Plasma and Erythrocyte Magnesium Concentrations in Thyroid Disease: Relation to Thyroid Function and the Duration of Illness

Yuhei SHIBUTANI, Toshihiko YOKOTA*, Satoshi IIJIMA*, Akihiro FUJIOKA*, Shingo KATSUNO and Kunihiro SAKAMOTO

To clarify magnesium metabolism in thyroid dysfunction, plasma and erythrocyte magnesium concentrations (P-Mg, E-Mg) were determined in patients with untreated thyroid diseases and their relations to thyroid hormone levels and the duration of illness were examined. P-Mg was significantly lower in hyperthyroid patients than in euthyroid or hypothyroid individuals. E-Mg was significantly higher in hypothyroid patients than in hyperthyroid or euthyroid individuals. In the entire series of 84 subjects, both P-Mg and E-Mg showed significant negative correlations with thyroid hormone levels, but the correlations were greater in P-Mg than E-Mg. In hyperthyroid patients, both P-Mg and E-Mg were negatively correlated with the duration of illness, but this correlation was greater in E-Mg than P-Mg. Also, both P-Mg and E-Mg were significantly higher in patients with destructive thyroiditis with a short duration (0.5 months) such as subacute or painless thyroiditis than in patients with Graves' disease (4.9 months). These results suggest that magnesium metabolism in thyroid dysfunction is affected not only by thyroid hormone levels but also by the duration of illness.

Key Words: Plasma magnesium, Erythrocyte magnesium, Hyperthyroidism, Hypothyroidism, Graves' disease, Destructive thyroiditis

Magnesium metabolism is known to be related to thyroid function. Improvements in clinical symptoms in hyperthyroid patients after administration of magnesium (1, 2) and reduction in thyroid function and enlargement of the thyroid gland in rats fed a magnesium-deficient diet (3, 4) have been reported. However, there is as yet no consensus about the effects of thyroid hormone on magnesium metabolism. Plasma magnesium concentration was reportedly reduced in hyperthyroid patients and increased in hypothyroid patients in many studies (5-9), but was not different as compared with normal subjects in some studies (10, 11). On the other hand, reports concerning erythrocyte magnesium concentration are few (6-9), and its relation to thyroid function remains to unclear.

In this study, we examined plasma and erythrocyte magnesium concentrations (P-Mg, E-Mg) in patients with untreated thyroid diseases, and their relations to thyroid hormone levels and the duration of illness to clarify magnesium metabolism in thyroid dysfunction.

SUBJECTS AND METHODS

The subjects consisted of 84 patients (13 males and 71 females) who were treated at the Thyroid Clinic, Internal Department, Hyogo Prefectural Amagasaki Hospital for the first time. The diagnoses were made on the basis of the history of present illness, physical examination, blood hormone levels, anti-thyroid antibody, scintigraphy, ultrasonography, and aspiration biopsy cytology. Patients

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with hypertension, diabetes mellitus, liver disease, or renal disease were excluded from this study. Table 1 shows the diseases and the number of patients with them in the 26 euthyroid, 45 hyperthyroid, and 13 hypothyroid subjects.

Blood was drawn between 9 and 10 a.m. after an overnight fast. Serum was isolated from a part of the blood, and the remaining blood was centrifuged with 5 mM EDTA-2K during refrigeration to separate plasma from erythrocytes. The erythrocyte were washed three times with isotonic choline chloride during refrigeration, as described previously (12). The serum, plasma, and erythrocytes samples were stored at −20°C until measurement.

Magnesium concentration was determined by atomic absorption spectrophotometry (Model AA-1; Nippon Jarrell-Ash, Co., Ltd, Kyoto, Japan), and P-Mg was expressed as mmol/l and E-Mg as mmol/l packed cell.

Triiodothyronine (T3), thyroxine (T4), and free thyroxine (Free T4) were determined by radioimmunoassay, and thyroid-stimulating hormone (TSH) by fluoroimmunoassay using commercially available kits. Table 2 summarizes the results of the thyroid function tests in the euthyroid, hyperthyroid, and hypothyroid patients.

All values were expressed as means ± SD. Student’s t-test was performed when the results of analysis of variance by one-way layout were significant. p-values of less than 0.05 were regarded as statistically significant.

RESULTS

Table 3 shows the mean values of age, anthropometric measurements, and serum albumin and creatinine levels in euthyroid, hyperthyroid, and hypothyroid patients. The age was slightly higher in the hypothyroid group, but the difference was not significant. There were no significant differences in body height or weight among the three groups. Serum albumin level of hyperthyroid patients was significantly lower than that of euthyroid or hypothyroid patients, and serum creatinine level was reduced in hyperthyroid patients but increased in hypothyroid patients, each group showing a significant difference as compared with the euthyroid group.

Figure 1 shows the mean values of P-Mg and E-Mg in euthyroid, hyperthyroid, and hypothyroid patients. P-Mg was significantly lower in the hyperthyroid group than in the euthyroid or hypothyroid group. Also, it was significantly higher in the hypothyroid group than in the euthyroid group. Since serum albumin level was significantly reduced in hyperthyroid patients, correction of the values was made according to the formula of Kroll and Elin (13). P-Mg for the hyperthyroid group was 0.77 ± 0.05, as compared to 0.73 ± 0.06 mmol/l before correction. The differences in P-Mg were statistically significant even after correction. E-Mg showed a similar tendency to P-Mg, and was significantly higher in the hypothyroid group than in the

Table 1. Number of patients with thyroid disease, by thyroid status.

<table>
<thead>
<tr>
<th></th>
<th>Euthyroid (26)</th>
<th>Hyperthyroid (45)</th>
<th>Hypothyroid (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple goiter</td>
<td>(8) Graves' disease</td>
<td>(39) Chronic thyroiditis</td>
<td>(8)</td>
</tr>
<tr>
<td>Chronic thyroiditis</td>
<td>(6) Subacute thyroiditis</td>
<td>(4) Thyroidectomy</td>
<td>(5)</td>
</tr>
<tr>
<td>Adenomatous goiter</td>
<td>(3) Painless thyroiditis</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>Benign tumor</td>
<td>(9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Measures of thyroid status in patients with thyroid disease.

<table>
<thead>
<tr>
<th></th>
<th>Euthyroid</th>
<th>Hyperthyroid</th>
<th>Hypothyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;3&lt;/sub&gt; (ng/dl)</td>
<td>133±20</td>
<td>449±176</td>
<td>59±27</td>
</tr>
<tr>
<td>T&lt;sub&gt;4&lt;/sub&gt; (μg/dl)</td>
<td>8.2±1.2</td>
<td>21.3±5.5</td>
<td>2.3±1.3</td>
</tr>
<tr>
<td>Free T&lt;sub&gt;4&lt;/sub&gt; (ng/dl)</td>
<td>1.24±0.26</td>
<td>6.15±0.18</td>
<td>0.24±0.15</td>
</tr>
<tr>
<td>TSH (μU/ml)</td>
<td>1.34±0.79</td>
<td>&lt;0.05</td>
<td>154.4±95.1</td>
</tr>
</tbody>
</table>
Table 3. Comparisons of age, anthropometric values, and serum albumin and creatinine levels among three groups.

<table>
<thead>
<tr>
<th>Item</th>
<th>Euthyroid</th>
<th>Hyperthyroid</th>
<th>Hypothyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>41.3±13.7</td>
<td>37.4±13.6</td>
<td>48.7±22.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155.9±6.4</td>
<td>157.8±5.7</td>
<td>157.7±8.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>51.7±5.4</td>
<td>51.3±6.9</td>
<td>56.4±10.4</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>4.3±0.2</td>
<td>4.0±0.3</td>
<td>4.2±0.3</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.80±0.14</td>
<td>0.65±0.15</td>
<td>1.24±0.40</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01

Fig. 1. Comparison of plasma and erythrocyte magnesium concentrations in euthyroid (EU, open bar), hyperthyroid (HYPER, hatched bar), and hypothyroid (HYPO, solid bar) patients. *p<0.05, **p<0.01.

Fig. 2. Relationships between plasma magnesium concentration and thyroid hormone levels. **p<0.01.

euthyroid or hyperthyroid group.

In the entire group of 84 subjects, P-Mg showed significant negative correlations with T3 (r = −0.669), T4 (r = −0.683), and Free T4 (r = −0.710) (Fig. 2). E-Mg also showed significant negative correlations with T3 (r = −0.299), T4 (r = −0.270), and Free T4 (r = −0.288) (Fig. 3). A significant positive correlation was observed between...
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P-Mg and E-Mg ($r=0.448$), but P-Mg had closer correlations with thyroid hormone levels than E-Mg.

The relationships of blood magnesium concentrations with thyroid hormone levels and the duration of illness was studied next in 45 hyperthyroid patients. In this study, the interval between the appearance of clinical symptoms and the first examination was regarded as the duration of disease. As shown in Table 4, both P-Mg and E-Mg were negatively correlated with not only thyroid hormone levels but also the duration of illness. P-Mg had greater correlations with thyroid hormone levels than with the duration of illness, whereas E-Mg showed greater correlations with the duration of illness than with the hormone levels. Between the group with

Table 4. Correlation coefficients between blood magnesium levels and thyroid hormones or duration of illness in hyperthyroid subjects.

<table>
<thead>
<tr>
<th></th>
<th>$T_3$</th>
<th>$T_4$</th>
<th>Free $T_4$</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-Mg</td>
<td>-0.350*</td>
<td>-0.310*</td>
<td>-0.456**</td>
<td>-0.174</td>
</tr>
<tr>
<td>E-Mg</td>
<td>-0.176</td>
<td>-0.085</td>
<td>-0.129</td>
<td>-0.393**</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01

Table 5. Comparisons between Graves' disease and destructive (subacute and painless) thyroiditis.

<table>
<thead>
<tr>
<th></th>
<th>Graves' disease</th>
<th>Destructive thyroiditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_3$ (ng/dl)</td>
<td>445±158</td>
<td>335±92</td>
</tr>
<tr>
<td>$T_4$ (μg/dl)</td>
<td>21.0±5.3</td>
<td>19.5±2.9</td>
</tr>
<tr>
<td>Free $T_4$ (ng/dl)</td>
<td>6.20±1.85</td>
<td>5.18±1.68</td>
</tr>
<tr>
<td>P-Mg (mmol/l)</td>
<td>0.72±0.05</td>
<td>0.80±0.06**</td>
</tr>
<tr>
<td>E-Mg (mmol/l)</td>
<td>2.09±0.21</td>
<td>2.31±0.33*</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>4.9±4.1</td>
<td>0.5±0.2**</td>
</tr>
</tbody>
</table>

*p <0.05, **p<0.01
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Graves' disease and the group with destructive thyroiditis such as subacute or painless thyroiditis, thyroid hormone levels were slightly higher in the first group, but the difference was not significant. However, the duration of illness was 4.9 months for Graves' disease and 0.5 months for destructive thyroiditis, and both P-Mg and E-Mg were significantly higher in the destructive thyroiditis group than in the Graves' disease group (Table 5).

**DISCUSSION**

Abnormal plasma magnesium levels are often observed in thyroid diseases, but it is considered to be secondary to thyroid dysfunction rather than specific to the disease themselves. There have been a number of reports that plasma magnesium concentration was reduced in hyperthyroidism but elevated in hypothyroidism (5–9). Moreover, plasma magnesium concentration is reported to be normalized as thyroid function is improved by treatment. Some authors, however, observed no difference in plasma magnesium concentration in hyperthyroid or hypothyroid patients as compared with normal controls (10, 11). These discrepancies among the reports may be ascribed to the unavailability of atomic absorption spectrophotometry for determination of magnesium concentration or the inaccuracy of evaluation of thyroid function because of the absence of radioimmunoassay in all these studies, which were performed more than 20 years ago. Recently, Dolev et al. (14) reported that a significant negative correlation was found between plasma magnesium concentration and thyroxine, seemingly suggesting that hyperthyroid patients have a lower plasma magnesium level than normal subjects, but that the difference between the two groups disappeared when the magnesium level was corrected for serum albumin. Since hyperthyroidism is often accompanied by hypoalbuminemia, they suggested the possibility that hypoalbuminemia is involved in the hypomagnesemia observed in hyperthyroid patients. In this study, plasma magnesium concentration showed a significant negative correlation with thyroid hormone levels, and was significantly lower in hyperthyroid patients but significantly higher in hypothyroid patients than in euthyroid controls. We corrected the magnesium concentration using the formula of Kroll and Elin (13) to eliminate the effect of serum albumin level, but similar significant differences were observed also after correction. Therefore, the changes in plasma magnesium concentration in patients with thyroid dysfunction cannot be regarded simply as a result of changes in serum albumin level. On the other hand, it is generally agreed that thyroid hormones increase urinary excretion of magnesium. It has been reported that an increase in glomerular filtration rate (8, 15) or in urinary calcium excretion (16) caused by thyroid hormones promotes urinary magnesium excretion. The significant decrease in hyperthyroidism or increase in hypothyroidism in serum creatinine level observed in this study suggest that changes in glomerular filtration rate associated with thyroid hormone levels affect urinary magnesium excretion. Also, thyroid hormones are reported to stimulate the renin-aldosterone system (17, 18). Urinary magnesium excretion is known to increase and serum magnesium concentration to decrease under conditions that the renin-aldosterone system is activated (19, 20). Wuttke and Kessler (21) suggested increase secretion of aldosterone in hyperthyroidism on the basis of the finding that the reduced magnesium concentration in hyperthyroid patients was improved by administration of spironolactone.

There have been few studies of erythrocyte magnesium concentration in thyroid diseases, and the findings have not been consistent. Zumkley (9) reported that erythrocyte magnesium concentration was reduced in hyperthyroidism or elevated in hypothyroidism as compared with normal controls. Several reports, however, showed no difference in erythrocyte magnesium concentration among the three groups (6–8). Moreover, a recent study by Dolev et al. (14) denied the presence of a significant correlation between erythrocyte magnesium concentration and thyroid hormone levels. In this study, erythrocyte magnesium concentration was significantly higher in hypothyroid subjects than in euthyroid or hyperthyroid subjects. In the entire group of subjects, erythrocyte magnesium concentration showed significant negative correlations with thyroid hormone levels, though they were not as great as the correlations of plasma magnesium...
concentration. We further studied the relationships of blood magnesium concentrations with thyroid hormone levels and the duration of illness in 45 hyperthyroid patients. Interestingly, plasma magnesium concentration showed a significant negative correlation with thyroid hormone levels rather than the duration of illness, whereas erythrocyte magnesium concentration showed a significant negative correlation with the duration of illness rather than the hormone levels. Since a significant positive correlation was found between erythrocyte and plasma magnesium concentration, the change in erythrocyte magnesium concentration is considered to be secondary to that in plasma concentration. However, the life span of erythrocyte may be involved in the relationship between erythrocyte magnesium concentration and the duration of illness. Considering the report that the life span of erythrocyte is reduced in hyperthyroidism (22), erythrocyte magnesium concentration may be altered with the duration of illness. Moreover, erythrocyte magnesium concentration is reported to be elevated with an increase in the activity of erythrocyte membrane Na-K ATPase (23, 24). In hyperthyroidism, protein degradation is promoted by excess thyroid hormones, and the amount of Na-K ATPase in the erythrocyte membrane is reduced (25, 26). However, the amount of Na-K ATPase in the erythrocyte membrane was shown not to be changed by short incubation with thyroid hormone, and the reduction in the amount of Na-K ATPase in the erythrocyte membrane is considered to be affected by the extent and the duration of the excess in thyroid hormones (27).

These results suggested that plasma magnesium concentration is reduced in hyperthyroidism, but that the reduction in erythrocyte magnesium concentration is brought about by excessive secretion of thyroid hormones for a certain period. Therefore, magnesium metabolism in thyroid dysfunction is considered to be affected not only by the thyroid hormone levels but also by the duration of illness. Plasma and erythrocyte magnesium concentration may be useful as indices, respectively, of the state of thyroid hormone secretion and its duration.

REFERENCES


