PARATHYROID FUNCTION IN HYPERTHYROIDISM

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Increased calcium and phosphorus excretion (Aub et al., 1929, Robertson, 1942) as well as decalcification of the skeletal system (Koppen, 1892; Plummer, 1928; Dunlap and Moor, 1929; Hunter, 1930; Askanazy and Rutishauser, 1933; Martos, 1938; Bartels and Haggart, 1938; Brunner, 1940; Stanley and Fazekas, 1949; Nielsen, 1952; Rose and Boles, 1953; Laake 1955; Epstein et al. 1958) has been frequently observed in hyperthyroidism. The increased excretion usually returns to normal after successful treatment surgically or with antithyroid medication (Robertson, 1942; Green and Lyall, 1951). The bones in clinical hyperthyroidism and in thyroid-fed animals are usually poor in calcium content (Smith and Mclean, 1938; Drill, 1941). Aub et al. (1929) were of the opinion that osteoporosis developed in hyperthyroidism due to the wasting of bone matrix by the special catabolic action of thyroid hormone. Histologically, however, osteitis fibrosa generalisata similar to that seen in the bones of hyperparathyroidism was observed in many cases of hyperthyroidism (Follis, 1953). Studies of Krane et al. (1956) using Ca$^{45}$ observing increased bone formation and destruction in hyperthyroidism also suggested changes similar to osteitis fibrosa generalisata instead of osteoporosis. Hansman and Wilson (1934) suggested coexistence of hyperparathyroidism to explain the metabolic changes in hyperthyroidism.

Calcium tolerance test described by Howard et al. (1953) has been considered a practical and useful test for the estimation of parathyroid function (Chambers et al., 1956). One of the authors used calcium tolerance test in two cases of hyperthyroidism at the Chronic Disease Research Institute of the University of Buffalo and observed abnormal responses, one of which returned to normal after treatment with I$^{131}$ (Fujita, 1956). In order to express the phosphorus retention pattern on induced hypercalcemia quantitatively, one of the authors (Fujita, 1958) suggested a method of calculation of “Parathyroid Index” expressed as

\[
\frac{UP_0}{GFP_0}/\frac{UP_1}{GFP_1}
\]

The normal response to hypercalcemia is decrease of urinary P and elevation of serum P. Where UP$_0$ (Urinary P excretion on the day before calcium infusion)
is larger than UP₁ (Urinary P excretion on the day of calcium infusion) and GFP₁ (glomerular filtration of phosphorus on the day of calcium infusion) is larger than GFP₀ (glomerular filtration of phosphorus on the day before infusion) due to the elevation of serum P. "Parathyroid Index" is larger than 1.

On the contrary, urinary P excretion as well as serum P scarcely changes in response to hypercalcemia in the presence of abnormal parathyroid function. "Parathyroid Index" in this case should be close to 1.

MATERIAL AND METHOD

The calcium tolerance test was conducted on six cases of hyperthyroidism at the Noguchi Hospital, Beppu, Japan. These results together with the two cases mentioned above were compared with the results of the similar tests on ten euthyroid subjects, five of them at the Noguchi Hospital and the rest at the Chronic Disease Research Institute.

The patients were given a diet containing constant amount of calcium and phosphorus for 6 days. At the Noguchi Hospital, the diet contained 600 mg of calcium and 1000 mg of phosphorus per day, while at the Chronic Disease Research Institute, a diet with 150 mg of calcium and 600 mg of phosphorus a day was used. Twenty-four hour urine collection was made throughout this period. On the 5th day, 50 cc of 10% or 59 cc of 8.5% solution of calcium gluconate was dissolved in 500 cc of 5% glucose solution and was administered intravenously with a constant rate for 4 hrs., from 8 a.m. to noon, with breakfast omitted. Serum samples were obtained immediately before and after the infusion and 24 hrs. after the beginning of infusion. All serum and urine samples were analyzed for inorganic phosphorus content with the method of Fiske and Subbarow (1925).

RESULTS

The abnormal response to hypercalcemia in hyperthyroidism was found to be quite consistent as shown in Table 1. "Parathyroid Index" in hyperthyroidism was 1.16 in average, while that in euthyroid subjects was 3.05.

Comparison of the urinary phosphorus excretion from the first to the fourth day of the test period showed a reasonable agreement which indicated a good dietary control of phosphorus intake.

Table 1. Parathyroid index in hyperthyroidism

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Parathyroid Index</th>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Parathyroid Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>K. Y.</td>
<td>17</td>
<td>F</td>
<td>2.11</td>
<td>M. N.</td>
<td>36</td>
<td>M</td>
<td>0.86</td>
</tr>
<tr>
<td>C. K.</td>
<td>26</td>
<td>F</td>
<td>2.00</td>
<td>K. K.</td>
<td>27</td>
<td>F</td>
<td>1.15</td>
</tr>
<tr>
<td>Y. Y.</td>
<td>19</td>
<td>F</td>
<td>4.64</td>
<td>K. K.</td>
<td>28</td>
<td>F</td>
<td>1.16</td>
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<td>H. Y.</td>
<td>25</td>
<td>F</td>
<td>2.30</td>
<td>C. Y.</td>
<td>19</td>
<td>F</td>
<td>1.42</td>
</tr>
<tr>
<td>T. O.</td>
<td>21</td>
<td>F</td>
<td>1.18</td>
<td>M. Y.</td>
<td>20</td>
<td>F</td>
<td>1.52</td>
</tr>
<tr>
<td>*T. F.</td>
<td>25</td>
<td>M</td>
<td>2.53</td>
<td>F. M.</td>
<td>16</td>
<td>F</td>
<td>1.24</td>
</tr>
<tr>
<td>*E. H.</td>
<td>20</td>
<td>F</td>
<td>3.31</td>
<td>*E. J.</td>
<td>41</td>
<td>F</td>
<td>1.19</td>
</tr>
<tr>
<td>*E. B.</td>
<td>49</td>
<td>F</td>
<td>2.54</td>
<td>*R. H.</td>
<td>62</td>
<td>F</td>
<td>0.73</td>
</tr>
<tr>
<td>*A. B.</td>
<td>45</td>
<td>F</td>
<td>5.98</td>
<td>Average</td>
<td></td>
<td></td>
<td>1.16</td>
</tr>
<tr>
<td>*D. H.</td>
<td>33</td>
<td>F</td>
<td>3.95</td>
<td>&quot;Student's t&quot; = 4.23 P &lt; 0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td>3.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Tests conducted at the Chronic Disease Research Institute.
In Table 2, the serum phosphorus level before the infusion was compared between euthyroid and hyperthyroid subjects. Serum phosphorus appeared to be slightly elevated in hyperthyroid subjects.

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Serum P mg/100 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>K. Y.</td>
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<td>F</td>
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<td>F</td>
<td>4.0</td>
</tr>
<tr>
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<td>3.5</td>
</tr>
<tr>
<td>T. O.</td>
<td>21</td>
<td>F</td>
<td>4.3</td>
</tr>
<tr>
<td>*T. F.</td>
<td>25</td>
<td>M</td>
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<td>F</td>
<td>4.0</td>
</tr>
<tr>
<td>*L. B.</td>
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<td>F</td>
<td>4.2</td>
</tr>
<tr>
<td>*D. H.</td>
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<td>F</td>
<td>4.0</td>
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<tr>
<td>Average</td>
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<td></td>
<td>3.9</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Serum P mg/100 ml</th>
</tr>
</thead>
<tbody>
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<td>M. N.</td>
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<td>M</td>
<td>4.1</td>
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<tr>
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<tr>
<td>K. K.</td>
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<td>F</td>
<td>5.3</td>
</tr>
<tr>
<td>C. Y.</td>
<td>19</td>
<td>F</td>
<td>4.3</td>
</tr>
<tr>
<td>M. Y.</td>
<td>20</td>
<td>F</td>
<td>4.3</td>
</tr>
<tr>
<td>F. M.</td>
<td>16</td>
<td>F</td>
<td>4.9</td>
</tr>
<tr>
<td>*E. J.</td>
<td>41</td>
<td>F</td>
<td>4.4</td>
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<tr>
<td>*R. H.</td>
<td>62</td>
<td>F</td>
<td>4.7</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td>4.6</td>
</tr>
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</table>

* Tests conducted at the Chronic Disease Research Institute.

DISCUSSION

Metabolic changes in hyperthyroidism and hyperparathyroidism are different in several aspects. With the exception of Robertson (1942), who reported that both serum Ca and serum P were lower in hyperthyroidism than in normal subjects, serum Ca and serum P in hyperthyroidism have been considered to lie within normal limits. On the contrary, marked elevation of serum Ca and decrease of Serum P have been accepted as criteria for the diagnosis of primary hyperparathyroidism. According to Aub et al. (1929) both urinary and fecal Ca excretion were increased in hyperthyroidism but only urinary excretion was increased in hyperparathyroidism. On the other hand, Robertson (1942) showed normal fecal excretion of Ca in hyperthyroidism in contrast to a decreased fecal Ca excretion in hyperparathyroidism. Cope and Donaldson (1937) reported a case of coexisting hyperthyroidism and hypoparathyroidism as an evidence against hyperactive parathyroid as the cause of increased Ca and P excretion in hyperthyroidism. The effectiveness of thyroid substance on postoperative hypoparathyroidism observed by Aub et al. (1932), and Cope and Donaldson, (1937) suggested some functional relationship between these two organs. Engfeldt and Hjertquist (1954) produced hyperplasia and cytological picture of hyperfunction of parathyroid in rats using thyroxine or TSH and believed that the elevation of serum P due to thyroxine or TSH was responsible for the secondary hyperparathyroidism.

Gilligan et al. (1936) injected blood from hyperthyroid subjects to rabbits to test the parathyroid hormone like activity according to Hamilton and Highman's method (1936), and found an increased activity.

Our study indicates abnormal parathyroid function in hyperthyroidism in accordance with these observations. Whether this represents secondary hyperparathyroidism or is due to some other mechanisms such as regulations by hypophysis or autonomic nervous system remains to be investigated.
SUMMARY

Calcium tolerance test and calculation of “Parathyroid Index” was carried out on 8 hyperthyroid and 10 euthyroid subjects. Abnormal parathyroid response to hypercalcemia was observed in hyperthyroid subjects. Functional relationship between thyroid and parathyroid glands was briefly reviewed.

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REFERENCES

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