**Topic:** THYROGLOBULIN EPITOPES IN AUTOIMMUNE & NON AUTOIMMUNE THYROID DISEASES

**Title:** Characterization of thyroglobulin epitopes in patients with autoimmune and non-autoimmune thyroid diseases using recombinant human monoclonal thyroglobulin autoantibodies.

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**SUMMARY**

**Context:** Thyroglobulin (Tg) epitopes of serum Tg autoantibodies (TgAb) have been characterized using inhibition of Tg binding by human monoclonal TgAb in autoimmune thyroid diseases (AITD) [Hashimoto's thyroiditis (HT) and Graves' disease (GD)] but not in non-AITD [nontoxic multinodular goiter (NTMG) and papillary thyroid carcinoma (PTC)].

**Objective:** The objective was to compare Tg epitopes of serum TgAb from patients with AITD, non-AITD, and PTC associated with histological thyroiditis (PTC-T) using inhibition of Tg binding by 4 recombinant human TgAb-Fab (epitopic regions “A, B, C, and D”).

**Design:** Inhibition of Tg binding of 24 HT, 25 GD, 19 NTMG, 15 PTC, and 25 PTC-T TgAb-positive sera by each TgAb-Fab was evaluated in ELISA. Inhibition by the pool of the 4 TgAb-Fab was evaluated using labelled Tg.

**Results:** Levels of inhibition were different for TgAb-Fab regions A (P = 0.001), B (P = 0.007), and D (P = 0.011). Inhibition by region A TgAb-Fab was significantly higher in HT, GD, and PTC-T than in NTMG and PTC patients. Inhibition levels by region B TgAb-Fab were significantly higher in HT compared with NTMG and PTC patients and in GD compared with NTMG patients. Inhibition by D region TgAb-Fab was significantly lower in NTMG than in the other groups. Inhibition by the pool ranged from 44% (in NTMG) to 72% (in GD).

**Conclusions:** The pattern of Tg recognition is similar when HT patients are compared to GD and NTMG to PTC patients and differs when AITD are compared with non-AITD patients. In PTC-T patients, it is similar to that of AITD patients.

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**COMMENT**

Circulating antibodies to Tg and TPO are the hallmarks of autoimmune thyroid disorders (AITD). Characteristically, Tg-Ab and/or TPO-Ab are found in ~75% of patients with Graves’ disease (GD) and 100% (by definition) of patients with Hashimoto’s thyroiditis (HT), both in its goitrous presentation and atrophic variant. Low - but positive - titers of Tg-Ab can also be found in other thyroid diseases, such as nontoxic multinodular goiter (NTMG) and papillary carcinoma (PTC). Presence of Tg-Ab in PTC has a double importance. First, it is still debated today whether lymphocytic infiltration of the surrounding tissues (i.e. indicating focal thyroiditis) in the presence of PTC (PTC-T) might constitute a protective mechanism against tumour spreading (with better prognosis) or not. Second, the presence of Tg-Ab complicates the validity of serum Tg measurements in the follow-up of PTC.
Some authors consider that measurements of serum Tg are non reliable when Tg-Ab are present, while others (mainly in Europe) use a ‘correction’ factor based on an in vitro Tg recovery associated with Tg measurement in Tg-Ab positive serum.

In present study, 5 groups of patients were examined for differences in Tg-Ab epitopes, between AITD & non-AITD: 24 HT patients, 25 GD, 19 NTMG, 15 PTC and finally 25 PTC-T.

This in vitro study was based on the comparison of Tg-Ab binding to Tg (in Tg-coated ELISA wells) by four Tg-Ab-Fab corresponding to defined epitopic regions in the Tg molecule (‘A’ → ‘D’). Main results were that levels of binding inhibition were almost identical (as would have been expected) in GD & HT patients (thus in AITD). The two main Tg-Ab epitopes (A & B regions) were also recognized by non-AITD sera, namely NTMG & PTC, but to a lower extent and with some differences. Tg-Ab in patients with PTC-T behaved as in patients with AITD.

In summary, the pattern of Tg recognition is similar in Graves’ disease & Hashimoto, and differs from non-AITD (NTMG & PTC) where the results indicate a greater heterogeneity of Tg-Ab. In PTC patients, the pattern of Tg-Ab epitopes was quite variable, being on the non-AITD type in the absence of lymphocytic infiltration and more ATD-like in its presence.

One practical conclusion from the present work is the recommendation that Tg-Ab used to correct serum Tg measurements in PTC (with thyroid antibodies) should be carried out using the same manufacturer’s kit during the entire follow-up of PTC, to make sure that Tg results are not hampered by discrepancies in Tg measurements when using different methods. This is highly important since such patients will have a life-long follow-up and often travel or change their country of residence.

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See Figures below