Long-Term Results of Radioiodine ($^{131}$I) Therapy in 331 Patients with Graves' Disease

SHINTARO SAITO, TOSHIRO SAKURADA, MAKIKO YAMAMOTO, KATSUMI YOSHIDA, KAZUO Kaise, NOBUKO KAISE and KAORU YOSHINAGA

The Second Department of Internal Medicine, Tohoku University School of Medicine, Sendai 980

Radioiodine ($^{131}$I) has widely been used for treatment of Graves' disease over 30 years. It is well known, however, that hypothyroidism may develop insidiously many years after the treatment (late-onset hypothyroidism), and its incidence is increasing with the passage of time (Green and Wilson 1964; Dunn and Chapman 1964; Nofal et al. 1966). Accordingly, it has been urged that the $^{131}$I-treated patients be followed up as thoroughly and frequently as possible to detect an earliest sign of hypothyroidism to be in time for pertinent remedy.

We have been employing $^{131}$I since 1958 for the treatment of Graves' disease and the results were published in our original report (Saito et al. 1966) and the
national tabulation (Miyake and Torizuka 1966). However, since the original data were mostly obtained from the answers of the patients to our questionnaires, they may have been somewhat distorted by the personal dispositions. To overcome this difficulty, this time follow-up studies were performed contacting directly with the patients who had passed 5 years or more after the $^{131}$I therapy. In addition, examination on the thyroid conditions was carried out as far as possible studying serum levels of thyroid stimulating hormone (TSH), thyroxine ($T_4$), triiodothyronine ($T_3$), and other parameters to investigate the pathogenic factors in the late-onset hypothyroidism.

**MATERIAL AND METHODS**

Of a total of 538 patients with Graves’ disease who passed 5–17 years after receiving the last administration of $^{131}$I, 26 were excluded from the present series: 14 were dead and 12 were treated later by surgery or antithyroid drug therapy. The remaining 512 cases were the subjects of the current study. These patients were examined physically and hormonally as completely as possible for their thyroid functions. The reason for limiting the subjects to the patients who passed 5 years or more after the $^{131}$I treatment was that the main aim of the present study was to identify the incidence and the degree of late-onset hypothyroidism. Individual dosages of $^{131}$I were determined according to the following two formulas: 80 $\mu$Ci to 1 g of the estimated weight of the thyroid gland (80 $\mu$Ci $\sim$ grams/thyroidal 24 hr $^{131}$I uptake) and Werner-Quimby’s formula setting the radiation dose to the thyroid at 10,000 rads (10,000 $\times$ 100 $\times$ 8 $\times$ grams/160 $\times$ thyroidal $^{131}$I effective half-life $\times$ thyroidal 24 hr $^{131}$I uptake). Minor adjustments were made to meet the age and goiter condition of the patients.

Serum $T_4$ was determined by competitive protein binding analysis, Tetrasorb-125 kit (Dainabbot Co., normal value 5–14 $\mu$g/100 ml). Serum $T_3$ (Dainabbot Co., normally 70–180 ng/100 ml) and serum TSH (Daiichi Co., nomally below 10 $\mu$U/ml) were determined by radioimmunoassay using commercial kits. Antithyroglobulin antibodies and antimicrosomal antibodies were measured by Thyroid test kit and Microsome test kit, respectively (Fuji Zoki Co.); titers over 100-fold positive were taken as significant for either of them. Serum total cholesterol was determined by a modification of Zak-Henly’s method; normal values ranged between 132–198 mg/100 ml.

**RESULTS**

**Follow-up study**

Of the 512 subjects, follow-up studies could be performed in 331 cases (64.6%). Of these 331 patients, 25 were already hypothyroid and receiving thyroid medication at this or other institutions. The remaining 306 cases were studied anew regarding the thyroid function as mentioned above.

**The thyroid function in the 306 subjects**

$T_4$, $T_3$, and $TSH$. The 306 cases could be divided into 2 groups according to the levels of TSH; one group having elevated TSH (10 $\mu$U/ml or higher) and the other normal (less than 10 $\mu$U/ml) as shown in Table 1. Each group was further classified by the values of $T_4$ and $T_3$: normal, high, and low.

Of the 306 cases, 188 (61.4% – the percentage figure hereafter will show the proportion to the 306 cases unless otherwise indicated) had a normal level of TSH,
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TABLE 1. Distribution of serum T4, T3 and TSH levels in the 306 patients

<table>
<thead>
<tr>
<th>TSH normal (188 cases, 61.4%)</th>
<th>TSH high (118 cases, 38.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4 Low</td>
<td>Normal</td>
</tr>
<tr>
<td>T3 Normal</td>
<td>3 (1.0)</td>
</tr>
</tbody>
</table>

and 151 (49.3%) among them had normal levels of T4 and T3, indicating they were in a state of complete remission. But in 6 others (2%) both T4 and T3 were high and no TSH was detected; they also had clinical signs of hyperthyroidism.

On the other hand, 118 cases (38.6%) had high levels of TSH, and 22 (7.2%) among them had low levels of T4 and T3, indicating hypothyroidism. Of these 22 patients, 15 were in a myxedematous state. The other 7, though no conscious symptoms, physically proved to be myxedematous. Of the remaining 96 patients 36 cases (11.8%), nearly one-third of the elevated TSH group, had normal T3 and low T4. There were 4 cases (1.3%) having normal T4 and low T3, 53 cases (17.3%) with normal T4 and T3, and 3 cases (1.0%) with T3 slightly high against normal T4. Among these 96 patients, 14 were found to need immediate thyroid medication for clinically evident myxedema; normal T3 and low T4 were proved in these patients without exception.

Relation between post-radiation years and levels of T4, T3 and TSH. Table 2 shows the levels of T4, T3 and TSH expressed in terms of mean values±standard deviations (mean±S.D.) for the normal control and 3 groups of patients divided by the passage of time after 131I therapy for 5, 10 and 15–17 years. Compared with the normal figures, the levels of T4 were not significantly different in the 5-year group but evidently lower in the 10-year and 15–17 year groups (p<0.001). Likewise, the levels of T3 were significantly lower than normal in both 10-year (p<0.02) and 15–17 year groups (p<0.01). On the contrary, TSH was already significantly higher than normal in the 5-year group (p<0.05), and the rising tendency was even more conspicuous in the 10-year and 15–17 year groups (p<0.01).

TABLE 2. The comparison of serum T4, T3, and TSH levels between the normal cases and the cases of 5, 10, and 15-17 years after 131I therapy

<table>
<thead>
<tr>
<th>TSH (µU/ml)</th>
<th>Number of cases</th>
<th>T4 (ng/100 ml)</th>
<th>T3 (µg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>30</td>
<td>9.2±1.8</td>
<td>133.3±28.7</td>
</tr>
<tr>
<td>5 years after 131I therapy</td>
<td>37</td>
<td>9.0±3.1</td>
<td>136.0±55.6</td>
</tr>
<tr>
<td>10 years after 131I therapy</td>
<td>28</td>
<td>7.0±2.6</td>
<td>111.3±38.1</td>
</tr>
<tr>
<td>15–17 years after 131I therapy</td>
<td>17</td>
<td>6.4±2.9</td>
<td>105.2±18.8</td>
</tr>
</tbody>
</table>

Numbers in the Table are mean±S.D.
Fig. 1 shows the shifts in mean values of T4, T3 and TSH in relation to the lapse of years after 131I therapy. For T4 and T3, there was a clear negative correlation between values and years. By contrast, the correlation was positive for TSH.

Serum total cholesterol and antithyroid antibodies. The levels of serum total cholesterol were 217.5±51.3 mg/100 ml in the group with normal TSH, and were 238.5±55.2 mg/100 ml in the group with high TSH, significantly elevated (p<0.01) in the group with high TSH. But, when 6 cases of hyperthyroidism in the former group and 36 cases of myxedema in the latter group were excluded from the respective series, the serum total cholesterol values were 219.0±50.8 mg/100 ml in the former, and 226.8±49.6 mg/100 ml in the latter group, and there was no significant difference between the two.

Table 3 shows the rate (%) of positive antithyroglobulin antibodies and antimicrosomal antibodies in the two groups; normal vs. elevated TSH. There was no significant difference between the two groups in the occurrence of the two varieties of antibodies.

Incidence of hypothyroidism and patients with high TSH level

As was already shown, 22 patients were confirmed as hypothyroidism both
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**TABLE 3. The cases and incidence of positive antithyroid antibodies in the normal TSH group and the high TSH group**

<table>
<thead>
<tr>
<th></th>
<th>Normal TSH group (188 cases)</th>
<th>High TSH group (118 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid test positive</td>
<td>36 cases (19.1%)</td>
<td>16 cases (13.6%)</td>
</tr>
<tr>
<td>Micromsome test positive</td>
<td>152 cases (80.9%)</td>
<td>86 cases (72.9%)</td>
</tr>
</tbody>
</table>

Fig. 2. Yearly incidence of hypothyroidism and the patients with a high TSH level. ●, patients with hypothyroidism; ○, patients with high TSH level.

**TABLE 4. Yearly incidence of clinical hypothyroidism in the 331 follow-up cases and of the patients with high TSH level in the 306 tested cases**

<table>
<thead>
<tr>
<th>Lapse in years</th>
<th>Number of follow-up cases</th>
<th>Hypothyroidism* Number of cases</th>
<th>%</th>
<th>Number of tested cases</th>
<th>High TSH level Number of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>39</td>
<td>2</td>
<td>5.1</td>
<td>37</td>
<td>9</td>
<td>24.3</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>2</td>
<td>5.6</td>
<td>35</td>
<td>6</td>
<td>17.1</td>
</tr>
<tr>
<td>7</td>
<td>41</td>
<td>3</td>
<td>7.3</td>
<td>40</td>
<td>9</td>
<td>22.5</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>4</td>
<td>8.0</td>
<td>49</td>
<td>21</td>
<td>42.9</td>
</tr>
<tr>
<td>9</td>
<td>32</td>
<td>4</td>
<td>12.5</td>
<td>31</td>
<td>10</td>
<td>32.3</td>
</tr>
<tr>
<td>10</td>
<td>29</td>
<td>6</td>
<td>20.7</td>
<td>28</td>
<td>14</td>
<td>50.0</td>
</tr>
<tr>
<td>11</td>
<td>35</td>
<td>11</td>
<td>31.4</td>
<td>32</td>
<td>16</td>
<td>50.0</td>
</tr>
<tr>
<td>12</td>
<td>23</td>
<td>10</td>
<td>43.5</td>
<td>19</td>
<td>13</td>
<td>68.4</td>
</tr>
<tr>
<td>13</td>
<td>13</td>
<td>6</td>
<td>46.2</td>
<td>9</td>
<td>4</td>
<td>44.4</td>
</tr>
<tr>
<td>14</td>
<td>12</td>
<td>6</td>
<td>50.0</td>
<td>9</td>
<td>6</td>
<td>66.7</td>
</tr>
<tr>
<td>15-17</td>
<td>21</td>
<td>7</td>
<td>33.3</td>
<td>17</td>
<td>10</td>
<td>58.8</td>
</tr>
<tr>
<td>Total</td>
<td>331</td>
<td>61</td>
<td>18.4</td>
<td>306</td>
<td>118</td>
<td>38.6</td>
</tr>
</tbody>
</table>

* Patients who had already received thyroid medication are included.

clinically and functionally. Moreover, 14 cases were clinically hypothyroid with normal T₃ but low T₄ and high TSH. All these plus 25 patients who had been already receiving thyroid medication because of evident myxedema accounted for
the hypothyroid cases in the present series, the total number being 61 (18.4% of the 331).

Table 4 shows the yearly incidence of hypothyroidism in 331 patients followed, together with the incidence of patients with high TSH levels in 306 patients tested. Fig. 2 illustrates the shift with years in the incidence of hypothyroidism and that of high TSH patients.

Fig. 3 shows how the incidence of hypothyroidism and that of high TSH cumulatively increased with years after $^{131}$I therapy. The figures shifted linearly upward in both cases.

DISCUSSION

According to the reports of Bellabarba et al. (1972) and Herrmann et al. (1975) most of the patients subjected to $^{131}$I therapy can be classified into 5 types from their blood levels of thyroid hormones and TSH: i) both $T_4$ and $T_3$ high, ii) $T_4$ normal $T_3$ high, and TSH normal, iii) $T_4$, $T_3$ and TSH all normal, iv) either $T_4$ or $T_3$, or both normal and TSH high, and v) both $T_4$ and $T_3$ low and TSH high. The patients grouped in type i) are undoubtedly still in a stage of hyperthyroidism. This was found in 2% of our 306 cases undergone the thyroid function tests. About half (49.3%) of the 306 cases belonged to type iii), and these should be in a state of complete remission. The patients of type v) had a hypothyroidism. This type was identified in 7.2% in our series. There is no problem in classifying the three types mentioned above. But the type ii), normal $T_4$ and TSH with high $T_3$, found in 22 cases (7.2%) in the present series, is not easily classified. These patients had no clinical signs of hyperthyroidism. Herrmann et al. (1975) consider that such
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instances still remain in a state of T3-toxicosis. However, in a general concept, T3-toxicosis represents a hyperthyroidism in untreated patients who have a high level of T3 alone. Considering that the type ii) cases had undergone 131I therapy, and had no signs of hyperthyroidism, it seems inappropriate to label such instances as T3-toxicosis. Whether these patients later develop manifest hyperthyroidism or improve further to a complete remission with gradual normalization of T3 has yet to be observed.

Lastly, our 96 cases belonging to type iv) could be subdivided into 4: a) T4 and T3 both normal, b) T4 normal and T3 low, c) T4 normal and T3 high, and d) T4 low and T3 normal. Incidences of these 4 subgroups were 17.3%, 1.3%, 1.0%, and 11.8%, respectively, and 31.4% in total.

As to the type iv) it has been noted in several reports that some cases, 2 to 22 years after the 131I therapy, were euthyroid with normal T4 or protein bound iodine (PBI) contrasted with a high level of TSH. The incidence of this type was reported as 58% (Toft et al. 1975), 50% (Slingerland et al. 1972), and 46% (Tunbridge et al. 1974). It is a problem how to deal with these cases in relation to hypothyroidism, but no persuasive opinion has so far been offered. Elevation of TSH has been generally recognized as the most reliable diagnostic index for hypothyroidism caused by the thyroid gland itself. However, in true hypothyroidism, blood levels of thyroid hormones, particularly of T4, must be low. In the cases mentioned above, normal levels of T4 may had been brought above by the elevated secretion of TSH producing a state of compensated hypothyroidism (Tunbridge et al. 1974). That the patients under discussion were metabolically normal is substantiated by a finding that between the patients with normal TSH and those with high, except the patients with apparent hyperthyroidism or hypothyroidism, there was no significant difference in the levels of serum cholesterol. Toft et al. (1973), however, maintain that the raised plasma-TSH levels are the result of resetting of the brain-thyroid axis and not a sign of the imminent development of frank hypothyroidism.

In contradiction to the above postulations, some researchers insisted that T4 in the cited instances, though normal in level, was apparently insufficient for each individual to keep the metabolism ever normal, and TSH, sensitive to a very delicate change in T4 (Tunbridge et al. 1974), accordingly increased in levels; and hence they recommended to place these cases in the category of subclinical hypothyroidism (Herrmann et al. 1975). In another study, Toft et al. (1975) made 3-year observation of their patients divided in the following two groups; one with T4 and TSH both normal, and the other with normal T4 and high TSH.

They found that the yearly incidence of hypothyroidism was around 5% in the latter group against none in the former. Tunbridge et al. (1974) have also emphasized that the elevation of TSH, even not indicating impending hypothyroidism, is likely to lead its development.

In type iv) there were patients with high TSH accompanied by low T4 and normal T3. Such cases were already reported by Sterling et al. (1971) and Bellabarba et al. (1972). They suggested that TSH increased its secretion in response to
the decreased secretion of thyroid hormones from the destroyed gland by $^{131}$I, and this TSH probably stimulates the secretion as well as synthesis of T$_3$ more effectively than that of T$_4$ to help T$_3$ uphold its normal level or slightly higher leaving the level of T$_4$ low. The T$_3$, thus maintained, would eventually allow the patients to remain euthyroid.

In type iv) patients, all with normal T$_4$ were euthyroid irrespective of the level of T$_3$. And, 22 of 36 with normal T$_3$ and low T$_4$ were also euthyroid based on the above mechanism. But the other 14 of the 36 patients were clinically judged as hypothyroidism. Thus, it is presumed that the patients with high TSH need no immediate thyroid medication as far as the levels of their T$_4$ remain normal. By contrast, the patients with low T$_4$ involve a considerable percentage of hypothyroidism needing an immediate therapy. The low-T$_4$ patients, even euthyroid now, may harbor a risk for falling into hypothyroidism at any moment. Toft et al. (1974) also appreciate the post-$^{131}$I drop in level of T$_4$ as the most sensitive index to the impending hypothyroidism.

Instances of post-$^{131}$I hypothyroidism are roughly divided into early and late onset types. The early type represents the disorder developing 1–2 years after $^{131}$I therapy (early-onset hypothyroidism). When the patients were administered with $^{131}$I in a relatively small dose, the incidence of the early-onset hypothyroidism does not increase after the 1–2 year period up to the 5th year or so (Glennon et al. 1972). By contrast, the late-onset hypothyroidism, after the early-type cases attained a plateau, usually increases its incidence by 2–3% a year, almost straight in mode. According to some follow-up studies conducted for over 10 years after $^{131}$I therapy, the cumulative incidence of hypothyroidism obtained by applying the life-table method amounted to 40–70% in 10 years (Glennon et al. 1972).

In our cases, the follow-up frequencies were too low to use the life-table method and the data obtained mostly through questionnaires in the past, so we only calculate the incidence of hypothyroidism in the patients followed up each year after the $^{131}$I therapy. In our patients, the incidence of hypothyroidism was 18.4% as a whole. But in 10-year cases ($n=29$) and 15–17 year cases ($n=21$), the incidence was 20.7% and 33.3%, respectively; in 14-year cases, the incidence was as high as 50%. The incidence figures apparently undergo fluctuations with the number of cases followed up in each year.

On the other hand, the incidence of high TSH patients, irrespective of the levels of T$_4$ and T$_3$, was 38.6% of 306 cases as a whole. The incidence increased with year, and it was 50% in 10-year cases and about 60% in 15–17 year cases. Admitting that a high level of TSH, though not directly indicating hypothyroidism, is suggestive of an impaired thyroid function, the incidence of hypothyroidism will further increase with the passage of time after the $^{131}$I therapy.

The cumulative incidence of clinical hypothyroidism or high TSH patients was found increasing linearly from 5 years up to 15–17 years. This agrees well with the fact that the yearly incidence of early-onset hypothyroidism attained a plateau not later than the 5th year of $^{131}$I therapy, and thereafter the late-onset hypothyroidism
yearly increased. Apparently substantiating this postulation, the levels of \( T_4 \) and \( T_3 \) were lower than normal in 10-year and 15–17 year cases of \( ^{131}I \) treatment, while TSH was higher than normal even in 5-year cases. It should be noted that with the lapse of years the mean values of \( T_4 \) and \( T_3 \) declined linearly, contrasted with a straight rise in the mean level of TSH. This seems to emphasize that hypothyroidism tend to increase with years among the patients subjected to \( ^{131}I \) therapy.

One of the factors pointed out to explain the mechanism for late development of hypothyroidism is the action of antithyroid antibodies produced in response to \( ^{131}I \), which may promote degeneration of the thyroid gland. In our cases, however, there was no significant difference in the frequency of the appearance of antithyroid antibodies between the patients with normal TSH and those with high TSH. Certainly, in the present series, a precise comparison of the data before and after \( ^{131}I \) treatment could not be done because the check of the pre-\( ^{131}I \) antibodies was not complete. Nevertheless, the results presented above almost deny the possibility of the antithyroid antibodies as a cause of late-onset hypothyroidism. Einhorn et al. (1965) also denied in their report the influence of antithyroid antibodies on the development of hypothyroidism except for those patients who developed it within one year of \( ^{131}I \) therapy.

References

