Thyroglobulin assay in the follow-up of patients with differentiated thyroid carcinomas: comparison of its value in patients with or without normal residual tissue

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Abstract. The usefulness of serum thyroglobulin (Tg) assay in the follow-up of differentiated thyroid carcinomas has been evaluated in 109 subjects divided into two groups.

Group 1 included 64 patients who had undergone total thyroid ablation. In 40 of the 41 patients in complete remission serum Tg was undetectable during replacement therapy (TSH below 5 μU/ml). In 18 out of the 40 patients serum Tg was detectable following endogenous TSH stimulation. As 83% of these patients had ectopic uptake prior to the last radioiodine treatment, this release of Tg under TSH stimulation suggests the persistence of occult neoplastic tissue. Of the other 23 patients, 20 had bone or lung metastases and 3 patients had lymph node recurrences: in all these patients, serum Tg was detectable during replacement therapy and increased after TSH stimulation.

Group 2 included 45 patients in whom normal residual thyroid tissue was present at the time of the investigation. Of these, 35 patients were in apparent remission and 19 of them had detectable Tg level within the normal range. The other 10 patients had detectable metastases and in 4 of these the Tg level was also within the normal range. Thus, no conclusion can be drawn from a normal Tg level in the presence of residual thyroid tissue. Bovine TSH stimulation did not improve significantly the diagnostic value of Tg assay in this group of patients.

In 1975 thyroglobulin (Tg) was proposed as a tumour marker in the follow-up of patients with differentiated thyroid carcinoma (Van Herle & Uller 1975) and numerous reports (Lo Gerfo et al. 1977; Shlossberg et al. 1979; Tang Fui et al. 1979; Bridgman et al. 1980; Charles et al. 1980; Pacini et al. 1980) have since underlined the interest of its measurement. However surgical excision of thyroid cancer often leaves some residual normal tissue (Lacour et al. 1977) which can release Tg in the serum. Furthermore TSH increases the Tg release by both normal (Uller et al. 1973) and neoplastic tissues even when the latter are not able to take up radioiodine (Schlumberger et al. 1980).

The possible influences of these two factors on the serum Tg level as a marker have not yet been studied. Therefore the aims of the present study was – 1) to assess the usefulness of serum Tg assay in the follow-up of patients with or without residual normal tissue and – 2) to compare its diagnostic significance under replacement therapy and following TSH stimulation. Hence, this study was carried out in 2 groups of patients: those with residual normal thyroid tissue and those who had undergone total thyroid ablation. In both cases the patients were studied during replacement therapy and following TSH stimulation. The present data show that the presence of residual thyroid tissue decreases the diagnostic potential of Tg determination.
Patients and Methods

Patients

This study was performed in 109 patients with differentiated thyroid carcinoma who were divided into two groups:

Group 1 included 64 patients who had undergone total thyroid ablation by surgery and administration of one or more therapeutic doses of 100 mCi of radioiodine. No normal thyroid tissue was detected at the time of this investigation.

Group 2 included 45 patients who had undergone surgery only and in whom normal residual thyroid tissue was detected at the time of the present investigation.

All the patients of group 1 and 2 have been studied both during replacement therapy at suppressive doses and following stimulation by TSH during isotopic tests.

Protocol

All patients received replacement therapy with thyroid extract at a dose of approximately 0.1 g/m²/day (Parmentier et al. 1977). The dose adopted for each patient was that which induced a decrease of the TSH level to the normal range. A pilot study in 94 patients had shown that when basal serum TSH was below 5 μU/ml, maximal TSH level 20 min after injection of TRH (200 μg iv) was below 15 μU/ml. Hence the daily amount of thyroid extract was considered to be sufficient when basal TSH level was below 5 μU/ml.

In order to prepare the patients for isotopic tests, thyroid extract was replaced by T3 at a dose of 1 μg/kg/day during 3 weeks. T3 was then withdrawn and TSH stimulation was achieved by 2 different methods: in patients with residual thyroid tissue, exogenous stimulation was given by administering 10 IU of bovine TSH on each of 3 consecutive days and in patients who had undergone total thyroid ablation, T3 was discontinued.

Fig. 1.

Effect of endogenous TSH on serum Tg level of patients without normal residual thyroid tissue (group 1). Patients in apparent remission: without prior ectopic uptake △; with prior ectopic uptake ○; patients with metastases (lung or bone with or without radioactive uptake) ●.
Table 1.
Serum Tg levels in patients with lung or bone metastases under replacement therapy and following stimulation by TSH.

<table>
<thead>
<tr>
<th>Group 1: patients without thyroid tissue</th>
<th>TSH &lt; 5 μU/ml</th>
<th>After stimulation by TSH</th>
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<tbody>
<tr>
<td>Metastases with radioiodine uptake</td>
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<td>1</td>
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<tr>
<td>14</td>
<td>P</td>
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<tr>
<td><strong>Mean ± 1 sd</strong></td>
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<td></td>
<td>123.7 ± 87.8</td>
<td>500.1 ± 89</td>
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<th>Metastases without radioiodine uptake</th>
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<td><strong>Mean ± 1 sd</strong></td>
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<th>Group 2: patients with residual thyroid tissue</th>
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<td>27</td>
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<td><strong>Mean ± 1 sd</strong></td>
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1 P: Papillary; FWD follicular well differentiated; FMD: follicular moderately differentiated.
2 L: Lungs; B: bones.
for 10 days. Thereafter, 1 to 3 mCi of $^{131}$I were administered and quantitative scintigraphy was performed 3 days later. Clinical examination, lungs and eventually bone X-rays, were performed.

**Methods**

Serum TSH was measured by radioimmunoassay (RIA) with the CEA kit. Serum Tg was measured by RIA (Schlumberger et al. 1979), using the Van Herle technique (Van Herle et al. 1973). The first batch of Tg, used to raise the first antibody in the rabbit and to make the standards, was kindly provided by A. J. Van Herle (UCLA). The normal range of the RIA is 13.9 ± 6.9 ng/ml (mean ± SD). The limit of detection is usually 2.5 ng/ml. For a value of 17 ng/ml, intra-assay variation was 4.9% and inter-assay variation 11.4%. Dilution curves of serum from patients with metastases of thyroid carcinoma were parallel to the standard curves (Schlumberger et al. 1980).

Circulating Tg antibodies have been assayed in all the patients by the tanned red cell agglutination technique (Burroughs-Wellcome). Patients with detectable Tg antibodies were not included in this study. They account for 5.9% of the patients with differentiated thyroid carcinoma.

Quantitative scintigraphies were carried out using an Ohio Nuclear 84 FD scintiscanner equipped with two opposed heads, a memory band and a colour TV monitor (Parmentier et al. 1977). Each metastasis was delineated on the TV image and the integral of the counts within its area was calculated. Calibration of the equipment made it possible to assess the metastatic uptake to within ± 20%.

For the statistical analyses, the paired t-test was used. The data in the text are presented as the mean ± 1 SD.

**Results**

**Group 1 – 64 patients without normal thyroid tissue**

(Fig. 1)

Forty-one patients were in complete remission, i.e. without any detectable metastasis since the last therapeutic administration of radioiodine, 1 to 9 years prior to Tg assay (mean = 3.1 ± 2.5 years). In 40 of these 41 patients serum Tg was undetectable whilst receiving replacement therapy. In one patient the serum Tg level was equal to 4 ng/ml. Following TSH stimulation serum Tg remained undetectable in 23 patients: of these, 3 patients (13%) had ectopic uptake detected by scintigraphy prior to the last therapeutic administration of radioiodine. Therefore in 18 of the 41 patients serum Tg was detectable either during replacement therapy or following TSH stimulation, and ranged from 4 to 14 ng/ml: 15 of these patients (83%) had previous ectopic uptake. In the patient whose Tg level during replacement therapy was 4 ng/ml, it increased up to 14 ng/ml.

Twenty-three patients had metastases: – 1) 14 patients had bone or lung metastases with radioiodine uptake (Table 1). During replacement therapy, serum Tg level ranged from 9 to 320 ng/ml (m = 123.7 ± 87.8 ng/ml). Following TSH stimulation serum Tg level ranged from 13 to 3500 ng/ml; the mean level (500.1 ± 899 ng/ml) was significantly higher ($P < 0.01$) than that during replacement therapy. – 2) Six patients had bone or lung metastases which had never been able to take up radioiodine. No administration of iodine or X-ray contrast medium could explain the lack of uptake (Table 1). Under replacement therapy, the serum Tg level ranged from 24 to 115 ng/ml (mean = 66.8 ± 32.2 ng/ml). Following TSH stimulation serum Tg level ranged from 52 to 360 ng/ml; the mean level (162.5 ± 136.1 ng/ml), was significantly higher ($P < 0.01$) than that during replacement therapy. – 3) Three patients had metastatic lymph node recurrences but no bone or lung metastasis (Table 2). During replacement therapy serum Tg was detectable in all of them (8, 35 and 45 ng/ml), and increased following TSH stimulation, respectively, to 54, 72 and 57 ng/ml. One, 2 and 10 metastatic nodes were respectively found at the time of surgery. Serum Tg was thereafter undetectable in these 3 patients even following TSH stimulation.

**Group 2 – 45 patients with residual thyroid tissue**

(Fig. 2)

Thirty-five patients were in complete remission at the time of the study. During replacement therapy, serum Tg was undetectable in 16 of them (46%) and ranged from 3.5 to 28 ng/ml in 19 patients (mean 6.4 ± 6.8 ng/ml). Following exogenous TSH stimulation, Tg remained undetectable in 3 patients (9%) and ranged from 4.5 to 75 ng/ml in 32 patients (91%); its mean (19.7 ± 18.9 ng/ml) was significantly higher ($P < 0.001$) than that under replacement therapy.

Ten patients had known relapse at the time of the study, 7 of them had bone or lung metastases with radioiodine uptake (Table 1). During replacement therapy, serum Tg level ranged from 8 to 230 ng/ml (mean: 99 ± 91.9 ng/ml). Following TSH stimulation, serum Tg level ranged from 39 to 430 ng/ml; its mean level (150.4 ± 158.4 ng/ml)
Table 2.
Serum Tg levels in patients with lymph node metastases.

<table>
<thead>
<tr>
<th>TSH &lt;5 µU/ml</th>
<th>After stimulation by TSH</th>
<th>a Nodes</th>
<th>b Histological type</th>
<th>Post-operative level of Tg (ng/ml)</th>
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<td>Group 1: patients without thyroid tissue</td>
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<td>Group 2: patients with residual thyroid tissue</td>
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<td>4</td>
<td>&lt;2.5</td>
<td>31</td>
<td>2</td>
<td>P</td>
</tr>
</tbody>
</table>

a Nodes: number of involved nodes.
b Histological type:
P: Papillary
FWD: Follicular well differentiated.

TSH < 5 µU/ml

Effect of bovine TSH on serum Tg of patients with residual normal thyroid tissue (group 2). 29 ng/ml is the upper limit of the normal range in the control population. Patients in apparent remission: ▲; patients with metastases (lung and bone) ●.
was significantly higher \((P < 0.01)\) than that during replacement therapy. Three patients had metastatic lymph nodes but no bone or lung metastasis; during replacement therapy serum Tg was undetectable in 1 patient and normal in 2 patients (12.5 and 15 ng/ml). Following TSH stimulation serum Tg levels were, respectively, 38, 18 and 31 ng/ml; 3, 6 and 2 metastatic nodes were respectively found at surgery. Serum Tg was thereafter undetectable in these 3 patients during replacement therapy.

**Discussion**

The present data confirm that Tg determination is a sensitive tool in patients without residual normal tissue but show that its value is less satisfactory when normal thyroid tissue is present. This is interesting as none of the previous studies carried out on Tg determination during the follow-up of patients with thyroid cancer had compared results obtained in patients with or without residual normal tissue (Tang Fui et al. 1979; Pacini et al. 1980).

However, even in patients with normal thyroid tissue some results are unambiguous. During replacement therapy, when serum Tg level was above the normal range of the RIA, i.e. 29 ng/ml, lung or bone metastases were present in all the cases. When serum Tg was undetectable no metastasis was found except in one patient. This patient had two metastasis-bearing lymph nodes and the amount of neoplastic tissue was small, probably less than 1 g. Despite this patient the proportion of false-negative results is small: only 1 out of the 10 patients of group 2 with neoplastic tissue (about 3% of negative results if all the 35 patients with known metastases, with or without residual normal tissue, are considered). These findings are in agreement with previous reports (Schneider et al. 1977) in which a small proportion of occult carcinomas did not cause elevation of serum Tg level.

The problem is that a large proportion of patients with residual normal tissue has Tg levels within the normal range of the RIA, below 29 ng/ml: about half of the patients in apparent complete remission and a third of the patients with metastases or local recurrences. Thus in patients with normal thyroid tissue, despite a specificity of 97.5%, then sensitivity (49%) is rather low. Moreover TSH stimulation reduces only slightly the overlap of serum Tg levels between patients with or without metastases and does not improve significantly the diagnostic value of Tg assay.

The results are much better in patients studied after total thyroid ablation (group 1). As thyroid tissue is the only source of circulating Tg, patients from this group should have no detectable serum Tg except that which is produced by some metastatic tissue. There should therefore be no ‘normal’ upper limit for these patients as was given by Pacini et al. (1980). The presence or absence of tumour as determined by clinical examination, X-ray studies and isotopic scanning are in accordance with the serum Tg concentration during replacement therapy in 98% of the cases (63 out of 64 patients). During replacement therapy, a tumour of a few grams can be detected by Tg assay, as shown by patients with node metastases. There was no false-negative in this group as the minimal value observed in patients with metastases was 8 ng/ml.

Thus in these conditions (no residual thyroid tissue and serum TSH level below 5 μU/ml), specificity was 100% and sensitivity was 98%. Following TSH stimulation, when serum Tg was undetectable, no neoplastic tissue was found and when it was above 14 ng/ml, the presence of tumour has always been demonstrated.

The present data point out another interesting observation: Tg became detectable after TSH stimulation in 18 patients without normal tissue and without known neoplastic tissue (45% of the patients in complete remission). Such a finding has been previously reported by Tang Fui et al. (1979) and Pacini et al. (1980). Non-specific interference could be excluded as dilution curves of serum from these patients were parallel to the standard curves. This release of Tg following stimulation suggests the persistence of occult neoplastic tissue. However the relatively low Tg levels observed (below 14 ng/ml) suggest that only small amounts of neoplastic tissue were present. We are following-up these patients in order to assess the prognostic significance of these low Tg levels, but it should be stressed that late relapses may appear after many years or even decades of complete remission (Gardet et al. 1977).

Hence, the following strategy, which complements that proposed by Tang Fui et al. (1979), can be proposed for patients without residual normal thyroid tissue: – 1) when Tg is detectable even at low level, under replacement or following TSH stimulation, thorough investigation is necessary since in a patient, whose serum Tg level was 9 and
13 ng/ml, respectively in these conditions, lung metastases were found by radioiodine scanning – 2) serum Tg has to be assayed following TSH stimulation only in those patients with undetectable level during replacement therapy – 3) when serum Tg remains undetectable following TSH stimulation, it may be acceptable to omit or delay the whole body scanning. This group comprises more than one third of the patients who had undergone total thyroid ablation.

In conclusion, total thyroid ablation increases the efficacy of Tg assay in the follow up of patients with differentiated thyroid carcinoma. We are presently investigating whether this observation justifies systematic thyroid ablation in patients with poor prognostic indicators such as age over 45 years and/or moderately differentiated follicular histological type (Gardet et al. 1977).

Acknowledgments

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References


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