Unstimulated high sensitive thyroglobulin measurement predicts outcome of differentiated thyroid carcinoma

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Abstract

Background: Thyroglobulin (Tg) measurement following thyrotropin (TSH) stimulation is used in the follow-up of patients with differentiated thyroid carcinoma (DTC). However, high-sensitive assays allow accurate measurement of serum Tg even without TSH stimulation. Here, we prospectively evaluated the impact of unstimulated high-sensitive Tg measurement in early and long-term outcome of patients with DTC.

Methods: One hundred and ninety five patients affected with DTC were evaluated. Six months after thyroid ablation (i.e., thyroidectomy plus radioiodine) serum Tg was measured during TSH-suppressive thyroxine (T4) treatment (onT4-Tg). Patients with undetectable onT4-Tg and negative neck ultrasound (US) were considered disease free and onT4-Tg was measured every 12 months for a mean follow-up of 6.8 (4.7–8.9) years. Patients with an increase in onT4-Tg underwent specific diagnostic work-up and appropriate treatment if necessary.

Results: Four patients showed recurrence at first follow-up visit with a corresponding increase in onT4-Tg concentrations (sensitivity 100%). Three patients had false positive onT4-Tg measurement (specificity 98%) with a spontaneous decrease within 3–6 months in all cases (specificity 100%). Three of 188 patients with undetectable serum onT4-Tg at first follow-up showed recurrence later with an increase in onT4-Tg as the first (n=2) or unique (n=1) sign of relapse (sensitivity 100%). Among 185 disease-free patients in a prolonged follow-up, 12 had a transient increase in onT4-Tg (specificity 91.6%). However, a spontaneous reduction within 3–6 months occurred in all cases (specificity 100%).

Conclusions: Undetectable serum onT4-Tg using a high-sensitivity immunoradiometric assay 6 months after thyroid ablation predicts low-risk of DTC recurrence. When onT4-Tg became detectable during follow-up, the evaluation of Tg slope in a 3–6 months period accurately discriminated patients with DTC recurrence from those without recurrence. This helped avoid unnecessary diagnostic or therapeutic procedures.


Keywords: differentiated thyroid carcinoma (DTC); follow-up; thyroglobulin (Tg); thyroid.

Introduction

Thyroglobulin (Tg) measurement following thyrotropin (TSH) stimulation is a useful tool in the management of patients affected by differentiated thyroid carcinoma (DTC) treated by thyroid ablation (i.e., thyroidectomy and radioiodine) (1, 2). Recently, Tg measurement during thyroxine (T4) treatment using high-sensitive assays (onT4-Tg) proved to be effective, even without TSH stimulation (3, 4). Using a high-sensitive immunoradiometric Tg assay, we previously found a 96% negative predictive value among patients undergoing T4 treatment. A further increase to 99% was obtained by coupling onT4-Tg and neck ultrasonography (US) (5). Globally, as confirmed even by using different high-sensitive Tg assays, few patients with undetectable onT4-Tg had a pathological Tg response (i.e., >2 ng/mL) to recombinant human TSH (rhTSH) stimulation, and less actually recurred (6, 7). Otherwise, no prospective data are available (8). The present study was undertaken to evaluate the impact of onT4-Tg measurement on both early and long-term outcome of patients with DTC.

Materials and methods

Patients

We enrolled 231 of 288 patients with histologically proven DTC (mean (SD) age, 52 (18) years; 24% male) papillary: 197, follicular: 34 with a low-risk profile according to European Thyroid Association Guidelines (2). Excluded were patients with 1. aggressive histotypes (i.e., papillary: tall-cell, columnar-cell, diffuse sclerosing; follicular: Hurte-cell, widely invasive or poorly differentiated) (n=9); 2. maximum tumor diameter more than 40 mm and/or lymph-node(s) involve
Figure 1  Follow-up and outcome of 195 patients with low-risk of DTC.
metastases (6 and 8 mm) were detected by US with a corresponding onT4-Tg increase to 0.9 ng/mL. The second patient showed an increase in onT4-Tg (0.4 ng/mL) 15 months following thyroid ablation. Seven months later, neck US revealed an 11 mm lymph node recurrence with a corresponding onT4-Tg of 1.3 ng/mL. Recurring tumors were resected, and in both cases Tg became undetectable (even after rhTSH stimulation) with negative follow-up at 3.4 and 2.9 years, respectively (Figure 2). Finally, a progressive increase in onT4-Tg from <0.2 ng/mL to 1.3 ng/mL in a 32-month period was observed in a patient (0.5%) with negative results in multiple imaging procedures (i.e., biochemical recurrence). None of the remaining 185 patients (98.5%) showed recurrence over 6.8 (4.7–8.8) years of follow-up. Twelve of these (6.4%) exhibited a slight increase in serum onT4-Tg (ranging from 0.2 ng/mL to 0.6 ng/mL) that spontaneously fell to undetectable levels within 3–6 months (i.e., negative Tg-trend).

Discussion

European and American Thyroid Association Guidelines suggest that a patient with DTC can be considered free of disease when there is no clinical evidence of tumor, no imaging evidence of tumor and the serum Tg is undetectable during TSH suppression therapy and following TSH stimulation (1, 2). However, some authors found a negligible role for TSH stimulation in a large number of patients having DTC, primarily those with a low-risk profile (4–6, 11, 12). Accordingly, we selected DTC patients with a low-risk profile according to the European Thyroid Association Guidelines, and evaluated the impact of serum onT4-Tg measurement in both early and long-term outcome while TSH stimulation was omitted. Six months following thyroid ablation, an increase in serum onT4-Tg occurred in four and three patients with (n = 4) and without (n = 191) proven DTC recurrence, respectively (sensitivity 100%, specificity 98%, positive predictive value 98%, negative predictive value 100%, accuracy 98%). Our data agree with those of Schlumberger and co-workers who showed that Tg immunoassays, with a functional sensitivity of 0.2–0.3 ng/mL (comprising the assay employed in our study), are accurate enough to rule out TSH stimulation in the first follow-up visit of 944 patients with DTC (13). Here, we also show that false positive results were always associated with a spontaneous decrease within 3–6 months, proving that a negative Tg trend has 100% negative predictive value. Three of 188 patients negative during early follow-up showed recurrence with a progressive increase of onT4-Tg in all cases. These results agree with data from Zophel and co-workers who studied 126 patients with radically cured disease over a 4-year period. The Tg levels increased in five (4%) patients; proven recurrence was seen in four patients while the fifth remained well, despite rising serum Tg concentrations that could be stimulated by TSH (14). Finally, a transient increase in onT4-Tg occurred in 12 disease-free patients during long-term follow-up. However, the marker spontaneously declined within 3–6 months in all cases. As a result, monitoring the onT4-Tg trend allowed us to accurately discriminate between patients with recurrence of DTC from those without recurrences.

Limitations

DTC recurrence can occur decades following thyroid ablation. Consequently, life-long monitoring is required. In this respect, the follow-up period needs to be longer for our patients, and our data should be regarded as preliminary. However, most recurrent or persistent tumor is detected during the first 5 years following thyroidecomy (15). Our patients will be monitored further in order to evaluate overall survival and cancer related morbidity over a longer period.

![Figure 2](image-url)  
**Figure 2**  
Trend of serum onT4-Tg in two patients with recurrent DTC during long-term follow-up. The dashed line represents the functional sensitivity of the assay.
Conclusions

Undetectable serum onT4-Tg with a high-sensitive immunoradiometric assay following thyroid ablation predicts low-risk of DTC recurrence. When onT4-Tg became detectable during follow-up, the evaluation of the Tg-slope in a 3–6 month period accurately discriminated between patients recurrence of DTC from those without recurrence. This helps to avoid unnecessary diagnostic or therapeutic procedures.

References


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