

# Type 1 Diabetes Mellitus Associated With Autoimmune Thyroid Disorders in Iranian Children: A Review

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**Context:** Type one diabetes mellitus (T1DM) is an autoimmune disorder that is yet the most common type of diabetes in children and adolescents. Several genetic risk factors have been associated with T1DM, auto immune thyroiditis and other autoimmune disorder. Among autoimmune disorders, autoimmune thyroid disease (ATD) is the most frequent disorder associated with T1DM. Its prevalence varies depending on age, sex and ethnic origin of the subjects and is considerably higher than the general population and increases with duration of T1DM. The aim of this study was to review the prevalence of ATD in Iranian children with T1DM compared with other countries.

**Evidence Acquisition:** We conducted a review on all papers published on the association between autoimmune thyroiditis and T1DM, which was available on Google Scholar, Scientific Information Database (SID), Magiran and Iran Medex databases up to June 2014. Both Persian and English articles were checked. The searched terms were: diabetes mellitus, autoimmune thyroiditis, prevalence, frequency, Iranian children and adolescents. All papers which were done on patients with age under 20 years old and have used Anti-TPO and Anti-TG to evaluate patients were included.

**Results:** Six papers met all the criteria. A total of 736 participants were included in this review. After review of all the papers, the prevalence of Anti-TPO was reported between 8% and 30% and Anti-TG was reported 6.06% to 23.6% in diabetic children in Iran.

**Conclusions:** Autoimmune thyroid disorders are the most prevalent immunological diseases in patients with type 1 diabetes. All these studies have shown a higher prevalence of the disorder in patients with T1DM compared to the Iranian healthy population. Anti-TPO reported between 8% and 30% and Anti-TG reported 6.06% to 23.6% in diabetic children in Iran that was similar to the studies in other countries.

**Keywords:** Diabetes Mellitus; Autoimmune Thyroiditis; Prevalence; Frequency; Child; Adolescent; Iran

## 1. Context

Type one diabetes mellitus (T1DM) is an autoimmune disorder that is yet the most common type of diabetes in children and adolescents (1, 2). This disorder results from immune and non-immune destruction of  $\beta$ -cell islets of the pancreas (3). Therefore, children and adolescents with T1DM are at increased risk for developing other autoimmune diseases (3, 4). The most common autoimmune disorder that is associated with T1DM is autoimmune thyroiditis; however, its prevalence is dependent to age, sex and ethnic origin of the subjects and varies considerably (5-). Several genetic risk factors have been associated with T1DM, auto immune thyroiditis and other autoimmune disorder (12).

Several genes such as HLA-DQ alpha, HLA-DQ Beta, preproinsulin, PTPN22, CTLA-4, IL2 receptors and others have roles in increasing the risk of T1DM (13, 14). The major susceptibility gene for T1DM is in the HLA region of chromosome 6p, which contains the genes that code for major histocompatibility complex (MHC) Class II molecules

(15, 16). The highest-risk human leukocyte antigen (HLA) genotype for T1DM are DR3-DQ2 and DR4-DQ8 (17). In fact, children with this genotype have a 5% risk for T1DM by 15 years of age (17). In other hand, the same HLA alleles such as DQA1\*0102 and DQB1\*0602 is associated with a low risk for T1DM and are protective for disease development (18). Also, MHC susceptibility genes are not sufficient to induce T1DM; so in most cases, the polygenic inheritance can be suggested (16). The MHC I related gene A (MIC-A) has been associated with autoimmune disease (12).

Polymorphism of MIC-A associated with T1D and polymorphism in other genes are associated with many autoimmune diseases, suggests that these genes may play roles in susceptibility to autoimmunity (19, 20). Several auto antigens within the pancreas  $\beta$ -cells may play important roles in the initiation and/or progression of autoimmune islet injury (21-23). These auto antigens are proinsulin/insulin, islet-specific glucose-6-phosphatase catalytic-subunit-related protein (IGRP), glutamic-acid

decarboxylase (GAD), insulinoma associated protein 2 (IA-2 and IA-2 beta) and the auto antigen Zn T8, a zinc transporter of islet beta cells (24-27). It has been appeared that auto antibodies against these antigens develop sequentially (12), especially in young children often insulin autoantibodies are the first to appear that followed from birth and progressing to diabetes and are the highest in whom developing diabetes (28).

Antibodies to GAD-65 are found in about 70%, antibodies to insulinoma associated proteins were found in 58% and also auto antibodies to Zn T8 were founded in 60-80% of patients with T1DM at the time of diagnosis (29-32). Thus, one of the best predictors of progression to T1DM is an expression of two or more of these auto antibodies (33). In fact, family members who expressed these three auto antibodies have a 75% of five-year risk of diabetes compared with a 25% of five-year risk in relatives who expressed one of them (33). These auto antibodies may be present for years before the diagnosis of diabetes and the risk for diabetes does not decline over time (34-37). Among the genes mentioned above, CTLA-4 genes may play an important role in synergy with HLA for the development of both T1DM and auto immune thyroids (38, 39).

It is appeared that children with  $\beta$ -cell auto antibodies such as Anti-GAD and also specific HLA subtypes such as HLA-DIQB1\*0302 are associated with greater risk of developing anti-thyroid antibodies (40-43). Indeed, there is a close association between specific thyroid auto antibodies such as microsomal and peroxidase antibodies and anti-pancreatic  $\beta$ -cells auto antibodies and an increased prevalence of thyroid antibodies occur in T1DM patients with ATD, but the reasons for this increased frequency remained obscure (44-47).

Among auto immune disorders, autoimmune thyroid disease (ATD) is the most frequent with T1DM and prevalence of it that varies depending on the age, sex and ethnic origin of the subjects is considerably higher than the general population and increase with duration of T1DM (7, 48, 49). High titers of anti-TPO are highly suggestive of ATD and correlated well with thyroid dysfunction. Patients with circulating antibodies may be euthyroid, hypothyroid or rarely hyperthyroid (50-52). The presence of autoimmune thyroid disorder in patients with T1DM - even in subclinical hypothyroidism - can be associated with an increased risk of hypoglycemia, reduced linear growth and lower weight, better diabetes control, menstrual regularity and overall well-being (17, 53, 54). Current recommendations from the American Diabetes Association (ADA) are for screening TSH after stabilization at onset of diabetes, and every one to two years thereafter (53). It is also recommended that subjects with positive TPO auto antibodies and normal thyroid function should be screened on a more frequent basis, such as every six months to a year. The aim of this study was to review the prevalence of auto immune thyroid disorders in Iranian children with T1DM and compare it with other areas, and also present the importance of screening in this group of patients.

## 2. Evidence Acquisition

We conducted a review of all papers published on association between autoimmune thyroiditis and T1DM that was available on Google Scholar, Scientific Information Database (SID), Magiran and Iran Medex databases up to June 2014. Both Persian and English articles were checked. The searched terms were: diabetes mellitus, autoimmune thyroiditis, prevalence, frequency, Iranian children and adolescents. References of the found articles were used for finding more appropriate papers. Moreover, relevant national and regional conference proceedings were checked. All the studies that contained prevalence of autoimmune thyroiditis disease in children and adolescents who had T1DM were included. Articles with no information about autoantibody titer were excluded. The total number of participants with T1DM and the number of them with autoimmune thyroiditis were extracted from all papers.

## 3. Results

From all papers done in T1DM patients with age under 20 years old and used anti TPO and anti TG to evaluate patients, six papers met the all criteria. But in our research, we found three studies that the studied population was contained both adults and children. Three of which were published in English and three of them in Persian language. Three studies done in case control methods and other studies performed in cross sectional method. A total of 736 participants were checked in this review. After reviewing all the papers, the prevalence of anti-TPO was found between 8% and 30% and anti-TG was found between 6.06% and 23.6% in diabetic children in the Iran. Table 1 demonstrates the prevalence of autoimmune thyroid disorders in Iranian diabetic children derived from the selected papers.

**Table 1.** Prevalence of Autoimmune Thyroid Disorders in Iranian Diabetic Children <sup>a</sup>

Study	Population	Method	Anti-TPO	Anti-TG
Shiva (55)	99	Cross-sectional	8 (8.08)	6 (6.06)
Sharifi (56)	55	Case control	16 (29)	12 (23.6)
Bahrami (57)	386	Cross-sectional	115 (30)	-
Saffari (58)	65	Case control	7 (10.8)	11 (16.9)
Vakili (59)	48	Case control	9 (19)	10 (21)
Ardestani (60)	83	Cross-sectional	16 (19.3)	9 (11)

<sup>a</sup> Data are presented as No. or No. (%).

## 4. Conclusions

Autoimmune thyroid disorders are the most prevalent immunological diseases in patients with T1DM. In general population, this condition is affecting approximately 2% of the female population and 0.2% of the males (61).

Using case-control studies in Iranian healthy children, the prevalence of autoimmune thyroid disorders was approximately 5.7% (56, 58). According to Boelaert et al. study, the prevalence of autoimmune thyroid disease in United Kingdom population was estimated about 1.5% (62). Munteis et al. reported 2.24% in healthy Spanish people (63). Shiva et al. demonstrated that the prevalence of anti-TPO and anti-TG antibodies are 8 (8.08%) and 6 (6.06%) (55) in 2013, in a cross sectional study about thyroid autoimmunity at the onset of T1DM on 99 Iranian children patients. Bahrami just used the anti-TPO, but other researchers used both antibodies (57). In Bahrami et al. study, 386 diabetic patients screened for autoimmune thyroiditis, but they just used anti-TPO to investigate patients. The patients underwent follow up about  $9.8 \pm 4$  years. Anti-TPO checked for all participants every two years. At the end of this research, 115 (30%) patients were positive for anti-TPO (57). Sharifi et al. screened diabetic patients to determine antithyroid antibodies; although this research was done in all ages, the results included information of patient who had aged less than 20 years. Ninety one diabetic patients screened in this study, but 55 patients enrolled in our review (56).

Saffari et al. and Vakili et al. in case control studies checked the prevalence of Antithyroid Antibodies (58, 59). In Saffari et al. study, 65 diabetic patients screened for autoimmune thyroiditis along with 65 healthy children. Prevalence of anti-TPO was estimated about 16.9% and anti-TG was 10.8% (58). In Vakili et al. study, 48 diabetic children and 48 healthy children were enrolled and the prevalence of anti-TPO was estimated about 19% and anti-TG was 21% in diabetic children (59). In Ardestani et al. study on 83 children and adolescents with T1DM in Isfahan, the prevalence of anti-TPO and anti-TG antibodies was reported 19% and 11%, respectively (60). All these studies have shown higher prevalence in Iranian healthy population. Based on studies, 15-30% of T1DM patients had autoimmune thyroid disorders (ATD) (12, 60, 64-66).

ATD is a more prevalent autoimmune disorder associating with T1DM that is often clinically silent, but it may progress to obvious autoimmune thyroid disease (AITD), identified as overt or subclinical hypothyroidism and hyperthyroidism by prevalence of 1-5% and 0.5-7% for in young diabetic patients, respectively (67-69). Thyroid autoimmunity is increased in females and with longer duration of diabetes (2, 12, 37, 54). Prospective follow-up showed that the development of thyroid disease was related to the female gender and the presence of TPO antibodies, and measuring of circulating antibodies against thyroid peroxidase (anti-TPO Ab) and thyroglobulin (anti-Tg Ab) can be made easily (70).

Thyroid antibodies are more prevalent in T1DM patients compared with the general population with varying prevalence reported between 3% and 50%, based on the methodology of the study and patient's characteristics such as age, sex, ethnicity, and genetic background (68, 71). Laboratory result showed that 80% have elevated TSH

level and between 10% and 20% in those diabetic individuals having normal TSH levels. Anti-TPO reported between 8% and 30% and anti-TG reported 6.06% to 23.6% in diabetic children in Iran that was similar to other studies.

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