Serum calcitonin levels with calcium loading tests before and after total thyroidectomy in patients with thyroid diseases other than medullary thyroid carcinoma

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Abstract. Calcitonin is a very sensitive tumor marker of medullary thyroid carcinoma (MTC). Patients with MTC have usually very high levels of serum calcitonin that can be used to diagnose the disease. In order to improve diagnostic sensitivity in family members with small MTCs or to evaluate postoperative biochemical cure status, measurement of calcitonin stimulated with combined intravenous calcium gluconate and pentagastrin has been widely adopted; however, gastrin has become unavailable. Currently, a provocative test using only calcium gluconate is performed; however, the standard values for this test have not been reported. We therefore conducted calcium gluconate stimulation tests in 20 patients before and after total thyroidectomy for thyroid diseases other than MTC. Preoperatively, the mean basal calcitonin level was 24.1 pg/mL and increased to 46.9 pg/mL after calcium infusion. The ratio of the peak calcitonin level to the basal value ranged from 1- to 5.23-fold, with a mean of 1.94. The ratio was higher than 3-fold in 3 patients. In 2 patients, peak calcitonin levels exceeded 100 pg/mL. Postoperatively, the mean basal level slightly decreased to 21.15 pg/mL and the response to calcium stimulation markedly decreased, with the mean ratio decreasing to 1.1-fold (range, 0.86- to 1.73-fold, maximum peak level, 33 pg/mL). Thus, some subjects without MTC show response to the calcium stimulation test up to 5.24 times the ratio and a peak value of 160 pg/mL, suggesting the requirement for judicious judgment for the early diagnosis of MTC in family members; however, after total thyroidectomy, none of the subjects showed an increase of more than 2-fold or a peak value of 33 pg/mL, suggesting that responses greater than 2-fold after MTC surgery might be abnormal, indicating the presence of residual tumor.

Key words: Calcium-loading-test, Calcitonin, Thyroidectomy, Calcium-test, Medullary thyroid carcinoma

MEDULLARY thyroid carcinoma (MTC) is a thyroid malignancy originating from C-cells. About 70% of patients do not have any family history of the disease, while the remaining 30% express a hereditary autosomal-dominant trait based on the ret gene mutation [1-4]. Serum calcitonin is a very sensitive tumor marker for MTC; however, as shown in previous studies, calcitonin elevation cannot be observed in all MTC cases, especially those with a small MTC nodule [5-7].

In order to further improve the diagnostic accuracy of MTC and to screen family members for hereditary MTC, several protocols using provocative agents to stimulate calcitonin secretion have been proposed [8-11]. In 1978, Wells et al. demonstrated that combined administration of pentagastrin and calcium gluconate showed the most effective and reliable results for calcitonin secretion from MTC tumors [12]. Since then, this protocol has been widely accepted for screening, early diagnosis and evaluation of the postoperative biochemical cure of MTC patients; however, recently, this test has been halted because gastrin is no longer available for clinical use, not only in Japan but also in the United States. Thus, a provocative test using only calcium gluconate is currently performed. In addition, the assay system for serum calcitonin has changed during the past 25 years with changes in standard values, sensitivity and specificity; however, standard values for the calcium stimulation test using the current calcitonin assay system have not been reported. We therefore conducted stimulation tests for 20 patients before and after total thyroidectomy for thyroid diseases other than MTC.
Patients and Methods

Twenty patients undergoing a total thyroidectomy for thyroid diseases other than MTC in our hospital were enrolled in this study. They consisted of 3 males and 17 females, ranging from 37 to 62 years of age, with a mean of 48.8 years. Total thyroidectomy was performed for papillary carcinoma, multinodular goiter, suspicious follicular carcinoma and Graves’ disease in 16, 2, 1 and 1 patient, respectively. For each patient, 8.5% calcium gluconate (0.25 mL/kg) was intravenously injected for 1 minute, and blood samples for calcitonin measurement were drawn before and 3 and 5 minutes after the injection. The test was performed before and 3 days after surgery. Serum calcitonin was measured by a laboratory (SRL Co., Japan) using the solid two-site immunoradiometric assay (Mitubishi Chemical Co., Japan). According to the manufacturer, the normal ranges of basal serum calcitonin are 17.1 pg/mL to 58.7 pg/mL for female and 16.6 pg/mL to 95.4 pg/mL for male subjects. The present study was approved by the ethics committee of our hospital and written informed consent was obtained from each participating patient.

Results

Basal calcitonin levels before total thyroidectomy in 20 patients were 24.1 ± 5.6 pg/mL (mean ± SD). Following calcium loading, serum calcitonin increased with variable degrees in the majority of patients. Their calcitonin levels 3 and 5 minutes after calcium injection were 45.3 ± 35.5 pg/mL (P<0.01) and 41.2 ± 26.8 pg/mL (P<0.01), respectively (Fig. 1-a). The ratio of the peak to basal value (P/B ratio) ranged from 0.53- to 5.23-fold. The ratio was greater than 3 in 3 patients (Fig. 2). Peak calcitonin levels exceeded 100 pg/mL after stimulation in two patients (110 pg/mL and 160 pg/mL, respectively (Fig. 3). After total thyroidectomy, their basal calcitonin level slightly decreased to 21 ± 4.6 pg/mL, not significantly different from the preoperative basal value; however, calcitonin levels did not show a significant response to calcium loading after total thyroidectomy. The calcitonin values 3 and 5 minutes after calcium injection were 22 ± 4.7 pg/mL (P=0.62) and 21 ± 4.6 pg/mL (P=0.91), respectively (Fig. 1-b). Their P/B ratio ranged from 0.86- to 1.73-fold, and none exceeded 2-fold. Fig. 3 shows individual changes in basal and peaked calcitonin levels pre- and postoperatively in 20 patients. Before surgery, 6 patients (30%) had a more than 2-fold increase and 3 (15%) a more than 3-fold increase of the calcitonin
Serum calcitonin levels with calcium loading tests

the diagnosis of small MTC or C-cell hyperplasia in
the setting of family screening or to evaluate the extent
of surgical treatment. In order to improve sensitivity,
a combined intravenous calcium gluconate and penta-
gastrin stimulation test was widely used; however, gas-
trin has become unavailable for clinical use. Thus, cur-
cently, a provocative test using only calcium gluconate
is performed. The assay system for calcitonin has also
changed. As a consequence, reliable standard values
for this test are unavailable, which is why we con-
ducted calcium stimulation tests in 20 patients before
and after total thyroidectomy for thyroid diseases other
than MTC.

In previous studies, when basal and stimulated serum
calcitonin levels were within normal limits and the peak
stimulated levels were less than three-fold the basal
levels, patients were regarded as normal or biochemi-
cally cured [13-17]; however, in our series of patients
without MTC, 2 patients (10%) showed stimulated calci-
tonin levels exceeding the upper normal range and 3
patients (15%) showed a P/B ratio three-fold greater
after calcium injection. Pathological examination of
thyroidectomy specimens revealed MTC in none of
these patients. In our series of so-called prophylactic
total thyroidectomy for eight family members of hered-
itary MTC without detectable tumors by ultrasonogra-
y, the lowest peak calcitonin level and the minimum
P/B ratio of preoperative calcium stimulation tests with
or without pentagastrin in patients was 92 pg/mL and
2.7 (Table 1). This finding indicates that the calcium
infusion test is not always reliable for the preopera-
tive diagnosis of MTC. Such a discrepancy has also
been reported by Gibelin et al., who demonstrated that
not only basal but also pentagastrin-stimulated calcit-
onin levels overlapped among patients with medul-

Discussion

Although serum calcitonin is very useful for the
diagnosis of MTC, it may not be sensitive enough for
level after calcium injection, while none of the present
patients after total thyroidectomy showed an increase
of the calcitonin level of more than 2-fold, even after
stimulation (Fig. 2). Surgically resected thyroid glands
were pathologically examined and none was found to
contain medullary carcinoma foci.

Table 1 Preoperative calcium stimulation tests with or without pentagastrin in patients with hereditary MTC whose tumors were not detected by ultrasonography

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age</th>
<th>Sex</th>
<th>RET mutation</th>
<th>Pathology</th>
<th>Preoperative Ca test or Ca + pentagastrin test</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>test</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>M</td>
<td>634</td>
<td>CCH</td>
<td>Ca+Gastrion</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>F</td>
<td>634</td>
<td>MTC</td>
<td>Ca+Gastrion</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>M</td>
<td>634</td>
<td>CCH</td>
<td>Ca+Gastrion</td>
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<tr>
<td>4</td>
<td>49</td>
<td>F</td>
<td>611</td>
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<td>Ca+Gastrion</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>F</td>
<td>768</td>
<td>MTC</td>
<td>Ca+Gastrion</td>
</tr>
<tr>
<td>6</td>
<td>54</td>
<td>M</td>
<td>768</td>
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<td>7</td>
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<td>8</td>
<td>12</td>
<td>F</td>
<td>634</td>
<td>MTC</td>
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</tr>
</tbody>
</table>

CCH: C-cell hyperplasia. Ca+Gastrin: stimulation with calcium and gastrin. Ca: stimulation with calcium only. CT: Calcitonin.
lary carcinoma, micromedullary carcinoma and those without medullary carcinoma [18]. MTC can also be diagnosed by fine needle aspiration biopsy (FNAB), although its sensitivity was reported to be 63% [5]. We previously showed that calcitonin measurement in the wash-out of needles used for FNAB is another useful approach, especially to diagnose small MTC [19]. These approaches should also be adopted for the diagnosis of MTC together with measurements of basal and calcium-stimulated calcitonin levels. In order to screen for hereditary MTC, ret mutation analysis is mandatory rather than biochemical tests, since gene analysis is much more reliable [17]. The calcium infusion test might give false positive results as has been reported and as the present study suggests.

However, after total thyroidectomy, none of the 20 patients without MTC showed an increase of the calcitonin level more than 2-fold the basal level following the calcium stimulation test, indicating that responses greater than 2-fold after MTC surgery might be abnormal, indicating the presence of residual tumor.

In summary, some subjects without MTC may show a response to the calcium stimulation test up to 5.24-fold the basal level, suggesting the requirement of judicious judgment for the early diagnosis of MTC in family members; however, after total thyroidectomy, none of the subjects showed an increase more than 2-fold the basal level, suggesting that responses greater than 2-fold after MTC surgery might be abnormal, indicating the presence of residual tumor.

References

11. Wells SA, Cooper CW, Ontjes DA (1975) Stimulation of thyrocalcitonin secretion by ethanol in patient with medullary thyroid carcinoma – An effect apparently not mediated by gastrin Metabolism 24: 1215.

