Prevalence of Thyroid Autoantibodies in Children, Adolescents and Young Adults with Type 1 Diabetes in Kuwait

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Key Words

Thyroid autoimmune prevalence · Type 1 diabetes · Thyroid dysfunction · Anti-thyroid peroxidase · Anti-thyroglobulin

Abstract

Objective: To investigate the prevalence of thyroid autoimmunity among children and adolescents with type 1 diabetes in Kuwait. **Subjects and Methods:** In a mixed cross-sectional and longitudinal study, anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) were measured in 232 subjects (118 males and 114 females) with type 1 diabetes. **Results:** The mean age of the total study population was 10.9 ± 3.6 years (range 1–21), and the median diabetes duration was 3.9 years (range 0–16). At the initial screening, 57 out of 232 (24.6%) patients had positive antibodies, and of the remaining 175 patients, who were antibody negative, 131 (74.3%) were followed up for 4–9 years. 23 out of these 131 (17.7%) patients became antibody positive, with a cumulative prevalence of elevated antibodies of 34.5%. Anti-TPO was present in 34 (14.7%), anti-TG in 23 (9.9%) and both antibodies in 23 (9.9%) patients. Thyroid antibodies presented early within the first 5 years of the onset of diabetes (63.2 vs. 36.8%, $p < 0.05$). The prevalence of elevated thyroid antibodies increased after the onset of puberty in both females and males ($p < 0.0001$). A total of 58.7% of the patients with positive antibodies were females compared to 41% males ($p <$

0.0001). The basal thyroid-stimulating hormone was higher in subjects with positive antibodies (5.1 ± 10.7 mIU/l) compared to those who were antibody negative (1.79 ± 0.87 mIU/l, $p < 0.001$). Furthermore, 30 out of 232 (12.9%) patients developed thyroid dysfunction. **Conclusion:** In this study, a high prevalence of thyroid autoimmune antibodies was found in patients either at the onset of type 1 diabetes or within the 4–9 years of follow-up.

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Introduction

Autoimmune thyroid diseases are the most common form of autoimmune disorders occurring in patients with type 1 diabetes [1] and the most common autoimmune endocrinopathy occurring in their families [2, 3]. The frequency of thyroid autoimmune disease and the prevalence of thyroid autoantibodies (TAA) in patients with type 1 diabetes varies widely between 3 and 50% [4, 5] and is often related to age, gender or ethnic origin, whereas thyroid dysfunction has been reported in approximately 8% of patients [6]. Hashimoto's thyroiditis (chronic autoimmune thyroiditis) and Graves' disease (thyromegaly and hyperthyroidism) are the major autoimmune thyroid diseases that occur with increased frequency in patients with type 1 diabetes.

TAA are specific markers for autoimmune thyroid diseases with expression typically higher in Hashimoto's thyroiditis than in Graves' disease [7]. They occur in 17–40% of pediatric patients with type 1 diabetes [7, 8] appearing early before any clinical or biochemical signs of thyroid dysfunction. However, studies have shown that 50% of the subjects with positive antibodies may progress to develop autoimmune thyroid disease [4].

Antimicrosomal antibodies, whose specific antigen has been identified as thyroid peroxidase (anti-TPO), an enzyme that catalyzes the iodination of tyrosine residues on thyroglobulin, are more often seen in type 1 diabetes with a prevalence of 25–50% of cases, and thyroglobulin antibodies (anti-TG) are present in 20–30% of cases [1]. Only few longitudinal studies have assessed the risk of thyroid autoimmunity (Th-AA) and diabetes [4, 5] and the optimal method or frequency of screening for Th-AA in patients with type 1 diabetes is still controversial [2, 3, 5].

Kuwait has a high and increasing incidence of type 1 diabetes compared to other Arab countries [9–12]. The age-standardized incidence in children aged 0–14 years in Kuwait between 1992 and 1999 was reported as 20.9/100,000 [10]. Studies on the prevalence of Th-AA in Arab children with type 1 diabetes are scarce [6, 13, 14], and longitudinal studies assessing the risk of Th-AA are lacking. Therefore, we undertook this study to (1) investigate the prevalence and natural history of Th-AA among Arab children and adolescents with type 1 diabetes in Kuwait and (2) determine the clinical significance of the detection of TAA as a marker for autoimmune thyroid disease in children with type 1 diabetes.

Subjects and Methods

This study was done in the Pediatric Diabetes Unit, established at the Amiri Hospital, Kuwait, in 1998. Between 1992 and 1999, a total of 266 children and adolescents with type 1 diabetes were registered in the diabetes outpatient clinic using a computer-based program (MS access). The study population included 232 patients (114 males and 118 females) below the age of 22 years (range 1–21) [15] in whom thyroid antibodies and thyroid-stimulating hormone (TSH) were measured. All patients were diagnosed with type 1 diabetes according to standard criteria, which included polyuria, polydipsia and unexplained weight loss as well as a casual plasma glucose concentration of ≥ 11.1 mmol/l (200 mg/dl) [3]. All subjects were screened annually for thyroid disease by measuring the TAA: anti-TPO, anti-TG, free thyroxine (FT₄) and sensitive thyroid-stimulating hormone (sTSH). The diagnosis of autoimmune thyroid disease was based on the clinical evaluation and detection of thyroid antibodies and abnormal thyroid function tests including sTSH and FT₄.

Table 1. Clinical characteristics of the cross-sectional group of patients with type 1 diabetes with positive and negative TAA

	Group with positive TAA (n = 57)	Group with negative TAA (n = 175)	p value
Age, years			
Means $\pm$ SD	11.75 $\pm$ 3.46	10.63 $\pm$ 3.57	n.s.
Ranges	4–21	1–20	
Duration, years			
Means $\pm$ SD	4.94 $\pm$ 3.62	4.30 $\pm$ 3.09	n.s.
Ranges	0.57–16.13	0.16–13.8	
Males, n	23	91	n.s.
Females, n	34	84	
Puberty stage I, n	17	77	n.s.
Puberty stages II–V, n	40	98	
TSH, nmol/l			
Means $\pm$ SD	5.2 $\pm$ 10.6	1.79 $\pm$ 0.87	<0.005
Ranges	0.5–59.6	0.47–4.94	
n.s. = Not significant.			

Assays of anti-TPO and anti-TG were measured in the serum at the first clinic visit after the initiation of the study and repeated annually thereafter until a positive antibody test was found [2]. UniCAP™ (Pharmacia and Upjohn Company LLC, Kalamazoo, Mich., USA) anti-TG and anti-TPO are enzyme immunoassays for the qualitative and quantitative determination of anti-TG or anti-TPO in human serum or plasma, respectively. The cutoff values to enable clinical discrimination were: <60 IU/ml (normal), 60–100 IU/ml (equivocal) and >100 IU/ml (positive) for anti-TPO, and <280, 280–344 and >344 IU/ml for anti-TG. The negative control was <100 IU/ml. Thyroid function tests, sTSH and FT₄ were also measured in all the patients at their first clinic visit. These tests were repeated at a 6-month interval if TAA were detected and annually during the 4–9 years of follow-up if they were absent. The sTSH assay was determined by a continuous random access chemiluminescent immunoassay system (Abbott IMX). The test is a third-generation TSH assay having a functional sensitivity in the range of 0.01–0.02 μ IU/ml, usually expressed in mIU/l in accordance with the international system of units. The strategy is to test third-generation TSH as a first-line test and then to measure FT₄, if abnormal. The normal values for sTSH and FT₄ are 0.490–4.676 mIU/l and 9.14–23.81 pmol/l, respectively. Overt clinical hypothyroidism was defined as elevated TSH levels and triiodothyronine, thyroxine or FT₄ levels under the lower limit of normal. Subclinical hypothyroidism was defined as an elevated TSH level with normal triiodothyronine, thyroxine or FT₄ levels.

Statistical Analysis

The statistical analysis was carried out using descriptive statistics, including means and frequencies, and inferential statistics, that included using Student's t test and χ^2 test. Student's t test was used to test the significance of the differences between the mean values of two continuous variables. χ^2 analysis was performed to

Fig. 1. Association of positive Th-AA with duration of diabetes among 23 males and 34 females with type 1 diabetes in the cross-sectional group. * $p \leq 0.05$.

test the differences in proportions of categorical variables between ≥ 2 groups. In 2×2 tables, the Fisher exact test replaced the χ^2 test if the assumptions underlying the χ^2 test were violated. The level of $p < 0.05$ was considered as the cutoff value for significance. Data analysis was done using SAS software, version 9.2.

Results

The mean age of the study population was 10.9 ± 3.6 years (range 1–21), and the median diabetes duration was 3.9 years (range 0–16). Of the 232 pediatric subjects, 57 (24.6%) had positive TAA (23 males and 34 females), while 175 (75.4%) were antibody negative. The mean age of the subjects with type 1 diabetes who exhibited Th-AA was 11.75 ± 3.46 years (range 4–21) versus those without 10.63 ± 3.39 years (range 1–21), and the median duration of diabetes was 3.45 ± 3.73 and 3.79 ± 3.09 years in those with and without Th-AA, respectively. The clinical characteristics of the patients with positive and negative TAA are summarized in table 1.

Of the 232 patients, at least 1 thyroid antibody was elevated in 57 (24.6%) patients, 20% (23/114) males and 29% (34/118) females. Of 57 patients with elevated thyroid antibody, 36 (63%) developed positive TAA within 5 years of the onset of diabetes and 21 (37%) after a 5-year duration of diabetes. The difference was statistically significant ($p < 0.05$) (fig. 1).

Fig. 2. The association between thyroid antibodies and puberty stage (Tanner white-staging method) in both cross-sectional and longitudinal groups. * $p \leq 0.0001$.

Table 2. Cumulative frequency of TAA in both cross-sectional and longitudinal groups of patients with positive Th-AA

	Males	Females	Total
Anti-TPO	16 (6.8)	18 (7.78)	34 (14.65)*
Anti-TG	8 (3.4)	15 (6.5)	23 (9.9)
Both	12 (5.2)	14 (6)	23 (9.9)
Total	36 (15.5)	47 (20.3)	80 (34.5)

Values represent n (%). * $p \leq 0.05$ (χ^2 test).

A subset of the study population (131 subjects) was prospectively followed for 4–9 years: 68 (51.9%) and 63 (48.1%) patients for 4 and 9 years: respectively, during which time 17.5% of them became TAA positive. Females were significantly more likely to develop Th-AA (58.7%, 47/80) than males (41%, 33/80, $p < 0.0001$). The TAA appeared more often after the onset of puberty in both sexes 77.5% (62/80) versus their appearance before puberty (22.5%, 18/80, $p < 0.0001$) (fig. 2).

The cumulative prevalence rate for positive Th-AA from both cross-sectional and longitudinal studies was 34.5% (80/232). Anti-TPO was present in 34 (14.7%) patients, anti-TG in 23 (9.9%) and both antibodies in 23 (9.9%) patients, with a statistically significant p value of

≤ 0.05 . Furthermore, 12.9% (30/232) had laboratory evidence of thyroid dysfunction. Among these 30 patients, subclinical hypothyroidism was the most common diagnosis in 17 (7.3%) patients, i.e. 56.7%, followed by overt hypothyroidism that required replacement therapy with L-thyroxine in 10 (4.3%) patients, i.e. 33.3%, and hyperthyroidism in 3 (1.2%) patients, i.e. 10% (table 2).

Discussion

In this study, the prevalence of TAA observed in children with type 1 diabetes was high (34.5%) compared to other studies [7, 16, 17]. However, it is similar to the prevalence found in Iranian children (39.6%) [17]. Our results are considerably higher than those found in either Libyan [6], Jordanian [9], Saudi Arabian [13] and Sudanese children [14].

It is well known that genetic predisposition contributes to the risk of developing type 1 diabetes, and the HLA class II locus contributes to the shared risk for both type 1 diabetes and autoimmune thyroid disease. The major haplotype contributing to this association is DR3DQB1*0201 [6], which was significantly increased in Kuwaiti Arab children with type 1 diabetes [18] and may explain the high prevalence of Th-AA in the present study.

The frequency of thyroid antibodies in healthy Kuwaiti individuals in the general population was previously reported as 3.1%, being slightly higher in females [19] and increasing with other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and primary Sjögren's syndrome. In contrast, a high frequency of thyroid dysfunction (55%) and of Th-AA (52%) was found in Kuwaiti adults with Down syndrome [20]. No studies examined the prevalence of Th-AA in healthy children in the general population in Kuwait.

The overall prevalence of Th-AA appeared to increase over time as reported by different authors [1, 6]. However, in this study, 63% of autoantibody-positive children developed Th-AA within 5 years of the onset of diabetes, a finding that emphasizes the importance of screening for thyroid antibodies early after the diagnosis of type 1 diabetes.

Our data showed a significant increase in positive autoantibodies in females, similar to other studies in the literature [8, 12, 17, 21, 22] where female sex was reported as an important risk factor for Th-AA. Furthermore, TAA appeared significantly more often after the onset of

puberty in both sexes, 77.5 versus 22.5% before puberty. It is well accepted that in children at genetic risk of type 1 diabetes, seroconversion to anti-TPO peaks around the time of puberty, at which time the thyroid gland undergoes remodeling [6].

Biochemical thyroid dysfunction may be present at the diagnosis of type 1 diabetes [4, 23] or may be detected after several decades of diabetes [4, 21, 23]. A strong association exists between Th-AA and the risk of thyroid dysfunction in people with type 1 diabetes with a risk ratio of 49 in children (95% CI 16–120) [24]. Furthermore, a prolonged period of autoimmunity makes the clinical diagnosis of thyroid autoimmune disease difficult, as it often occurs in a subclinical state. Measurements of thyroid function tests in clinically suspected cases or in those who have positive TAA would confirm the disease [17].

Previous studies have shown a clear association of type 1 diabetes and autoimmune thyroiditis, often requiring treatment with L-thyroxine. The prevalence of autoimmune thyroiditis in our study as shown by abnormal thyroid function tests was 12.9% and compares well to other studies [8, 14, 25, 26]. The presence of subclinical hypothyroidism, which varies between 3 and 11% worldwide [6], was found to be the most common dysfunction in our study (7.3%), followed by overt hypothyroidism (4.3%) and hyperthyroidism (1.2%). The latter finding is low compared to the prevalence reported in other studies (3–6%) [24].

Despite the striking evidence that Th-AA with subclinical hypothyroidism [23, 26–29] is a frequent finding in children and adolescents with type 1 diabetes, there is still controversy concerning the necessity of therapeutic intervention in these patients [30]. Mild thyroid failure has been extensively evaluated as a cardiovascular risk factor in adults, and neurobehavioral changes, myocardial dysfunction and dyslipidemia have frequently been described in this population [26]. Children with diabetes and subclinical hypothyroidism had reduced growth rates, particularly in those with TSH values of >10 IU/l, and therapy, when started early, reduced the risk of hyperlipidemia and atherosclerotic heart disease [30]. Although our decision was only to treat patients with TSH levels of >10 IU/l, this strategy would entail a close follow-up, as previous studies have shown that progression to clinical hypothyroidism occurs in 3–18% of patients per year [26, 28, 29, 31]. It has been recommended to start treatment with L-thyroxine if TSH increases ≥ 4.5 mIU/l on two subsequent measurements and/or if a thyroid gland enlargement with diffuse parenchymal hypoechogenicity on ultra-

sound examination was present [4]. However, although thyroid imaging may be helpful, it is not a strict criterion for diagnosis.

Recently, the majority of studies have recommended annual screening for thyroid dysfunction and/or autoimmunity from diagnosis, while others recommend screening after the onset of puberty. However, the optimal methods and frequency of screening are yet to be established [24].

Conclusion

The cumulative incidence of Th-AA from this mixed cross-sectional and longitudinal study was high, and subclinical hypothyroidism was the most common disorder diagnosed. The appearance of Th-AA early after diagnosis strongly supports the recommendation of screening all patients at the onset of diabetes, as early detection has the potential to prevent significant morbidity related to unrecognized disease.

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