Recovery and Maintenance of Copper Levels in Geriatric Patients on Enteral Feeding for a Prolonged Period

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Summary Latent copper deficiency develops after 3 mo in patients receiving enteral feeding solutions with low copper levels. We examined whether a copper-rich enteral solution restores and maintains the level of copper in serum for a prolonged period. The study group consisted of 13 patients (eight males and five females). Commercial preparations, F2α8 and Lifelon-PZ®, for enteral administration were used. F2α8 and Lifelon-PZ® contain 1.6 and 0.13 mg/L, respectively, of copper. Serum copper levels were monitored in patients before and after administration of F2α8, a copper-rich enteral solution, at the neurological ward of Nagoya Daini Red Cross Hospital. Four of the 13 patients received Lifelon-PZ®, a copper-poor enteral solution, before this trial. Blood samples were taken every month. The daily average copper dosage with F2α8 was 1.8±0.4 mg/d (1.0–2.4 mg/d). The copper level in the four patients who received Lifelon-PZ® was 10.5±5.5 μmol/L before this trial. The level rose to 18.9±3.6 μmol/L 1 mo after the change to the copper-rich, F2α8. The average serum copper level in the other patients before the start of enteral feeding was 15.3±5.0 μmol/L. The proper copper level was maintained with F2α8 in the long term. A copper-rich enteral preparation could easily restore and maintain serum copper levels for a prolonged period. A dose of 1.8±0.4 mg copper/d (1.0–2.4 mg/d) was sufficient for our patients.

Key Words copper, enteral nutrition, deficiency, nutritional assessment, dietary intake

Copper is an essential trace element in humans (1). Copper deficiency has been regarded as a rare complication of enteral nutrition: In 1988, Higuchi et al. reported the first case of neutropenia due to copper deficiency and the required dose of copper in children and young adults receiving enteral nutrition (2). Since then, several reports of neutropenia and anemia in copper-deficient patients receiving enteral nutrition have been published (3, 4), since some formulas do not contain a sufficient amount of copper. Therefore, one should monitor serum copper level closely during long term enteral nutrition. We have reported the relationship between copper deficiency and the period of enteral nutrition (5). Latent copper deficiency develops after 3 mo in patients receiving copper-poor enteral solutions. However, only a few patients develop overt copper deficiency, since plasma copper level declines when copper stores of the body are depleted. There is no available data in English on copper requirement to maintain plasma copper level in geriatric patients receiving enteral nutrition for a prolonged duration. There are few reports about copper deficiency and recovery of serum copper level (3, 4), but no study to determine the copper requirement for geriatric patients receiving enteral nutrition for a prolonged period.

In this study, we concluded that a copper-rich enteral solution could easily restore the copper level and maintain a proper serum copper level for a prolonged period.

PATIENTS AND METHODS

Patients. The study group consisted of 13 patients (eight males and five females). The mean age of the patients was 72.3±14.9 (range, 41–92) yr. Serum copper levels were monitored before and after the administration of F2α8, a copper-rich enteral solution, at the neurological ward of Nagoya Daini Red Cross Hospital. Patients on enteral tube feeding were placed on a standard protocol. Patients with abnormalities of liver or kidney function were excluded. Four of the 13 patients received Lifelon-PZ®, a copper-poor enteral solution, before this trial. Experiments met all ethical and scientific standards embodied in the World Medical Association Declaration of Helsinki. Informed consent was obtained from the patients after providing sufficient information on the experiments.

Nutrient content of the diet. Two commercial formulations, F2α8 and Lifelon-PZ®, for enteral administration were used. F2α8 and Lifelon-PZ® contain 1.6 and 0.13 mg/L, respectively, of copper. The formulations are shown in Table 1. No supplement of zinc or iron was administered during this experiment.

Sample collection and processing. Blood samples were taken every month. Blood was collected at 8 AM. The concentration of copper was measured by flameless
atomic absorption spectrophotometry. Other blood chemistry tests were made using routine methods and protocols. The tests were conducted at the Nagoya Daini Red Cross Hospital. All data are expressed as mean±standard deviation (SD).

RESULTS

Nutritional status

The clinical details and indication for enteral nutrition are presented in Table 2. The daily average dosage of energy was 1107.7±284.2 kcal/d (600–1500 kcal/d). The daily average dosage of copper was 1.8±0.4 mg/d (1.0–2.4 mg/d). The study included 13 patients and 76 measurements.

Monitoring of serum copper levels

Table 1. Formula of enteral feeding in 1 L.

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>F2α°</th>
<th>Lifelon-PZ°</th>
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</thead>
<tbody>
<tr>
<td>Energy (kcal)</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>22</td>
<td>28</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>151</td>
<td>138</td>
</tr>
<tr>
<td>Water (g)</td>
<td>840</td>
<td>850</td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Copper (mg)</td>
<td>1.60</td>
<td>0.13</td>
</tr>
<tr>
<td>Zinc (mg)</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Manganese (µg)</td>
<td>250</td>
<td>270</td>
</tr>
<tr>
<td>Selenium (µg)</td>
<td>50</td>
<td>22</td>
</tr>
<tr>
<td>Vitamin B12 (µg)</td>
<td>4.5</td>
<td>11.3</td>
</tr>
<tr>
<td>Folic acid (µg)</td>
<td>200</td>
<td>750</td>
</tr>
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</table>

Table 2. Clinical data on patients.

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Disease</th>
<th>Energy (kcal/d)</th>
<th>Dose of copper (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>55</td>
<td>ALS</td>
<td>600</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>79</td>
<td>CVD</td>
<td>900</td>
<td>1.4</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>67</td>
<td>CVD</td>
<td>900</td>
<td>1.4</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>77</td>
<td>CVD</td>
<td>900</td>
<td>1.4</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>67</td>
<td>ALS</td>
<td>900</td>
<td>1.4</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>54</td>
<td>ALS</td>
<td>900</td>
<td>1.4</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>87</td>
<td>CVD</td>
<td>1200</td>
<td>1.9</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>87</td>
<td>PD</td>
<td>1200</td>
<td>1.9</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>92</td>
<td>CVD</td>
<td>1200</td>
<td>1.9</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>80</td>
<td>CVD</td>
<td>1200</td>
<td>1.9</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>76</td>
<td>AE</td>
<td>1500</td>
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<tr>
<td>12</td>
<td>F</td>
<td>41</td>
<td>CVD</td>
<td>1500</td>
<td>2.4</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>78</td>
<td>CVD</td>
<td>1500</td>
<td>2.4</td>
</tr>
</tbody>
</table>


The four patients who received Lifelon-PZ° had copper levels of 10.5±5.5 µmol/L, which rose to 18.9±3.6 µmol/L 1 mo after the change to the copper-rich F2α°. The average serum copper level in the other patients before the start of enteral feeding was 15.3±5.0 µmol/L (reference value: 10.0–24.6 µmol/L). After the administration of F2α°, no significant decrease in the copper level was observed in the long term. There were two patients with high copper levels (Fig. 1A) who received copper at a dose of 1.4 mg/d or 1.9 mg/d.

Fig. 1. The period of enteral feeding and serum levels of copper (A), ceruloplasmin (B) and zinc (C). The study of A, B and C involved 13 patients and 76 measurements. The levels of copper were measured by flameless atomic absorption spectrophotometry. ▲: In the four patients who received Lifelon-PZ° before this trial, copper levels rose immediately after the change to F2α°, a copper-rich enteral formula.

Monitoring of ceruloplasmin levels

Ceruloplasmin levels were monitored since ceruloplasmin has the capacity to form copper complexes and is a multifunctional protein involved not only in the mobilization of plasma iron but also in copper transport and in the regulation of biogenic amines. The average level of ceruloplasmin in the patients before the start of enteral feeding was 263±84 mg/L (Fig. 1B, reference value: 180–370 mg/L). There was a correlation between serum copper level and serum ceruloplasmin level (Fig. 2A, R²=0.842). No significant decrease in serum ceruloplasmin level was observed in the long term with F2α°.

Monitoring of zinc levels

Zinc levels were monitored, since zinc interferes with
copper utilization by inducing intestinal metallothionein. The average serum zinc concentration in the patients before the start of enteral feeding was 11.0±4.28 µmol/L (Fig. 1C, reference value: 9.8–17.0 µmol/L). No significant decrease in serum zinc level was observed in the long term after administration with F2α®. There was no relation between serum copper level and serum zinc level (Fig. 2B, R²=0.0006).

**Monitoring of selenium levels**

Selenium levels were monitored only in four patients who received Lilon-PZ®️, which contain 22 µg/L of selenium. The average serum selenium concentration in the patients before the start of this study was 1.2±0.4 µmol/L (reference value: 1.2–2.0 µmol/L), which remained at 1.1±0.4 µmol/L 3 mo after the change to the F2α®, which contains 50 µg/L of selenium. Neither a significant decrease nor an increase in selenium level was observed in the long term after administration with F2α®.

**Monitoring laboratory tests**

No significant decrease in hemoglobin level was observed in the long term, although there were three patients with low hemoglobin levels (Fig. 3A). Their hemoglobin levels were low before the start of enteral feeding, and did not recover. There was no relationship between hemoglobin level and serum copper level (data not shown). The average of mean corpuscular volume (MCV) in the patients was 87.3±2.9 fl (reference value: 80–94 fl). No significant decrease in WBC level was observed in the long term after the administration of F2α®️ (Fig. 3B). No significant change in neutrophil number, electrolytes, serum albumin or serum protein was observed either (data not shown). No toxic effects on liver function were observed (Fig. 4), although liver damage was observed in one patient who had hepatitis.

**Copper dosages**

There was no relationship between copper dosage...
Recovery and Maintenance of Copper Levels

3.0 mg of copper per day was in the range of recommended values. Although the patients received relatively narrow ranges of dietary copper, serum copper levels differed among individuals. However, serum copper levels did not increase even when the dosage of copper was increased. The present study showed that 3 mo after the start of enteral feeding the serum copper level was at a normal level. There were no clinical symptoms of copper deficiency in any of the subjects. Almost all the patients had an adequate copper balance. This suggests that dietary intake of 1.8±0.4 mg/d is sufficient to meet the needs of this group of subjects. In addition, there was no abnormality in nutritional state, physical state or biochemical parameters. There are few reports about treatment of copper deficiency with copper sulfate (3, 5) or prevention of copper deficiency with cocoa which contains 3.8 mg copper/100 g (8). If patients receive these supplements with no attention of total amount of copper dosage, chronic excessive intake may accumulate a toxic level of copper in the body. Therefore, patients should receive a defined-formula diet containing enough copper to maintain copper status.

We have reported that the serum level of copper decreased gradually below the normal range after 3 mo in patients receiving copper-poor enteral nutrition (5). The early stage of copper deficiency is defined as latent copper deficiency and the last stage appears as anemia, leukopenia, neutropenia and skeletal abnormalities. Hemoglobin levels were slightly low in all patients from the start of the study, because the subjects were elderly, 72.3±14.9 y. The increased incidence of anemia with aging has led to speculation that lower hemoglobin levels may be a normal consequence of aging (9). The patients suffered from the main hematological disorder, normocytic anemia. In the patients with moderate anemia, no cause was found, and the prognosis was good. Only two patients suffered from macrocytosis. Anemia with macrocytosis is the most common form of anemia in geriatric patients (9). A deficit of other nutrients such as vitamin B12 or folic acid causes macrocytosis, but F2a® contained enough vitamin B12 and folic acid. There was no postgastrectomy patient.

It has been suggested that the copper requirement is influenced by the protein content of the diet (10), but the amount of protein in the diet used in our study was the recommended amount.

In the present study, no patients suffered from copper deficiency. The subjects of this study were able to maintain copper status. On the other hand, it is well known that concentrations of serum copper and ceruloplasmin increase under conditions of stress. Copper concentrations increase in response to inflammation and infections and in various chronic diseases such as arthritis and neoplasia (11). There were two patients with high copper levels in the present study. One of the two

and serum copper level, serum zinc level or liver function (Fig. 5). Serum copper and zinc levels did not increase after the dosage of copper was increased. Liver function did not change after the dosage of copper was increased, either.

DISCUSSION

Copper maintenance

A wide variety of enteral feeding solutions are available in Japan. However, non-prescription solutions are prepared from a limited number of food items and are not always sufficient nutritionally. Japanese law prohibits adding trace elements to commercially available non-prescription solutions (5). Copper deficiency symptoms have recently been reported in patients receiving copper-poor enteral nutrition (3, 4). Adult dietary recommendations have been estimated at between 1.5 and 3.0 mg of copper per day (6). Higuchi et al. have reported the amount of dietary copper in children and young adults required to maintain reference serum levels as ~20 μg/kg/d (2). Turnlund et al. have suggested that 0.8 mg/d over a 42-d period is sufficient to maintain copper status (7). 1.8±0.4 mg of copper per day was in the range of recommended values. Although the patients received relatively narrow ranges of dietary copper, serum copper levels differed among individuals. However, serum copper levels did not increase even when the dosage of copper was increased. The present study showed that 3 mo after the start of enteral feeding the serum copper level was at a normal level. There were no clinical symptoms of copper deficiency in any of the subjects. Almost all the patients had an adequate copper balance. This suggests that dietary intake of 1.8±0.4 mg/d is sufficient to meet the needs of this group of subjects. In addition, there was no abnormality in nutritional state, physical state or biochemical parameters. There are few reports about treatment of copper deficiency with copper sulfate (3, 5) or prevention of copper deficiency with cocoa which contains 3.8 mg copper/100 g (8). If patients receive these supplements with no attention of total amount of copper dosage, chronic excessive intake may accumulate a toxic level of copper in the body. Therefore, patients should receive a defined-formula diet containing enough copper to maintain copper status.

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patients had pneumonia at the time. The patient once again had a normal copper level at 9 mo after recovering from pneumonia. The other patient was discharged after the final measurement. The amount of copper, 1.4 mg/d, might have been excessive but there was no toxic effect in the patient. We should continue to measure copper levels.

Copper toxicity

When we take in too much copper, nausea, vomiting and diarrhea occur to create excessive copper. This mechanism prevents serious manifestations of copper toxicity such as coma, ploguria, hepatic necrosis, vascular collapse and death. The World Health Organization (WHO) recommends an intake of below 10 mg/d for women and 12 mg/d for men (12). The amount of orally ingested copper needed to produce toxic effects is not well established, but liver damage in two infants may be related to consuming water with 2 to 3 mg Cu/L (31-47 μmol Cu/L) in early infancy (13). Chronic copper intoxication has been observed in dialysis patients following months of hemodialysis using copper tubing and in vineyard workers who used copper compounds as pesticides (1). Wilson’s disease, a genetic disorder, and certain liver and biliary diseases are associated with the accumulation of toxic levels of copper in the liver and other tissues, without excessive intake (1). Subtle deleterious effects of high dietary copper have been observed.

In the patients of the present study, no toxic effect was observed. The liver function of all patients was in the normal range except one. Liver damage in the patient may be related to his hepatitis, since his abnormality was observed from the start of enteral feeding. High doses of copper, such as 1.4 mg/d and 1.9 mg/d, did not always cause liver damage. The reason for the highly significant differences in indices of copper status in each patient was not clear but it seems from Fig. 5C that they are independent of dietary copper intake.

Zinc status

The specific enzymatic activity of ceruloplasmin is sensitive to copper status (14). A previous study has reported that a high-copper diet reduces zinc absorption slightly and increases the excretion of zinc in young men but does not impair zinc status (15). A high molar ratio of zinc to copper interferes with copper metabolism (14). In the present study, there was a good correlation between serum copper level and ceruloplasmin level. However, there was no relation between serum copper level and zinc level, and no reduction in zinc level by copper. Serum zinc levels did not increase or decrease even if the dosage of copper was increased. The ratio of zinc to copper is recommended to be over 10 to one (16). The F2αβ’s ratio of zinc to copper was six to one. Further research should be performed on whether the results of the present study could be extrapolated to maintain a proper copper and zinc status. There was no reduction in selenium level by copper or zinc. Wakugami et al. reported that there was no relation between the serum selenium level and copper or zinc level (16).

Conclusion

In conclusion, patients should receive a defined-formula diet containing enough copper to maintain copper status. A copper intake of 1.8±0.4 mg/d is recommended for geriatric patients to maintain copper status for a prolonged period of enteral feeding.

REFERENCES