



THE PREDICTIVE VALUE OF THYROID-ANTIBODIES AND TSH-LEVELS IN A LONGITUDINAL STUDY OF FIRST-DEGREE RELATIVES OF TYPE 1 DIABETIC PATIENTS

E. Hatziagelaki¹, C. Jaeger², J. Seissler³, W. Scherbaum³, S.A. Raptis¹, R.G. Bretzel²

¹ 2nd Department of Internal Medicine, Research Institute and Diabetes Center, Athens University, Greece

² Third Medical Department, University Hospital, Giessen, Germany;

³ Diabetes Research Institute, University of Düsseldorf, Germany



OBJECTIVE

Type 1 diabetes mellitus resulting from autoimmune destruction of pancreatic β -cells is frequently associated with organ-specific autoimmune diseases, including autoimmune thyroid disease.

The aim of the present study was to determine the significance of **Thyroid-Abs** as well as the **TSH- levels** in first-degree relatives of type 1 diabetic patients who are at risk for diabetes (islet autoantibody positivity), in order to evaluate the predictive value of these markers for impaired thyroid function in these subjects

MATERIAL AND METHODS

This study was performed in 425 first-degree relatives of patients with type 1 diabetes mellitus (mean age 29.2 ± 14.4 yrs). All patients participated in the prospective Giessen-Bad Oeynhausen Family Study (Jaeger et al., Exp Clin Endocrinol Diabetes 107: 496-505, 1999). The distribution of the relatives was: **siblings/offsprings** 199 (**Group A**) and **parents** 226 (**Group B**).

In all cases, serum samples were analyzed for **ICA, IA-2ic, GAD 65 Abs, thyroid (TG/TPO) antibodies** as well as for **basal TSH-levels** at study entry and at 7 years.

The antibody status of these subjects is shown in **Table 1**.

Table 1: Antibody (Ab) characteristics of the study population (n=425). Data are given as absolute numbers and percentage.

Study Population (n=425)	Number of Subjects (%)
ICA pos.	28 (6.6)
IA-2ic pos.	29 (6.8)
GAD65 Ab pos.	18 (4.2)
Thyroid Ab pos.(total) (TG and TPO)	50 (11.8)
Thyroid Ab pos. (Group A)	24 (12.1)
Thyroid Ab pos. (Group B)	26 (11.5)

Islet cell antibodies: Islet cell antibodies (ICA) were determined by indirect immunofluorescence technique using cryostat sections of human pancreas as substrate. This assay is regularly tested in the IDW proficiency workshop series on standardization of the ICA assay. Titres have been converted to Juvenile Diabetes Foundation (JDF) units using a JDF standard reference serum. The detection limit of the assay is 5 JDF units.

GAD 65 antibody assay: GAD 65 antibodies were detected in a radioligand GAD 65 assay using as tracer recombinant, in vitro translated, human [35S]- methionin-labelled GAD 65. The cut-off index level for GAD 65 antibody positivity was determined from 150 healthy control subjects. Sera with GAD 65 antibody index values above the mean index plus three times the standard deviation were regarded as positive. This assay has been evaluated in the first IDW proficiency workshop on GADA, all samples were tested in duplicate.

IA-2ic antibody assay: Autoantibodies to the intracytoplasmic domain of IA-2 (anti-IA-2ic) were determined using radiolabelled recombinant antigens in a 96-well assay format. Recombinant autoantigens were produced by coupled in vitro transcription and translation of human IA-2ic cDNA. To achieve high specificity the cut off for antibody positivity was set at mean + 4 SD of antibody levels in 100 normal controls. In the combined IDW autoantibody workshop this assay had a diagnostic sensitivity of 73% and a specificity of 96% for type I diabetes.

Thyroid autoantibodies were determined with a commercially available enzyme-linked immunosorbent assay, using recombinant human TG or TPO as substrate.

Basal TSH-levels

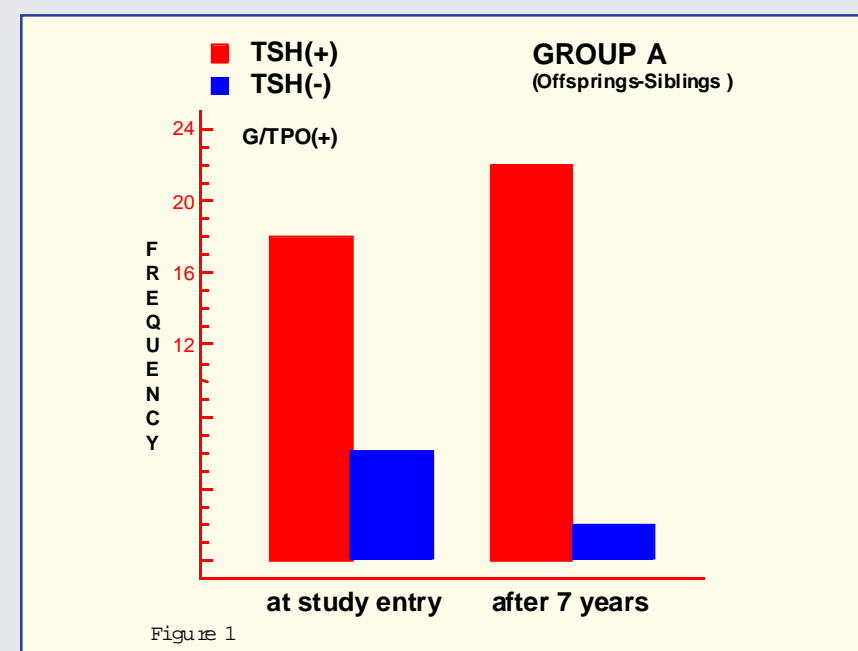
were measured by commercially available Assay-System (Immolite DPC Biermann, Germany), normal range 0.3 - 2.5 mU/L.

Statistical analysis

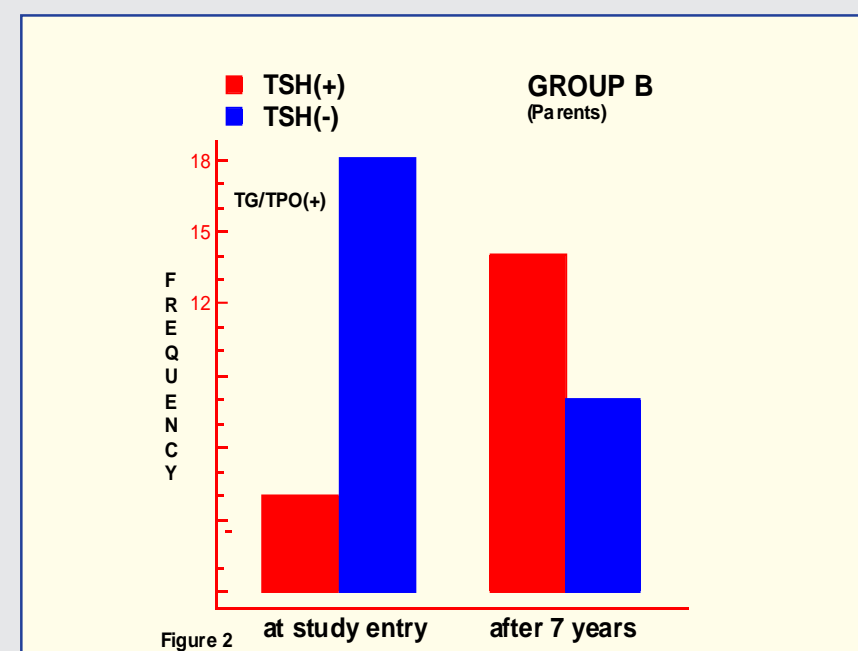
Correlations were calculated according to Spearman rank correlation coefficient. Two sample analysis according to t-test was applied to compare TSH-levels between groups. Kolmogorov-Smirnov test was applied to examine normal value distribution. A p-value of ≤ 0.05 was considered to be significant.

RESULTS

- TSH- levels** at study entry were at the upper limit of the normal range (2.5 ± 1.8 mU/L). For subjects with thyroid Ab positivity in comparison to those tested negative for TPO.
- TSH levels after 7 years** were elevated to 3.6 ± 1.9 mu/L.
- In Group A**, a positive correlation ($r=0.45$, $p \leq 0.001$) was observed between **TPO-Abs and TSH- levels**, i.e higher TSH-levels were observed in subjects with TPO-Ab positivity in comparison to those tested negative for TPO-Abs. The above correlation became stronger **after 7 years** ($r=0.53$, $p < 0.001$). (**Figure 1**)



- A significant positive correlation was also observed between IA-2ic and TPO-Ab positivity ($r=0.31$, $p < 0.001$) regarding **Group A**, which also became stronger ($r=0.42$, $p < 0.001$) after 7 years.
- In contrast**, no significant correlation was observed regarding the **Group B**. (**Figure 2**)



SUMMARY and CONCLUSION

Our results indicate that in a cohort of subjects at risk for type 1 diabetes (first-degree relatives of type 1 diabetic patients) signs of thyroid autoimmunity are observed in approximately 11.8%.

In these subjects TSH-levels are elevated (indicating subclinical hypothyroidism) and appear to increase progressively over time, which is well in accordance with the reported high rate of conversion of subclinical hypothyroidism to overt hypothyroidism in the presence of circulating anti-thyroid antibodies (Vanderpump et al., Clin Endocrinol 43: 55-68, 1995).

We therefore conclude, that first degree relatives of patients with type 1 diabetes (in particular siblings and offsprings) should be tested regularly and on a long-term basis for anti-thyroid antibodies.

In antibody positive individuals with elevated TSH-levels isohormonal treatment should be considered as suggested in a recent work by Cooper DS, N Engl J Med 345: 260-265, 2001