

# Younger Age at Onset of Type 1 Diabetes in Concordant Sibling Pairs Is Associated With Increased Risk for Autoimmune Thyroid Disease

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Individuals with type 1 diabetes are at increased risk for the development of additional autoimmune disorders compared with the general population (1–11). Autoimmune thyroiditis (AIT) and celiac disease are relatively common among patients with type 1 diabetes, with prevalence rates of ~17 and 6%, respectively (4). We sought to examine the relationship between age at onset of type 1 diabetes and prevalence of additional autoimmune disorders in a sample of sibling pairs concordant for type 1 diabetes.

## RESEARCH DESIGN AND METHODS

— Sibling pairs concordant for type 1 diabetes who visited the Joslin Diabetes Center's Pediatric, Adolescent, and Young Adult Section between June 2002 and March 2005 were identified via a search of the electronic patient database. All identified patients were insulin dependent since diagnosis and showed no evidence of insulin resistance. Monozygotic twin pairs were excluded from the study. Charts were analyzed for evidence of additional autoimmune disorders. The institutional review board approved the study protocol.

Sibling pairs were classified according to age at type 1 diabetes diagnosis. Group 1 was composed of pairs in which both proband and sibling were diagnosed at <10 years of age. Group 2 was composed of all other pairs (i.e., at least one

sibling diagnosed at 10–18 years). Screening for thyroid dysfunction was performed by obtaining thyroxine (T4 and T3RU) and/or serum thyrotropin (TSH).

At least one screening was performed every 2 years in 90% of the patients. Screening for celiac disease was obtained on any patient with symptoms suggestive of celiac disease (10). The presence of AIT was determined by the following criteria: TSH level outside the assay reference range (0.35–5.5  $\mu$ U/ml) and positive thyroid antibodies, normal TSH and positive thyroid antibodies, or abnormal TSH alone. Thyroid antibody studies were obtained in patients with an enlarged thyroid gland, abnormal TSH, or first-degree relative with AIT.

Analyses were conducted with SAS version 8.2 (SAS Institute, Cary, NC). Group comparisons were performed using unpaired *t* tests,  $\chi^2$  analysis, and Fisher's exact test.

**RESULTS** — Of the 138 patients (69 sibling pairs, age  $14.4 \pm 5.4$  years), 49% were male. At least one comorbid autoimmune disorder was found in 27 patients (20%). There were 38 sibling pairs in group 1 and 31 pairs in group 2. Mean age at type 1 diabetes diagnosis was  $3.8 \pm 2.4$  years for probands and  $5.3 \pm 3.0$  years for siblings in group 1 and  $8.0 \pm 4.5$  years for probands and  $13.1 \pm 3.0$  years for sib-

lings in group 2. Duration of type 1 diabetes was similar between groups (group 1,  $7.5 \pm 4.8$  years; group 2,  $6.9 \pm 4.7$  years).

At least one additional autoimmune disorder was identified in 19 of 76 patients in group 1 (25%) and 8 of 62 patients in group 2 (13%). Among the 27 patients, there were 33 autoimmune conditions: 25 AIT (19 in group 1), 5 celiac disease (3 in group 1), 1 juvenile rheumatoid arthritis (group 1), 1 premature ovarian failure (group 2), and 1 vitiligo (group 2). Occurrence of AIT was significantly higher in group 1 (25%) than group 2 (10%) ( $P = 0.02$ ). Of the 25 patients with AIT, 12 had elevated TSH and positive thyroid antibodies, 10 had normal TSH and positive thyroid antibodies, and 3 had elevated TSH alone (antibody results unavailable).

In group 1, 58% of patients with AIT were female; 100% of patients with AIT in group 2 were female (NS). In families where one or both siblings had AIT, a family history of AIT was present in 4 of 12 families in group 1 and 1 of 5 families in group 2 (NS). Overall, thyroid hormone replacement was required in 14% of patients in group 1 compared to 6% in group 2 (NS).

To further explore the relationship between age at onset of type 1 diabetes and occurrence of AIT, we examined patients with AIT independent of group assignment. Patients with AIT were significantly younger at type 1 diabetes diagnosis ( $4.7 \pm 4.0$  years) than patients without AIT ( $7.8 \pm 4.8$  years) ( $P = 0.003$ ). Attained age did not differ between those with and without AIT ( $13.9 \pm 5.4$  vs.  $14.5 \pm 5.4$  years). Duration of type 1 diabetes was  $9.2 \pm 4.2$  years in patients with AIT compared with  $6.8 \pm 4.8$  years in patients without AIT ( $P = 0.02$ ). The majority of patients with AIT were diagnosed with type 1 diabetes when very young. Of the 33 patients diagnosed at <3 years of age, 36% had AIT, compared with 14% of those diagnosed at  $\geq 3$  years of age ( $P = 0.005$ ). Prevalence of AIT declined with increasing age at on-

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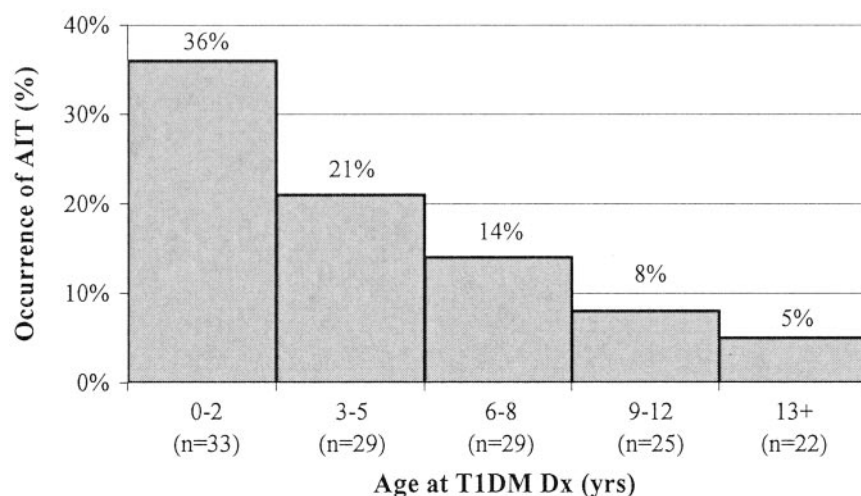
**Abbreviations:** AIT, autoimmune thyroiditis; TSH, thyrotropin.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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**Figure 1**—Occurrence of AIT by age at type 1 diabetes (T1DM) diagnosis (Dx). Younger age at onset of type 1 diabetes was significantly associated with increased occurrence of AIT in our sample of youth with type 1 diabetes ( $\chi^2 = 12.4$ ,  $df = 4$ ,  $P = 0.01$ ).

set of type 1 diabetes ( $P = 0.01$ ) (Fig. 1). Notably, within each age strata, patients with and without AIT had similar duration of diabetes.

**CONCLUSIONS**— Sibling pairs concordant for type 1 diabetes commonly develop other autoimmune disorders. Overall, 1 in 5 patients (20%) from multiplex families with sibling pairs concordant for type 1 diabetes had an additional autoimmune disorder, and most of these patients (25 of 27) had AIT. Occurrence of AIT was associated with age at onset of type 1 diabetes. One-fourth of sibling pairs in which both siblings were diagnosed with type 1 diabetes at <10 years had AIT, as compared with 10% of other sibling pairs. Five of six patients with multiple additional autoimmune disorders were diagnosed with type 1 diabetes at <10 years. Remarkably, one-third of patients who were diagnosed with type 1 diabetes at <3 years of age had AIT.

A limitation of our study was the absence of uniform thyroid-screening parameters, possibly leading to an underestimation of the prevalence of AIT in our population. Those patients with longer duration of diabetes were likely screened for AIT more frequently than those with shorter duration. However, our sample's prevalence of AIT (18%) is

consistent with other studies in pediatric type 1 diabetes (1,8). Because our sample was selected to include multiplex families with type 1 diabetes who were likely to be enriched for autoimmunity, our findings may not be directly applicable to simplex families.

In summary, the high occurrence of AIT underscores the importance of ongoing surveillance in this population, particularly for those with a younger age at onset of type 1 diabetes.

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