4 <11.5 pmol/L or TSH >10 mIU/L)	17/256 → 6.6%	4/52 → 7.7%
Prevalence of celiac disease antibodies		
1-ATT IgA>10	18/365 → 5.0%	4/46 → 8.7%
2-ATT IgG>10	16/365 → 4.3%	0%
3-Both	11/365 → 3.0%	0%

diagnosed in 3.5% of T1DM and 8% of T2DM. High anti TPO was detected in 27.2% of T1DM and 34.6% of T2DM. High anti TPO with normal thyroid function were found in 22.7 % of T1DM and 23.1% of T2DM.

ATT IgA was high in 5% of T1DM and 8.7% of T2DM patients, whereas ATT IgG was high in 4.4 % of T1DM and not detected in any patient with T2DM. Mucosal biopsy proved celiac disease in 9 out of 12 patients (75%) with positive ATT IgA and IgG antibodies.

Twenty nine percent of our children and adolescents with the provisional diagnosis of T2DM based on the presence of obesity, acanthosis nigricans, family history of T2DM and C-peptide level >0.2 nmol/L had autoimmune antibodies against β-cells and thyroid, as well as significant thyroid dysfunction proposing the diagnosis of double diabetes (DD), or hybrid diabetes.

Figure 1 presents the prevalence of autoantibodies in children and adolescents with T1DM and T2DM, as well as the presence of family history of the disease in the family.

Discussion

In children and adolescents, T1DM is caused by autoimmune destruction of the β-cells of the pancreas leading to insulin deficiency. T1DM is classified as either autoimmune (type IA) or idiopathic (type IB) diabetes.

The major form of T1DM is type 1A, which occurs when autoantibodies attack and destroy pancreatic islet β-cells (80-90%), causing little or no insulin production. Islet autoantibodies are not present in type 1B disease. The positive rates of β-cell autoantibodies differed in the different studies, depending on the duration of diabetes and the age of the patient at the onset of the disease (15-19).

In our children and adolescents with T1DM, anti β-cell antibodies positivity, at first presentation, were detected in 75.5% of patients. As the disease progresses and the number of pancreatic β-cells decrease, the autoantibody titer shows a significant decrease. ICA shows a peak concentration during the early stages of T1DM and slowly decreases afterwards. The concentration of anti-GAD Ab also decreases as T1DM pro-

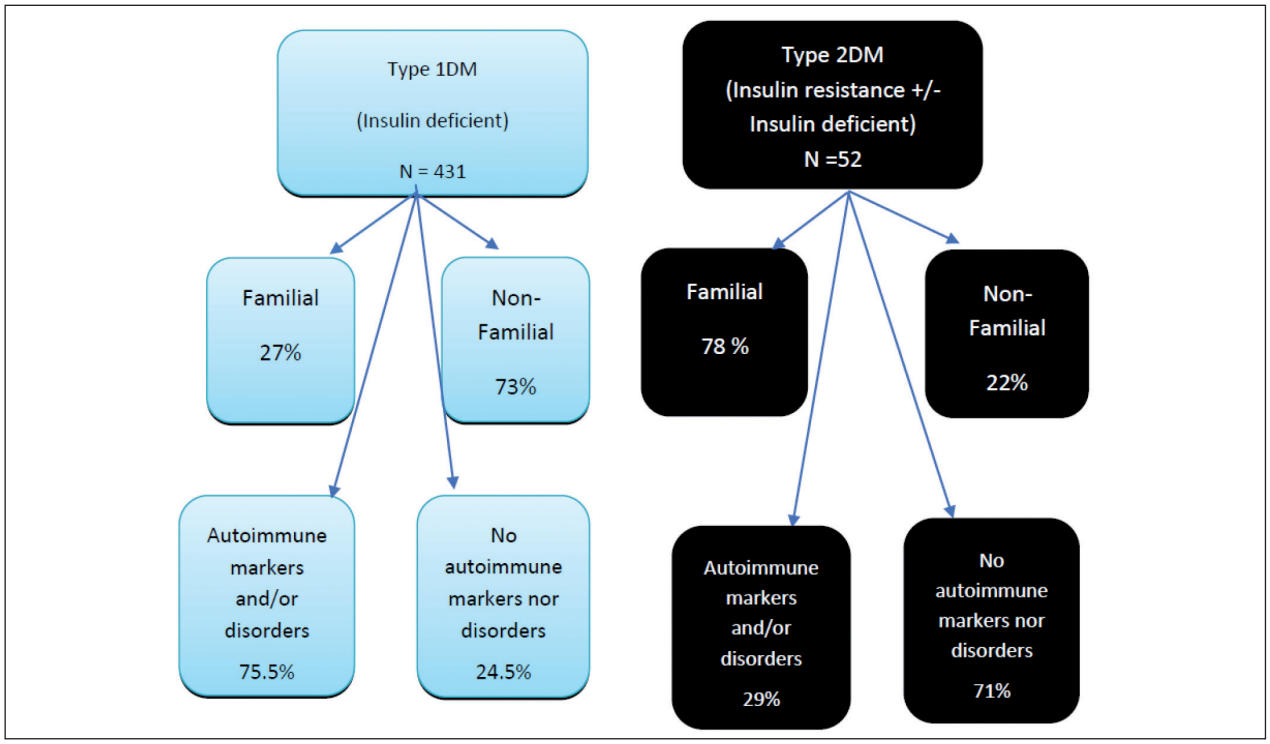

Figure 1. Prevalence of autoantibodies in children and adolescents with T1DM and T2DM in Qatar and their family history of DM

gresses. Some reports indicate that the anti-GAD Ab shows a slower reduction in titer than ICA. Therefore, the early detection of β-cell antibodies appears to be more accurate in diagnosing autoimmune T1DM versus the idiopathic type (20-22).

Type 2 diabetes (T2D) results from a combination of insulin resistance (IR) and β-cell insulin secretory insufficiency. The prevalence of T2D is significantly increased in the pediatric population, which is affected by obesity. Before 2008, no T2DM cases were reported in Qatar, thereafter the incidence increased to reach 4.4 /100,000/year in 2014. This can be explained partially by the higher prevalence rate of obesity in children and adolescents (28%) reported in Qatar. Obese children and adolescents affected by impaired glucose tolerance (IGT) and T2DM are characterized by severe IR, which is associated with an increased lipid accumulation in visceral compartments, liver and muscle tissues, and by reduced sensitivity of β-cell to first and second-phase insulin secretion (23, 24).

However, the rising incidence and high prevalence of obesity in the community involve also patients with T1DM. Although obesity is associated primarily with T2D due to IR, it may also impact T1DM morbidity and phenotype by causing earlier exhaustion of the β-cells through IR. This has made it more difficult to differentiate between these types of diabetes in children, especially at their presentation.

A new variant of diabetes in children designated as DD or hybrid diabetes, in which both T1D (antibody positivity) and T2D (insulin resistance and insufficiency) coexist in the same individual.

Zimmet et al. (25) studied 65 patients who presented with 'adult-onset' diabetes after the age of 30 years. Of these patients, 19 required insulin therapies. The insulin-treated patients were significantly younger, their diabetes onset was at an earlier age, and their postprandial serum C-peptide levels were lower than those with non-insulin-treated group. Moreover, the insulin-treated subjects had a higher mean concentration of GAD and their frequency of anti-GAD positivity was 73.7% versus 4.3% ($p<0.001$) compared to patients who did not required insulin. The authors concluded that the majority (73.7%) of subjects who presented with diabe-

tes after 30 years of age and who subsequently required therapy with insulin, actually have the islet β-cell lesion of Type 1 diabetes which progresses at a slower tempo than in children and recommended testing for anti-GAD in adult-onset non-obese diabetic patients as a routine procedure in order to detect latent insulin-dependency at the earliest possible stage.

In the present study, our children and adolescents with the provisional diagnosis of T2DM based on the presence of obesity, acanthosis nigricans, family history of T2DM and C-peptide level >0.2 nmol/L had higher frequency of autoimmune antibodies against β-cells (~29%) and thyroid (29%) as well as significant thyroid dysfunctions proposing the diagnosis of double diabetes.

Umpaichitra et al. (26) evaluated the frequency of anti-GAD and IAA in 37 children and adolescents with T2DM, defined by fasting and 90-min standard liquid meal-stimulated serum C-peptide levels of >0.2 and >0.5 nmol/l (0.7 and 1.5 ng/ml), respectively. Similar to our findings, 11 out of their 37 patients (29.7%) were positive for at least one autoantibody and 4 out of 37 patients (10.8%) were positive for GAD and IA-2 together (versus 8.3% of our patients). In support of our data, about 35% of children and adolescents with T2D had at least one diabetes-associated antibody (27, 28).

Evia-Viscarra et al. (29) described this DD or hybrid diabetes form in 17 (features of T2DM with autoimmune antibodies) versus 32 children with T2DM (without autoimmune antibodies). All children had overweight or obesity, family history of overweight/obesity and T2DM and acanthosis nigricans. Von Oettingen et al. (30) reported that 28.6% of their children with T2DM had anti GAD antibodies.

The coexistence of T1D and T2D in an individual should in principle denote and may impose a higher risk for developing microvascular and metabolic complications of T1D and the macrovascular complications of T2D. Such a double-hit effect may also predispose to poorer health outcomes. Thus, it is timely to devise an appropriate diagnosis and set up a management protocol to improve glycemic control in these patients (31, 32).

The most common autoimmune disorder related with T1DM is autoimmune thyroid disease (AIT). The frequency of thyroid autoantibody positivity in children with T1DM varies significantly in different populations. In addition, thyroid disorders may occur in a high number of cases (50%) within 3-4 years in thyroid autoantibody positive subjects. It has been suggested that T1DM and AIT have common genetic sources since they often co-occur in the patients and their families. The risk for this autoimmune disorder is known to increase in first-degree relatives of T1DM subjects, and 8% of first-degree families have AIT (33- 36).

The prevalence rate of anti-thyroid antibodies in our T1DM patients, at the diagnosis, was 27.2%. Our findings are in agreement with previous studies, of the same age-group, reporting a prevalence of thyroid antibody positivity of 14.8%-26% (Table 2) (37-42).

A significant percentage (10.1%) of our diabetic children and adolescents presented with subclinical and clinical hypothyroidism which appears to be relatively early compared to other studies (43-45). There-

Table 2. Comparison between the prevalence of thyroid autoimmune markers and dysfunctions in different studies

Studies/country	Number of children with T1DM	High Anti-TPO	Subclinical / Overt hypothyroidism	Anti-tissue transglutaminase (AAT)
Our Study / (Qatar)	352	27.2%	3.5% + 6.6%	5%
Ardestani SA / (Iran)	83	19.3%	19.3%	21.7%
Mantovani RM / Brazil	383	16.7%	7.2%	ND
Jung ES / Korea	98	26%	ND	22.2%
Orzan A / Romania	256	18.3 %	0% at the diagnosis	ND
Kakleas K / Greece	47	14.8%	0% at the diagnosis	ND

ND = not reported

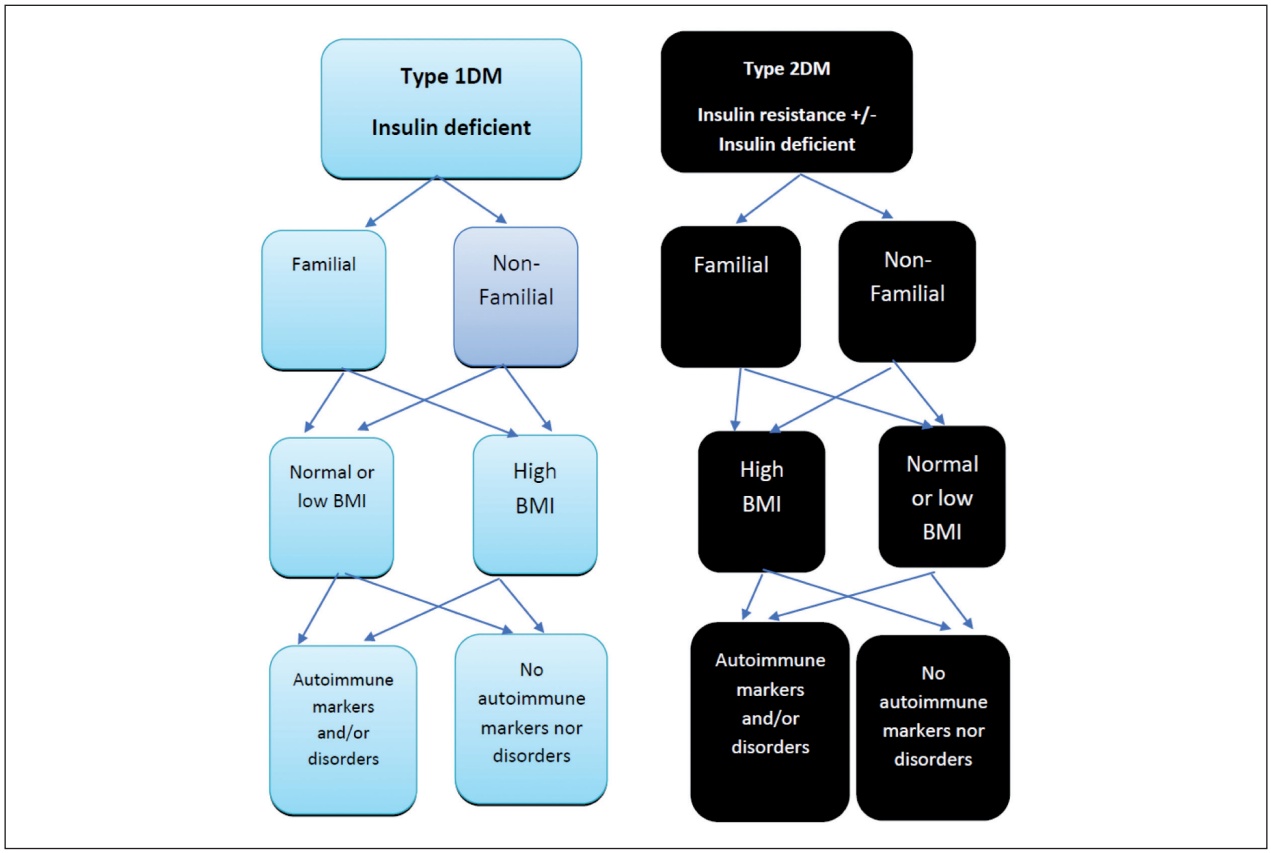

Figure 2. Suggested clinical classification for DM types and subtypes in children and adolescents

fore, early detection of autoimmune thyroiditis in children with T1D, measurement of anti-TPO and TSH at T1DM onset and in yearly intervals after the age of 12 years is recommended. Moreover, many studies confirm significant progression of thyroid disease in children with T1DM, from euthyroid status at presentation, to hypothyroid status within 5 years after diagnosis in those with positive thyroid antibodies.

In adults with T1DM the prevalence rates of thyroid antibody positivity are higher than the ones in children and adolescents and range from 20% to 40%, with the highest rates observed in middle-aged women, while the prevalence of autoimmune thyroiditis in the general population fluctuates from 6.6% to 13.9% (46).

The presence of thyroid autoimmune markers in our T2DM patients, all positive for anti-GAD antibodies, support the autoimmune background of DD or hybrid diabetes in these patients. To the best of our knowledge, this is the first report about thyroid function in children with T2DM at presentation. This is important because the presence of abnormal thyroid function has been shown to be a chief cause of poor control in T2DM (46, 47).

Conclusions

We report the prevalence of DD or hybrid form of DM in 29% of children and adolescents with obesity, acanthosis who were provisionally diagnosed with T2DM. In addition, we noticed the occurrence of significant thyroid dysfunction in children and adolescents with T1DM and T2DM at their first presentation. It appears important to measure antibodies against β-cells and thyroid in children and adolescents

with T1DM and T2DM at presentation to identify those who require regular monitoring of thyroid function and other autoimmune disorders. A practical algorithm for clinical classification of diabetes in children and adolescents is reported in figure 2.

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