Thyroid autoimmunity at onset of type 1 diabetes mellitus as predictor of thyroid dysfunction

**Short running title:** autoimmune thyroid disease in type 1 diabetes

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Type 1 diabetes (T1D) and autoimmune thyroid diseases (AITD) often coexist in the same individual and in the same family. In the general population, AITD is more frequent in females and prevalence increases with age. In diabetic patients, age and sex distributions are similar, but the prevalence is higher and increases with duration of the disease (1,2,3,4). Thyroid dysfunction can affect metabolic control in T1D, and some studies (3) have shown a higher severity of diabetes when it is associated with AITD, although other studies (4) did no find these differences. Nevertheless, there is general agreement (5,6) on the utility of systematic screening of AITD in the T1D population given its high prevalence, but procedure and frequency remain controversial. The aim of the present study was to determine the presence of thyroid autoantibodies at T1D onset and its predictive capacity for the future development of thyroid dysfunction.

**Research Design and Methods:**
Between September 1987 and January 1994, 204 patients were consecutively diagnosed of T1D at our institution. One patient had developed primary hypothyroidism three years before the development of T1D, 10 patients were not followed up after a few months from diagnosis, and thyroid autoimmunity at diagnosis was not determined in 17 patients. The remaining 176 patients were included in the study. The mean age at diabetes diagnosis was 24.4 +/- 9.4 years, 65% were males, and the percentage of islet cell antibody positivity was 76%. The mean follow-up was 9.6 +/- 4.3 years. Thyroid autoimmunity was determined at onset by hemagglutination, measuring autoantibodies to thyroperoxidase (TPO-Ab) and to tyroglobulin (Tg-Ab), and were considered positive at a dilution of 1/100 or more. All patients underwent clinical follow-up and TSH was monitored every 1-2 years, using commercial non-competitive immunoassay. Thyroid dysfunction was diagnosed in the presence of a serum TSH alteration (normal range 0.3-5 mUI/l) with or without symptoms. Statistical analysis was performed with SPSS 14.0 for windows statistical package, using the $\chi^2$ test and student’s t-test. Data are expressed as means +/- SE. Statistical significance was established at p <0.05.

**Results**
Twenty-five out of 176 patients (14.2%) were TPO-Ab positive at T1D diagnosis. Eighteen of these 25 patients developed thyroid dysfunction at follow-up: primary hypothyroidism, defined as TSH > 5 mUI/l, in 17 cases and hyperthyroidism in 1 case. Only 1 of the 151 negative subjects at T1D diagnosis developed hypothyroidism: he was a 14 year-old subject at T1D onset, TPO-Ab turned later to positive and he developed hypothyroidism 15 years after diabetes diagnosis. Tg-Ab were less sensitive than TPO-Ab, being negative in 8/18 patients who developed hypothyroidism. The mean time to thyroid dysfunction development from T1D onset was 8.1 +/- 4.2 years. Interestingly, the 7 TPO-Ab positive patients who maintained normal thyroid function after 8.0 +/- 5.0 years of follow-up were younger at T1D onset than the patients who developed thyroid dysfunction (20.1 +/- 6.2 vs 29.5 +/- 11.8 years; p<0.05). Furthermore, patients who developed thyroid dysfunction were older at T1D diagnosis than those who did not (28.7 +/- 12 versus 23.9 +/- 8.9 years; p<0.05). As expected, there were also gender differences, with thyroid dysfunction being more frequent in females than in males (11/61 or 18.3% and 8/114 or 7.0% respectively; p<0.05)

Table 1 shows the prevalence of thyroid dysfunction according to the presence of TPO-Ab at T1D onset. Further data analysis showed that the presence of TPO-Ab at T1D onset can predict the
development of thyroid dysfunction with 95% sensitivity (18/19 cases of future thyroid dysfunction were detected), 96% specificity (150/157 patients were correctly classified as normal), a 99% negative predictive value (only 1/151 patients classified as normal later developed thyroid dysfunction) and 72% positive predictive value (7/25 patients remained normal in the follow-up).

Conclusions
The present study confirmed the high prevalence of thyroid autoimmunity and thyroid dysfunction in young adults with T1D. In addition, the determination of TPO-Ab at T1D onset was highly sensitive in the prediction of the development of thyroid dysfunction. Although there is general agreement that the high prevalence of thyroid dysfunction in T1D subjects justifies screening in all patients (5,6), it is not clear which is the best procedure and how often to performed it. The American Diabetes Association (ADA) (7) and several authors (8,9) recommend annual screening for thyroid disease in all T1D subjects with TSH measurement; this procedure is considered the most sensitive way to identify patients with thyroid dysfunction as autoantibodies may persist for many years without thyroid dysfunction. However, the ADA recommendations note that the presence of thyroid autoantibodies increase the risk for thyroid disease and Hansen et al (8) did not find any initial TPO-Ab negative patient that developed thyroid disease after 3 years of follow-up. Other authors (10,11) recommend screening using TSH and TPO-Ab. In a cohort of 58 type 1 diabetic patients enrolled in the DCCT study and followed for 18 years, Umpierrez et al (10) observed that TPO-Ab positive subjects were 17.9 times more likely to develop thyroid dysfunction. These authors recommended annual screening using TSH determination, particularly in patients with positive TPO-Ab. Barker (11) screen T1D patients with TPO-Ab and thyroid function at onset and every 1-2 years thereafter, and patients with positive TPO-Ab every 6-12 months. Finally, a third group of authors (1,12) recommends TSH determination only in TPO-Ab positive patients. In our study, the high sensitivity and specially the high negative predictive value of TPO-Ab for the development of thyroid dysfunction over a mean follow-up of 9.6 years, support a screening strategy with determination of TPO-Ab in all T1D subjects at diagnosis. In agreement with previous studies (8,13), Tg-Ab were less sensitive and did not increase TPO-Ab positive predictive value. Thereafter, an annual TSH determination would be performed only in subjects with positive autoantibodies. Using this procedure, only 1 case of hypothyroidism would be missed, appearing 15 years after the onset of diabetes, in a patient who was a 14 year-old at diabetes onset and who became later TPO-Ab positive.

Considering that the prevalence of TPO-Ab positivity may increase with time (1,3,8), further studies are required to investigate if additional determination of TPO-Ab after diagnosis may be useful, specially in younger patients

Acknowledgments
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References

Table 1: Prevalence of thyroid dysfunction according to the presence of antibodies to thyroperoxidase (TPO) at type 1 diabetes (T1D) onset

<table>
<thead>
<tr>
<th></th>
<th>Thyroid dysfunction</th>
<th>No Thyroid dysfunction</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-TPO + at T1D onset</strong></td>
<td>18 (10.2%)</td>
<td>7 (4%)</td>
<td>25 (14.2%)</td>
</tr>
<tr>
<td><strong>Anti-TPO – at T1D onset</strong></td>
<td>1 (0.6%)</td>
<td>150 (85.2%)</td>
<td>151 (85.8%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>19 (10.8%)</td>
<td>157 (89.2%)</td>
<td>176 (100%)</td>
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</tbody>
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