Autoimmune thyroid disease in northern Iranian children with type 1 diabetes mellitus in Amirkola Endocrine Clinic

Original Article

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Abstract:

Background: Type 1 diabetes mellitus (T_1DM) as an autoimmune disorder is associated with other autoimmune diseases such as autoimmune thyroid (AIT) disease. The aim of this study was to determine the prevalence of AIT in children who were referred to Amirkola Endocrine Clinic (north of Iran).

Methods: This cross-sectional study was carried out on 100 diabetic children aged 1-15 years during 2008-2013, who were referred to the pediatric endocrine clinic. Serum levels of anti-thyroid peroxidase (Anti-TPO) and anti-thyroglobulin (anti-Tg) antibodies and Thyrotropin Stimulating Hormone (TSH) were measured by Immune Chemiluminescence assay, and demographic information was obtained from patients'medical records. The collected data were analyzed using SPSS 18.

Results: AIT was found in 13% of patients (8% female and 5% male). Significant levels were found for Anti-TPO (3%), anti-Tg (2%), and both antibodies (8%) in patients with AIT. Thyroid dysfunction was observed in 8 of 13 patients with AIT versus 2 of 87 patients without AIT ($P<0.001$). AIT was seen in 9% of diabetic children who had diabetes for less than one year versus 4% of the rest of diabetic children with duration more than one year ($p<0.0001$).

Conclusion: Because the majority of diabetic children with significant titers of antibodies developed thyroid disease, so thyroid function tests are necessary to reduce the risk of undiagnosed hypothyroidism in these patients.

Key Words: Anti Thyroid Peroxidase Antibody, Anti-Thyroglobulin Antibody, Autoimmune Thyroid Disease, Hypothyroidism, Type 1 Diabetes Mellitus.

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Introduction:

The association between type 1 diabetes mellitus (T_1DM) and other autoimmune diseases, particularly autoimmune thyroid disease (AIT) has been reported in many populations [1, 2]. The prevalence of positive thyroid autoimmune antibodies in children with T1DM varies considerably from 3% to 50% in different countries [3, 4], whereas there is low prevalence of autoimmune thyroiditis, 3.4-4.5% in general population [5]. The AIT includes variable degrees of lymphocytic infiltrations of the thyroid gland and this process is an important source of thyroid autoantibody production, along with the surrounding lymph nodes and bone marrow. Chronic autoimmune thyroiditis (Hashimoto's thyroiditis) and Graves' disease are the major causes of hypothyroidism and hyperthyroidism, respectively [6]. Up to now, there is no consensus neither on screening for autoimmune thyroiditis nor the time point of therapeutic intervention in children with T_1DM unless clinical symptoms of thyroid dysfunction appear [3, 4]. Because of the high association between AIT and thyroid dysfunction in patients with T_1DM and also probable effects on glycemic control and lack of enough information and

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studies on AIT and thyroid dysfunction in diabetic children in our area (north of Iran), we investigated the prevalence of AIT antibodies in children with T_1DM.

Methods:

This respective and cross-sectional study was conducted on children with previous T_1DM who were diagnosed and managed at the pediatric endocrine clinic, Amirkola Children's Hospital, from 2008 to 2013. Eligibility criteria included patients with 1-15 years old, lack of previous thyroid medication and intercurrent illness. Finally, 100 children with T_1DM were studied during this period that included 52 males and 48 females. They were routinely screened for autoimmune thyroid antibodies and thyroid dysfunction. Anti-TPO and anti-Tg antibodies were measured and thyroid dysfunction was determined by measurement of TSH and T4.

Measurement of Anti-TPO, anti-Tg and TSH was performed via Immune Chemiluminescence assay (MONOBIND kit, Costa Mesa, USA). Values exceeding 40 IU/ml and 125 IU/ml for anti-Tg and anti-TPO were considered as positive autoimmune thyroid antibodies, respectively. The normal range determined for TSH was according to the instruction of kit, 0.5-5.5 mIU/ml (Iran Kavoshyar Co.,Tehran, Iran). Clinical hypothyroidism was defined as elevated TSH and low T4, versus subclinical hypothyroidism as elevated TSH with normal T4.

Data were analyzed using SPSS 18 and statistical tests including Chi- square, T-test, and Mann-Whitney test. Correlations between antibody concentrations and TSH values were determined using regression analysis. $P \leq 0.05$ was considered significant level.

Results:

Screening for thyroid antibodies showed that 13% patients had significantly elevated titers of antibodies. There was no significant difference in the mean age between two groups (p=0.59). Based on the age group, 18%, 46% and 36% of the patients were 1-5, 5-10 and 10-15 years old, respectively.

Thyroid antibodies titers were enhanced with increasing age and anti-TPO positive and both anti-TPO and anti-Tg positive were more common in 10-15-year-old group but anti-Tg positive was more common in the age group 5-10 years old. AIT was observed in 16.6% (8/48) of females and 9.6% (5/52) of males with female to male ratio of 1.6:1 but the difference was not significant (p=0.3).

A total of 46.2% of diabetic children with AIT had abnormal TSH levels compared to 2.3% of diabetic children without AIT (p=0.001). The biochemical characteristics in diabetic children are illustrated in table 1. TSH values were different according to the pattern of elevated thyroid antibodies: anti-Tg positive with 2.92±1, anti-TPO positive with 16.6±17.39 and both anti-TPO and anti-Tg positive with10.59±9 (IU/ml), but there was no significant difference in mean of TSH values among them (p=0.21).

A significant relationship between the level of TSH and anti-TPO (β=0.01, p<0 .0001) (figure 1) but there was no significant correlation between the level of TSH with anti-Tg (p=0) and a diabetes duration (p=0.2). Eight from 13 patients with AIT progressed to thyroid dysfunction (one clinical hypothyroidism and 7 subclinical hypothyroidism) but 2 patients without AIT progressed to subclinical hypothyroidism.

Thyroid dysfunction was observed in 2 of 3 (66.6%) patients with only anti-TPO positive and 6 of 8 patients (75%) with both anti-TPO and anti-Tg positive (p=0.91).

AIT was founded in 9% of diabetic children who had diabetes for less than one year versus 4% of the rest of diabetic children with a diabetes duration of more than one year (p=<0 .0001).

Table 1: The biochemical data in diabetic children with or without AIT.

Biochemical data	Patient with AIT Mean ±SD	Patient without AIT Mean ±SD	P.value
Anti-TPO titer (IU/ml)	374.76±512.8	8.18±11.1	<0 .0001
Anti-Tg titer (IU/ml)	376.98±497.2	11.8±8.7	<0 .0001
TSH (IU/ml)	9.97±10.4	2.81±1.35	0 .001
T4 (µg/dl)	8.28±1.9	8.57±1.6	0.54

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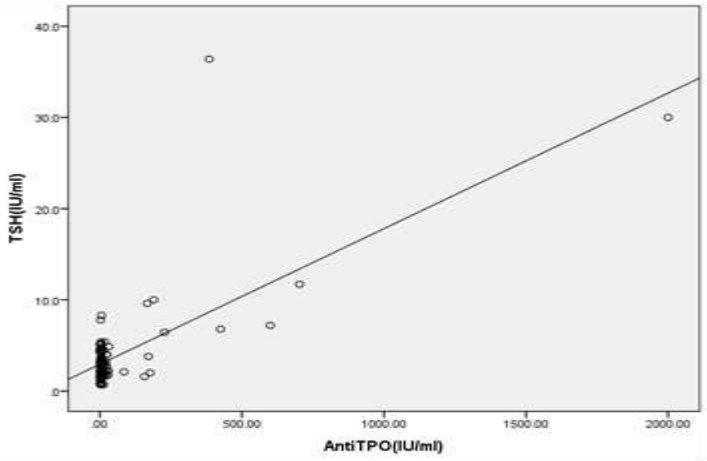

Figure 1: The relation between level of TSH and anti-TPO according to scatter plot (r=0.51)

Discussion:

In this study, the prevalence of AIT was 13% in children with T1DM. It was reported by Kordonouri et.al 10%, severenski 15.5% [4, 5]. Karavanaki et al's reported anti-TPO and anti-Tg antibodies positivity in 17.4 and 11.1% of the patients, respectively, and 7.6% of them were positive for both anti-thyroid antibodies [7], while in our study Anti-TPO, anti-Tg and both antibodies were positive in 3, 2 and 8%, respectively.

A few studies in Iran showed that the prevalence of AIT was 9% and 22% in children of Tabriz and Isfahan, respectively [3, 8]. The lowest and highest prevalence rates of AIT in children and adolescents with T_1DM were 3.9% in Italy and 50% in USA, but many studies represented that the prevalence rates were 15-20% [5]. A wide variation of AIT prevalence in diabetic children could likely be illustrated through the difference in genetic factors, different methods for detection of thyroid antibodies and sensitivity of diagnostic tests [8,9].

The results of the present study demonstrated that AIT was more prevalent in female than male and was nearly two folds while it was not significant, which accords with some studies [10-13]. Many studies emphasized female gender as a predisposing factor for AIT in both diabetic patients and general population [5]. On the other hand, the prevalence of T_1DM was equal between two genders, so more frequent occurrence of AIT could be related to the risk factors, exclusive of induced causes of diabetes, for example, hormone influences [2, 5].

Although the prevalence of thyroid antibodies was risen with increasing age of the children in the current study, it did not reach statistical significance, which agrees with that of Araujo et al's [2]. In another study, the frequency of positive anti-Tg and anti-TPO was 37 and 15% during the first year of diabetes diagnosis, respectively [7]. In the general population without diabetes, the prevalence of thyroid-antibody positivity increased with age [1, 2, 4]. The age-dependent increase in autoantibody positivity suggests that autoimmune disease is the final phase of a process starting with autorecognition, passing through immunity with the appearance of autoantibodies, and finally leading to cell destruction and autoimmune disease [14]

The current study founded that thyroid antibodies were determined in the majority (10/13) of diabetic children with duration of less than one year that is agreement with some studies [5, 9, 12, 13]. These data suggested the importance of screening near to the time of diabetes diagnosis.

Our findings represented that children with TID had higher TSH level than without T_1DM and the elevated anti-TPO associated with higher value of TSH, so it seemed that elevated anti-TPO than anti-TG was more specific for thyroid dysfunction that is consistent with others [3, 5, 13, 15-17].

The results of the present study demonstrated that thyroid dysfunction developed in 8% of total children and 61.5% of diabetic children with AIT, of whom53.8% and 7.7% had subclinical and clinical hypothyroidism, respectively. So significant difference was observed between diabetic children with and without AIT, which is agreement with other studies [2, 3, 5]. Ardestani et al's explained that 38.8% of diabetic patients with AIT had subclinical hypothyroidism without any case of clinical hypothyroidism. In many researches, it was found that the prevalence rate of autoimmune thyroid disease in children with newly diagnosed T_1DM was 4.5-29.4% [9]. In the present

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study, AIT in patients who had diabetes for less than one year was more common because 5 of 8 patients with thyroid dysfunction had diabetes less than one year. Limitations of the current study were the small sample size of diabetic children to determine the prevalence of AIT.

Moreover, in this retrospective study, the screening of TSH, anti-TPO and anti-Tg was not performed annually in all patients. Due to the irregular screening tests, this disease may be detected with delay, some years after development. Therefore, regular testing of TSH and auto-antibodies are recommended for patients with T_1DM.

According to close association of autoimmune thyroid disorders with T_1DM in children, evaluation of these patients in terms of thyroid function and thyroid autoantibodies is suggested to reduce the risk of undiagnosed hypothyroidism in these patients.

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