

# Thyroid Autoimmunity and Function in Type 1 Diabetic Children and Adolescents in Armenia

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**Abstract:** The literature and research clearly supports an increased incidence of autoimmune thyroid disorders (mostly autoimmune thyroiditis) in type 1 diabetics as well as increased incidence of type 1 diabetes mellitus (DM) in autoimmune thyroid disease. The objective of current epidemiological screening study is to investigate thyroid autoimmunity and function in a large cohort of children and adolescents with type 1 DM in Armenia. Moreover, this screening study is done to determine the incidence of thyroid autoimmunity and hypothyroidism (including sub clinical hypothyroidism) and to give its structural analysis. The findings of current study illustrate 30.5% of hypothyroidism, including subclinical hypothyroidism, in type 1 diabetic children and adolescents. What is more important, 24.8% of type 1 diabetic children and adolescents have thyroid autoimmunity – positive antithyroid peroxidase autoantibodies (Anti-TPO), 44% from which were found to be significantly high. Any sex predominance was not found in AIT and thyroid autoimmunity in general. In type 1 diabetics with associated thyroid autoimmunity autoantibody positivity precedes thyroid ultrasound changes and predisposes to the development of further hypothyroidism without any sex predominance. The number of cases of hypothyroidism is quite high in the group of diabetics with DM duration of 5 years. It is recommended that diabetics who have no TSH elevation and thyroid ultrasound changes, but who have increased Anti-TPO, should be formed as a group of high risk for further development of thyroid disorders, although TSH elevation showed having no influence on the compensation of diabetes. We fully recommend the patients to test the TSH and anti-TPO levels once a year, particularly after puberty and with DM duration over 5 years.

**Keywords:** Autoimmune thyroiditis, autoantibodies, hypothyroidism, hyperthyroidism, diabetes compensation, autoimmune polyglandular syndrome.

## BACKGROUND

Nowadays, it is believed that in endocrinology the coexistence of the pathology of more than one endocrine gland is one of the most important and interesting research areas. During the past decade this direction has been growing intensively resulting in revealing the new syndromes, genes, associations, pathways for the development of mentioned endocrine disorders. In most of associated endocrine diseases the disorders of thyroid gland is prevalent, i.e. in autoimmune polyglandular syndromes, in multiple endocrine neoplasms etc. Patients with an autoimmune condition are mostly known to be in a higher risk of development than other autoimmune disorders. In childhood and adolescence association of thyroid disorders and type 1 diabetes mellitus (DM) is the most wide spread disease over the world [1, 2]. However, the clinical relationships between DM and thyroid diseases cannot be clearly explained. There are many complex and still unclear interactions of the pathogenic mechanisms of these diseases. Moreover, some scholars classify the presence of AIT in type 1 diabetics as the autoimmune polyglandular syndrome (APS) type III, which can also be associated not only with glands

and other organ-specific autoimmune disorders, but also with other organs, i.e. celiac disease, pernicious anemia, myasthenia gravis, alopecia areata etc.

There are numerous experimental, clinical, genetic and epidemiological studies that have been done during last decades to determine various cases about common genetic factors and pathways in autoimmune diseases. In many countries the number of cases of thyroid autoimmunity in type 1 DM has been shown to be vary from 7% to 38% [3-6], compared with the general population (1-7%) [1, 2, 7]. In addition, about 10% of practically healthy people in general population are autoantibody-positive [8].

Type 1 DM is a typical organ-specific autoimmune disease, resulting from the autoimmune destruction of pancreatic beta-cells. The final observation of the destruction is absolute insulin insufficiency and clinical manifestation of type 1 DM, mostly with ketoacidosis. Another frequent autoimmune disorder in pediatric endocrinology is autoimmune thyroiditis (AIT, Hashimoto's thyroiditis) - the most common cause of hypothyroidism. The pathway of AIT seems to be similar to the pathway of type 1 DM which is expressed with autoimmune attacks against the thyroid cells resulting in thyroid insufficiency [6, 9]. Number of scholars also stressed two main reasons of association of these diseases. First one is the common genetic

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base (including some HLA – Human Leukocytes Antigens alleles). Second one is the theory about the cross-sectional interaction of the autoantibodies of one disease with the antigens of another endocrine gland [10]. The two mentioned above disorders are autoantibody-mediated. Thus, the elevated organ-specific serum autoantibodies are present: anti - GAD65 (glutamate decarboxylase), anti- ICA (Islet cell antigen) and anti-insulin -for type 1 DM, and anti-TPO (antithyroid peroxidase) and anti-TG (antithyroglobulin) – for AIT. What is worth mentioning is that every elevated antiTPO or anti-TG has not been AIT yet. Nevertheless, it is a marker of thyroid autoimmunity. The major histocompatibility complex (MHC) has been studied extensively in the mentioned two autoimmune diseases. The high-risk genotype for type 1 DM is DR3-DQ2, DR4-DQ8, and for associated AIT – DR3-DQ2, DR4-DQ8 and haplotype DR3-DQ2 [9].

Because hypothyroidism interferes with metabolic control of DM and may cause serious health disturbances by itself, early determination of the clinical features or subclinical laboratory findings has its important implication in everyday practice of pediatric endocrinologists [11, 12, 17].

Taking into consideration some genetic, social, nutritional and cultural characteristics of the Armenian population, there is still a lack of data concerning this problem in Armenia. In this current article the data of the investigation of thyroid autoimmunity and function will be shown, where type 1 diabetic children and adolescents in Armenia were investigated. As problem of vital importance, this research is being done in Armenia for the first time.

## STUDY DESIGN AND METHODS

In this study 367 children and adolescents with type 1 DM registered in Armenia were examined in endocrinology clinic of “Muratsan” hospital of Yerevan State Medical University from 2009 to 2012. They were matched by sex, age (within 1 year), and year of diagnosis (within 1 year). The inclusion criteria were:

- admission to the department with new-onset of DM or documented the previous diagnosis of type 1 DM;
- age less than 18 years old;
- Administration of insulin therapy at the time of hospital discharge.

Exclusion criteria – all cases of secondary diabetes.

The function of thyroid gland was assessed only after 7-10 days after elimination of ketoacidotic state and glycemic stabilization.

Glycemic control was evaluated by glycated hemoglobin – HbA1c levels: HbA1c < 8% as compensated DM, 8 – 13% - as sub compensated, and > 13.0% as decompensated DM.

The Thyroid function was evaluated by the serum levels of thyroid stimulating hormone (TSH) and free-thyroxin (fT4). Besides, as the euthyroidism, TSH <4,0 IU/ml with normal fT4 and TSH ≥4,0 IU/ml with normal fT4 were prescribed. What concerns subclinical hypothyroidism and TSH ≥ 4.0 IU/ml with low fT4, the overt hypothyroidism was prescribed.

Autoimmunity of thyroid gland was determined by serum levels of Anti-TPO (autoantibodies against thyroid peroxidase) and by ultrasound (USG) examination of thyroid gland underlying the autoimmune classical USG characteristics of thyroid autoimmunity: echogenicity, vascularization, enlargement or atrophy etc. Anti-TPO titers exceeding 34 IU/ml were determined as high and ≥ 100 mU/l – as significantly high. Ultrasound examination was done with linear probe of 10 MHz.

Autoimmune thyroiditis (AIT) was defined as positivity of antibodies against thyreoperoxidase or typical USG image of AIT together with elevated TSH ≥ 4.0 IU/l.

Statistical analyzes were performed to determine the significance of findings. Non-parametric Pearson's chi-square test (Yates corrected if table 2x2) was used. Rates and ratios were calculated; where appropriate, z-test or t-test were applied. In all cases null hypothesis was rejected if  $p < 0.05$ .

## RESULTS

In the present research with a prior diagnosis of type 1 diabetes there were 367 children and adolescents to be evaluated. Patients were divided into groups in accordance with their ages ≤ 4-yr (28/367), > 4 - ≤ 8-yr (53/367), > 8 - ≤ 12 (111/367), > 12 - ≤ 16-yr (127/367), and > 16 - ≤ 18-yr (48/637), as well as with the duration of diabetes into <1-yr (108/367), 1- to 3-yr (82/367), 3- to 5-yr (67/367), and >5-yr.

The male/female ratio of investigated patients was 195/172 (1.134), which reflects and is close to the sex distribution of population in this particular age group in

**Table 1: Number and Percentages of Type 1 Diabetic Patients with Positive and Negative Anti-TPO (Sex, USG Findings, TSH Associations)**

	Positive Anti-TPO (n=91)	Negative Anti-TPO (n=276)	p-values
Female sex	52.8% (n=48)	45% (n=124)	0.195
Male sex	47.2% (n=43)	55% (n=152)	
USG changes	22.0% (n=20)	3.3% (n=9)	< 0.0001
TSH elevation	40.66% (n=37)	27.2% (n=75)	0.015

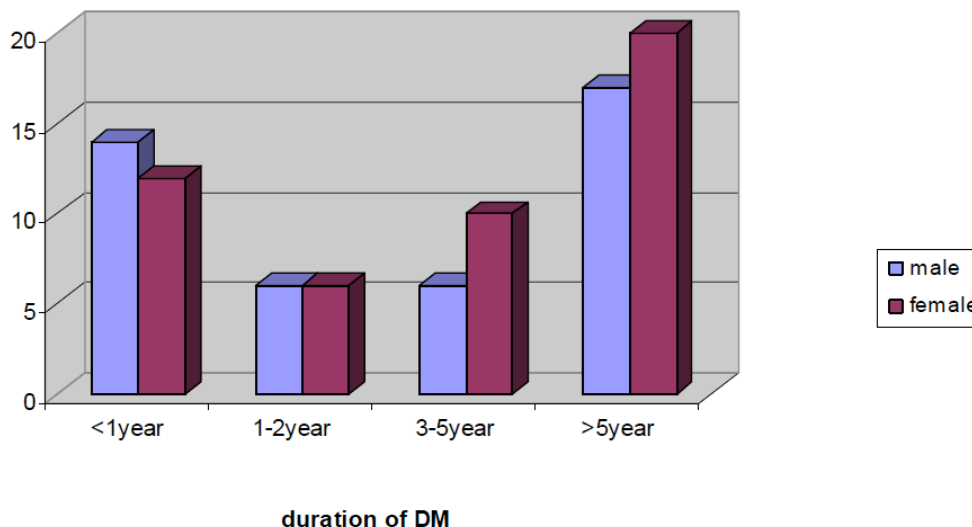
Armenia (1.148). The number of cases rate of DM is 40.9 per 100 000 population and slightly vary from 40.3 for female to 41.4 for male ( $p=0.4$ ).

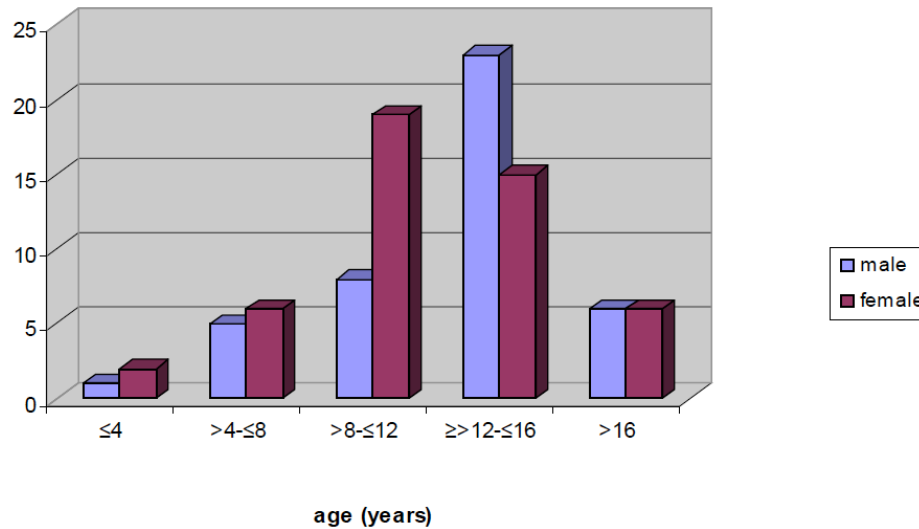
Table 1 summarizes the results of the thyroid function and autoimmunity number of cases in evaluated type 1 diabetics. The anti-TPO antibody test was positive in 91 of the 367 patients (24.8%), 40 (44%) from which were found to be significantly high, and among 3 patients Anti-TPO was on upper limit of the normal range. The male/female ratio of positive Anti-TPO diabetics is 43/48. There has not been found significant female predominance of Anti-TPO positivity in type 1 diabetics ( $\chi^2=1$ ; 68  $p=0.19$ ) in all over type 1 diabetic population.

20 patients with positive Anti-TPO had statistically significant USG changes compared with 9 in Anti-TPO negative group ( $\chi^2= 32,94$ ;  $p<0,0001$ ). A total of 40.66% (37) patients with positive Anti-TPO had abnormal TSH levels with male/female ratio of 15/22 compared with 27.2% (75) in the group with negative Anti-TPO ( $\chi^2=5,86$ ;  $p= 0.0154$ ) with male/female ratio of 38/37.

According to the data of 367 tests of thyroid function in type 1 diabetics 112 (30.5%) increased TSH levels were registered, from which 92 (82%) are subclinical cases, i.e. the elevation of TSH with normal ft4 has been found. The male/female ratio was 53/59 ( $\chi^2=2.2$ ;  $p=0.14$ ). Thus, the sex number of cases of increased TSH has not been found. Moreover, the results of the study shows that 64 (57,1%) patients with hypothyroidism had decompensated HbA1c versus to 139 (54.3%) without hypothyroidism ( $\chi^2=0.255$ ;  $p=0,61$ ). Therefore, increased TSH doesn't have any influence on the compensation of diabetes.

Figure 1 shows the number of cases of Anti-TPO positivity according to the age, the Figure 2 shows the same according to the duration of diabetes. The positive Anti-TPO number of cases has been found to be higher in the group of diabetics with duration of DM  $\geq 5$  years (27 from 91), data was not statistically significant ( $p=0.5$ ), than it was described in the literature. Although predominance of Anti-TPO positivity has been found in  $>12\leq 16$  post pubertal age group ( $\chi^2=2.73$   $p=0.098$ );, significant female predominance of Anti-TPO positivity (male/female ratio

**Figure 1:** The number of cases of Anti-TPO positivity according to the DM duration.



**Figure 2:** The number of cases of Anti-TPO according to ages of diabetics.

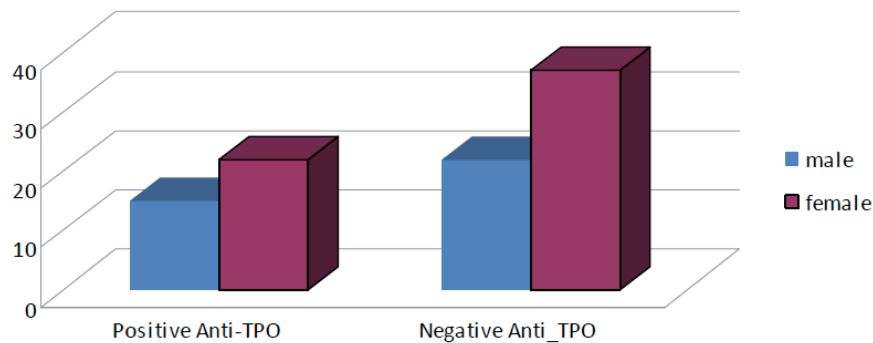
was 8/19) has been found in the pubertal age group of diabetic children and adolescents ( $\chi^2=5.66$ ;  $p=0.017$ );).

Figure 3 demonstrates the number of cases of hypothyroidism, both overt or sub clinical, in Anti-TPO positive group of diabetics compared with those Anti-TPO negative with statistical significance ( $p<0.015$ ). It is obvious that patients having positive Anti-TPO compared with those having negative Anti-TPO are more likely to have hypothyroidism later in their life.

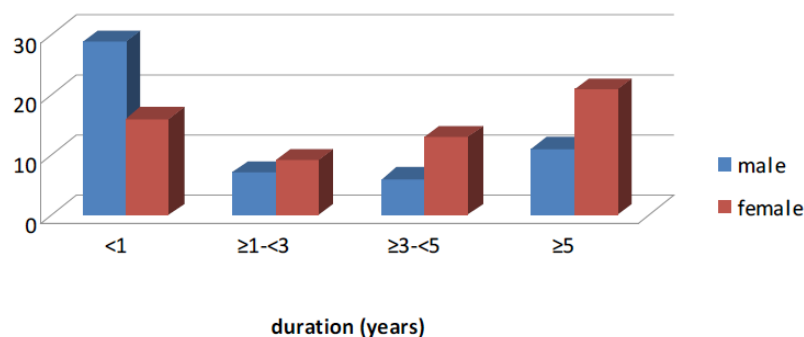
In the Figure 4 the number of cases of hypothyroidism is demonstrated to be high in the group of diabetics with DM duration  $\geq 5$  years with female predominance over male ( $p=0.08$ ).

**DISCUSSION**

Autoimmune thyroid disorders are common in children and adolescents with type 1 DM. However, frequencies differ among studies [13, 14]. This study found serological marker for thyroid autoimmunity in



**Figure 3:** Number of cases of hypothyroidism according to Anti-TPO positivity in diabetics.



**Figure 4:** Number of cases of hypothyroidism according to the duration of DM.

24.8% of young patients with type 1 diabetes, and these results were comparable to previous studies researched in different countries. The results of the current study show, in type 1 diabetic children and adolescents 30.5% of hypothyroidism, including subclinical hypothyroidism. It is also noticeable that the hypothyroidism is significantly due to thyroid autoimmunity, excluding not endemic or of other causes. As a consequence, Anti-TPO positivity predisposes to the development of hypothyroidism, in accordance with the literature [16]. Moreover, the presence of hypothyroidism doesn't play any role in the compensation of diabetes.

It is also necessary to notice that the group of diabetics, having no TSH elevation and thyroid ultrasound changes, but having increased Anti-TPO, should be formed as a group of high risk for further development of thyroid disorders.

Our data demonstrated that there is no sex predominance (male/female ratio hadn't statistical significance) versus to the literature [15]. Only for pubertal age group the female predominance of Anti-TPO positivity was found with statistical significance.

In our study although it didn't reach statistical significance, there was a tendency of an increased number of cases of thyroid autoimmunity with increasing age and diabetes duration,

In patients with type 1 diabetes and accompanied by thyroid autoimmunity, diabetes onset precedes the diagnosis of thyroid autoimmune diseases, according to our data: 71% (65) from 91 patients demonstrate thyroid autoimmunity after the manifestation of diabetes, and only 24% of patients have thyroid autoimmunity at the onset or before the manifestation of diabetes (without statistical significance).

In patients with type 1 diabetes and associated AIT elevation of Anti-TPO precedes ultrasound findings typical for AIT.

Based on our data we recommend testing of TSH and anti-TPO levels once a year the patients with the previous diagnosis of type 1 DM, especially in pubertal period (age of 8-12 years) and/or with duration of DM over 3 years without any dependence on sex. We fully recommend to form a group of high risk for hypothyroidism development - Anti-TPO significant positivity with or without USG findings, and to evaluate TSH levels more frequent for early diagnosis of AIT and hypothyroidism.

## ACKNOWLEDGEMENTS

This work was supported by the Scientific Research Center of Yerevan State Medical University after M. Heratsi.

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Received on 27-11-2012

Accepted on 05-01-2013

Published on 20-05-2013

<http://dx.doi.org/10.6000/1929-4247.2013.02.02.10>