## Trace Elements

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What are Trace Elements?
—Their deficiency and excess states—

Osamu WADA

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Abstract: Elements which are detected in small but not precisely known amounts in the living body were called “trace elements” in the past. Recent advances in analytical technologies, such as the development of atomic absorption spectrometry, have made it possible to measure these elements precisely and to determine their functions and the characteristics of their deficiency and excess states. The so-called vitamin boom has passed, and it now appears to be boom-time for trace elements. Nowadays, cases with trace element deficiencies are often encountered clinically, especially during high-calorie parenteral therapy or enteral nutrition, and congenital abnormalities of trace element metabolism have been clarified successively. Thus, knowledge of the clinical aspects of trace elements is becoming indispensable for front-line clinicians. Meanwhile, epidemiological surveys and animal studies have suggested the possibility that some trace element deficiencies are associated with a reduced anti-oxidant potential in organisms (which is believed to possibly underlie the onset of cancer and atherosclerosis), accelerated aging, developmental retardation in children, and an increased incidence of abnormal pregnancies, immunological abnormalities, and lifestyle-related diseases. Thus, from the viewpoint of prophylactic medicine, study, survey, and prophylaxis of trace elements are also attracting close attention.

Key words: Trace element; Trace element deficiency; Excess of trace elements; Congenital abnormality in trace element metabolism

What are Trace Elements?

The human body is composed of elements which can be roughly divided into abundant elements and trace elements. Abundant elements consist of the major elements that are involved in the formation of covalent bonds and are important constituents of tissues (oxygen, carbon, hydrogen, nitrogen, etc.), and semi-major elements, which often exist in the ionic state, and are involved in functions of the living body through maintenance of osmotic pressure and membrane potentials (potassium, sodium, etc.). Major elements account for 96%
<table>
<thead>
<tr>
<th>Trace element</th>
<th>Enzymes containing the elements and active forms</th>
<th>Physiological functions</th>
<th>Symptoms of deficiency state</th>
<th>Symptoms of excess state</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>Carbonic anhydrase, Peptidase, Alcohol dehydrogenase, Alkaline phosphatase, Polymerase, Zinc finger etc.</td>
<td>Protein metabolism, Lipid metabolism, Carbohydrate metabolism, Bone metabolism</td>
<td>Major symptoms:</td>
<td>Acute:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gradually exacerbating eruptions, first affecting the face and perineum, fever</td>
<td>Relative Fe-Cu deficiency, nausea, vomiting, abdominal pain, melena, hyperamylasemia, somnolence, hypotension, lung edema, diarrhea, jaundice, oliguria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Associated symptoms: Stomatitis, glossitis, alopecia, nail changes, abdominal symptoms (diarrhea, vomiting), fever</td>
<td>Chronic: Reduced reproductive function, dwarfism, taste disorder, hypopsmia, anemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Delayed wound healing, dwarfism Growth retardation, negative N balance, Immunosuppression, Mental symptoms (depression), Taste disorder, anorexia</td>
<td></td>
</tr>
<tr>
<td>Copper</td>
<td>Ceruloplasmin, Monoamine oxidase, Cytochrome oxidase, Ascorbic acid oxidase, Superoxide dismutase etc.</td>
<td>Hemopoiesis, Bone metabolism, Connective tissue metabolism</td>
<td>Anemia, Leukopenia, Neutropenia, Disturbed maturation of myeloleukocytes Bone changes (children): Reduced osseous age, irregular/spurring metaphysis, bone radiolucency, bone cortex thinning</td>
<td>Nausea, vomiting, heartburn, diarrhea, jaundice, hemoglobinuria, anemia, noria, hypotension, coma, melena</td>
</tr>
<tr>
<td>Chromium</td>
<td>Glucose tolerance factor, (GSH-Px), 5'-deiodinase (type I), Various selenoproteins</td>
<td>Carbohydrate metabolism, Cholesterol metabolism, Connective tissue metabolism, Protein metabolism</td>
<td>Abnormal glucose tolerance, Reduced respiratory quotient, Peripheral neuropathy, Increased serum free fatty acids, Abnormal nitrogen balance, Metabolic consciousness disturbance</td>
<td>Nausea, vomiting, peptic ulcer, CNS disorder, Liver/kidney dysfunction, growth retardation</td>
</tr>
<tr>
<td>Selenium</td>
<td>Glutathione peroxidase (GSH-Px), 5'-deiodinase (type I), Various selenoproteins</td>
<td>Antioxidant action, T4→T3 conversion, Reduced carcinogenicity action</td>
<td>Myalgia (lower extremities), Cardiomyopathy (myocardial cell collapse, fibrosis), Nail bed whitening</td>
<td>Seleniumosis (alopecia, nail detachment, CNS disorder)</td>
</tr>
<tr>
<td>Manganese</td>
<td>Arginase, Pyruvate carboxylase, Superoxide dismutase, Glycosyltransferase</td>
<td>Bone metabolism, Carbohydrate metabolism, Lipid metabolism, Reproduction, Immunity</td>
<td>Reduced serum cholesterol, Reduced coagulation, Hair reddening, Dermatitis (miliaria crystallina), Growth retardation, Increased radiolucency at the epiphyses of long bones</td>
<td>Parkinsonian syndrome Early chronic: Impotence, loss of vigor, somnolence, anorexia, edema, myalgia, headache, excitement, fatigue, Extrapyramidal disorder</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>Xanthine oxidase, Xanthine dehydrogenase, Aldehyde oxidase, Nitrous acid oxidase</td>
<td>Amino acid metabolism, Uric acid metabolism, Sulfuric acid/sulfurous acid metabolism</td>
<td>Tachycardia, Polyneuropathy, Night blindness, Scotoma, Irritability, Somnolence, Disorientation, Coma</td>
<td>Hyperuricemia, gout</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cobalt</td>
<td>Vitamin B12</td>
<td>Hemopoiesis</td>
<td>Pernicious anemia, methy/malonic acidemia</td>
<td>Cobalt poisoning</td>
</tr>
<tr>
<td>Iodine</td>
<td>Thyroid hormone</td>
<td>Tissue metabolism</td>
<td>Goiter, hypothyroidism</td>
<td>Goiter, hypothyroidism</td>
</tr>
</tbody>
</table>

(Summary of many reports)
of the total body weight, and the semi-major elements account for 3 to 4% of the total body weight. Deficiency of major elements can lead to nutritional disorders, and their presence in excess can cause obesity. Deficiencies or excess states of semi-major elements often result in water and electrolyte abnormalities.

Essential trace elements of the human body include zinc (Zn), copper (Cu), selenium (Se), chromium (Cr), cobalt (Co), iodine (I), manganese (Mn), and molybdenum (Mo). Although these elements account for only 0.02% of the total body weight, they play significant roles, e.g., as active centers of enzymes or as trace bioactive substances. A major outcome of trace element deficiencies is reduced activity of the concerned enzymes. However, since each trace element is related to so many enzymes, deficiency of a single trace element is often not associated with any specific clinical manifestations, but rather manifests as a combination of various symptoms. Because of the presence of trace elements in very small amounts and the absence of specific clinical features associated with their deficiency, it is often difficult for clinicians to identify deficiencies of some particular trace elements.

Table 1 lists the enzymes containing trace elements, and summarizes the physiological functions of trace elements and the characteristics of their deficiency and excess states.

Trace Elements as Nutrients or Medicines

Like vitamins, trace elements were also originally viewed as nutrients. They are listed in the Japanese recommended dietary allowance (RDA). Because of the tendency in recent times towards unbalanced food intake, excessive purification of crops, and dieting practiced widely to reduce body weight, deficiency of zinc (a trace element abundantly contained in animal foods and crops) are encountered relatively frequently.

Trace elements exert pharmacological actions if they are ingested in amounts several to ten times higher than the nutritional requirements. Excessive ingestion of trace elements as medicines has also been reported, which may occasionally lead to poisoning. To avoid such poisoning, the RDA table displays also the reference dose (RfD, i.e., the highest permissible dose) for each element. However, the RfD shown in the RDA table is relevant as reference values only when trace elements are ingested as ordinary nutrients. Table 2 lists the pharmacologically effective actions of trace elements when they are consumed in excess. However, when dealing with trace elements, caution must be exercised to avoid excessive dosage.

### Table 2 Trace Elements and the Potential Effects of Replenishment, Prophylaxis, and Pharmacological Effects

<table>
<thead>
<tr>
<th>Trace element</th>
<th>Potential effects of replenishment, prophylaxis, and pharmacological effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Correction of latent iron deficiency Resistance to infections</td>
</tr>
<tr>
<td>Zinc</td>
<td>Wound healing Improved resistance to infections and immune functions Correction of developmental retardation and gonadal hypoplasia Correction of taste disorder</td>
</tr>
<tr>
<td>Chromium</td>
<td>Correction of carbohydrate metabolism Prevention of atherosclerosis</td>
</tr>
<tr>
<td>Selenium</td>
<td>Anti-cancer activity Prevention of ischemic heart disease Vitamin E-like activity</td>
</tr>
<tr>
<td>Fluorine</td>
<td>Prevention of dental caries</td>
</tr>
<tr>
<td>Iodine</td>
<td>Correction of latent iodine deficient goiter</td>
</tr>
</tbody>
</table>

(Quoted from Wada, O. et al.: Trace elements and their abnormalities. Integrated Handbook of Internal Medicine 6, Nakayama-Shoten Co., Ltd., Tokyo, 1995; pp. 253–263.)

### Daily Intake, Recommended Dietary Allowance, Reference Dose, and Safety Margin of Trace Elements, and Causes of Deficiency States

Table 3 summarizes these parameters in
relation to trace elements. It is noteworthy that the mean daily intake and the RDA are approximately the same for most trace elements. This can be interpreted as evidence that over the long history of humankind, dietary styles allowing approximately stable supply of trace elements have become established, and that the amounts of trace elements ingested via food represent the appropriate levels. In other words, trace element deficiencies are unlikely to occur unless the dietary patterns of individuals change dramatically, or the metabolism of trace elements is disturbed. Table 4 shows the major causes of trace element deficiencies. High-calorie parenteral therapy and enteral nutrition can be viewed as representing dramatic alterations of the dietary pattern, while extremely low intake and congenital metabolic abnormalities can be viewed as representing disturbed metabolism of trace elements. In recent years, the prevalence of these metabolic abnormalities has been on the increase, and their pathophysiology has been clarified in depth, highlighting the importance of trace elements in clinical practice.

It is also important to note that the ratio of the RfD to RDA, i.e., the safety margin between daily requirements and toxic levels, is not very large. Amidst the tendency of people to consume health promotion foods based on their distrust of medicines, preparations of trace elements are available commercially, and inappropriate use of these preparations can cause excess states of these trace elements. It is also noteworthy that the doses at which trace elements exert pharmacologically effective actions are much higher than the RfD.

Table 3  Daily Dietary Requirements of Trace Elements in Adult Japanese Males (body weight: 50kg)

<table>
<thead>
<tr>
<th>Trace element</th>
<th>Mean daily intake</th>
<th>“No adverse effects” level (NOAEL)</th>
<th>“Lowest adverse effect” level (LOAEL)</th>
<th>Effective replenishment/pharmacological dose</th>
<th>Recommended dietary allowance (RDA)</th>
<th>Reference dose (RfD)</th>
<th>RfD/RDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>7–11 mg</td>
<td>30 mg*</td>
<td>600 mg</td>
<td>−200mg (immune functions, etc.)</td>
<td>9.6 mg</td>
<td>30 mg</td>
<td>3</td>
</tr>
<tr>
<td>Copper (III)</td>
<td>1–4 mg</td>
<td>9 mg*</td>
<td>10 mg</td>
<td>—</td>
<td>1.8 mg</td>
<td>9 mg</td>
<td>5</td>
</tr>
<tr>
<td>Chromium</td>
<td>28–62 μg</td>
<td>1,000 μg*</td>
<td>—</td>
<td>150–1,000 μg (diabetes mellitus, etc.)</td>
<td>35 μg</td>
<td>250 μg</td>
<td>7</td>
</tr>
<tr>
<td>Selenium</td>
<td>41–168 μg</td>
<td>400 μg</td>
<td>750 μg*</td>
<td>−200 μg (cancer prevention, etc.)</td>
<td>55 μg</td>
<td>250 μg</td>
<td>4.5</td>
</tr>
<tr>
<td>Manganese</td>
<td>3–4 mg</td>
<td>10 mg*</td>
<td>—</td>
<td>—</td>
<td>4 mg</td>
<td>10 mg</td>
<td>2.5</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>135–215 μg</td>
<td>350 μg</td>
<td>7 mg*</td>
<td>—</td>
<td>30 μg</td>
<td>250 μg</td>
<td>8</td>
</tr>
<tr>
<td>Iodine</td>
<td>200–30,000 μg</td>
<td>3,000 μg*</td>
<td>23,000 μg</td>
<td>—</td>
<td>150 μg</td>
<td>3,000 μg</td>
<td>20</td>
</tr>
<tr>
<td>Arsenic</td>
<td>10–34 μg</td>
<td>40 μg*</td>
<td>700 μg</td>
<td>—</td>
<td>10–34 μg</td>
<td>140 μg</td>
<td>4</td>
</tr>
</tbody>
</table>

* Basis for calculation of RfD
  • The mean daily intake is approximately equal to the RDA.
  • RfD/RDA indicates the safety margin between daily requirements and toxic levels, and is not very large.
  (Quoted from Wada, O.: Usefulness and safety of trace chemicals. Proceedings of Trace Nutrients Research 2001; 18: 1–10.)

Table 4  Major Causes of Trace Element Deficiency

1. Inadequate supply
   1) Congenital metabolic disorders:
      Acrodermatitis enteropathica (zinc), Menkes disease (copper)
   2) Inadequate intake:
      Unbalanced nutrition, excessive purification of crops, ingestion of foods poor in trace elements, undevlopment of the food transportation system

2. Iatrogenic:
   High-calorie parenteral therapy, chelating drugs, surgery, etc.

3. Diseases, etc.: Pregnancy, excessive alcohol consumption, liver disease, nephropathy

Note: Underlined factors are predominant.
Deficiency and Excess States of Trace Elements

As shown in Table 5, deficiency and excess of trace elements are either congenital or acquired. Deficiency states of trace elements are most frequently seen during high-calorie parenteral therapy or enteral nutrition. Zinc deficiency can develop within 2 weeks after the start of such therapies. Therefore, while administering these therapies, caution must be exercised to ensure that all trace element deficiencies are prevented.

Congenital abnormalities of trace element metabolism are rare. Abnormal intestinal absorption or disturbed transport of absorbed trace elements more often lead to deficiency of trace elements. Acrodermatitis enteropathica due to disturbed zinc absorption and Menkes disease due to abnormal copper transport through the intestinal mucosa are some examples of such conditions.

If the site of uptake of trace elements into an active form is disturbed, the trace element is pooled there, causing excess of the element. In cases of Wilson disease characterized by disturbed uptake of copper into ceruloplasmin, tissue damage and fibrosis due to copper occur in the liver and other sites.

Trace Element Deficiencies as Viewed from the Standpoint of Prophylactic Medicine

Many epidemiological surveys and animal
### Table 5  Clinical Deficiency and Excess States of Trace Elements

<table>
<thead>
<tr>
<th>Trace element</th>
<th>Deficiency</th>
<th>Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Congenital</td>
<td>Acquired</td>
</tr>
<tr>
<td>Iron</td>
<td>Atransferrinemia</td>
<td>Iron-deficiency anemia</td>
</tr>
<tr>
<td>Zinc</td>
<td>Acrodermatitis enteropathica</td>
<td>High-calorie parenteral therapy, enteral nutrition, drugs (chelating agents), inadequate intake</td>
</tr>
<tr>
<td>Copper</td>
<td>Menkes disease</td>
<td>High-calorie parenteral therapy, enteral nutrition</td>
</tr>
<tr>
<td>Manganese</td>
<td>Acerochloasmaemia</td>
<td>High-calorie parenteral therapy (1 case)</td>
</tr>
<tr>
<td>Selenium</td>
<td>Some types of pancreatic cysts</td>
<td>High-calorie parenteral therapy (several cases), dietary Keshan disease, Kaschin-Beck disease, ischemic heart disease, cancer</td>
</tr>
<tr>
<td>Chromium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodine</td>
<td>Abnormal iodine metabolism</td>
<td>Goiter</td>
</tr>
<tr>
<td>Cobalt</td>
<td>Pernicious anemia</td>
<td></td>
</tr>
<tr>
<td>Molybdenium</td>
<td></td>
<td>High-calorie parenteral therapy (1 case)</td>
</tr>
</tbody>
</table>

### Table 6  Trace Element Deficiency as Viewed from the Standpoint of Preventive Medicine

<table>
<thead>
<tr>
<th>What needs to be prevented</th>
<th>Elements involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in antioxidant potential</td>
<td>Zinc, iron, manganese, selenium, copper</td>
</tr>
<tr>
<td>Promotion of aging and its cause</td>
<td>Zinc, copper, selenium, chromium</td>
</tr>
<tr>
<td>Developmental retardation of children</td>
<td>Zinc</td>
</tr>
<tr>
<td>Abnormal pregnancies, infertility, fetal abnormalities</td>
<td>Zinc, iron, copper, selenium</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Zinc, selenium, iron, copper, chromium</td>
</tr>
<tr>
<td>Increased carcinogenicity</td>
<td>Zinc, selenium, vanadium</td>
</tr>
<tr>
<td>Promoted atherosclerosis</td>
<td>Copper, zinc, selenium</td>
</tr>
<tr>
<td>Increased incidence of diabetes mellitus</td>
<td>Zinc</td>
</tr>
<tr>
<td>Predisposition to hypertension</td>
<td>Zinc</td>
</tr>
<tr>
<td>Predisposition to senile dementia</td>
<td>Zinc</td>
</tr>
<tr>
<td>Predisposition to taste disorder</td>
<td>Fluorine</td>
</tr>
<tr>
<td>Predisposition to dental caries</td>
<td>Iodine</td>
</tr>
<tr>
<td>Predisposition to goiter</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2  Anti-oxidative actions of trace elements

The characteristics of trace element deficiency, especially in the case of adults, may be explained by a reduction in the antioxidative actions.

(Quoted from Wada, O.: Trace elements and sugar and lipid metabolism — Overview. *Endocrinology & Diabetology* 1998; 6: 109–117.)
studies have demonstrated that health problems are caused by deficiency of trace elements (Table 6). It has been shown that the deficiency of many trace elements, especially zinc, is associated with accelerated aging, immunodeficiency, accelerated progression of HIV infection, increased incidence of abnormal pregnancies, developmental retardation in children, and taste disorder. It has also been shown that deficiency of chromium is related to the development of diabetes mellitus and atherosclerosis, and that selenium deficiency is associated with the increase of cancer and ischemic heart disease. Clarifying these abnormalities clinically and establishing countermeasures against them are important issues that must be addressed by regional hospitals engaged in both prophylactic medicine and clinical medicine. Studies in this field may be expected to advance rapidly from now on and contribute to improving the dietary habits of populations in local communities.

Decreased anti-oxidant potential of the living body, which is a subject that has recently attracted close attention, is thought to underlie the development of numerous lifestyle disease conditions. Several trace elements have been shown to be involved in the anti-oxidant efficacy of the body (Fig. 2).

Conclusion

In this article, the basic biology of trace elements and features of their deficiency and excess states have been presented to provide an overview of these elements. Clinically, as well as in nutritional evaluations, one of the most difficult problems concerning trace elements is the difficulty of diagnosing trace element deficiencies. Although the currently available methods of diagnosis are listed in Table 7, there are few methods that allow accurate diagnosis, especially in cases with mild to moderate deficiency. The development of more accurate methods is an issue that must be addressed in future.

REFERENCES


Zinc Deficiency and Clinical Practice

Hiroyuki YANAGISAWA
Associate Professor, Department of Hygiene and Preventive Medicine, Saitama Medical School

Abstract: In recent years, the number of patients visiting outpatient clinics with complaints of abnormal sense of taste or olfaction has been on the increase. It has been estimated that about 30% of these patients may have dietary zinc deficiency. This deficiency is more likely to develop among children whose daily requirements of zinc are greater, among elderly people whose dietary consumption of nutrients is poor, and among young women who are often on diets for weight reduction. Zinc deficiency may be associated with features such as hypogeusia, hyposmia, growth retardation, dermatitis, alopecia, compromised gonadal function, susceptibility to infections, and delayed wound healing. At present, measurement of the serum zinc level is considered to be the most reliable means of diagnosing zinc deficiency. It has been proposed that if the serum copper level were also measured, then the ratio of the serum copper to zinc level (serum copper/zinc ratio) can be used as reference information for diagnosing zinc deficiency. For the treatment of zinc deficiency, zinc replacement therapy at a daily zinc dose of about 30 mg is considered to be relatively safe. However, further study of the safety and adverse effects of zinc replacement therapy is necessary.

Key words: Zinc; Essential trace elements; Deficiency

Introduction

The number of patients visiting outpatient clinics with complaints of abnormal sense of taste or olfaction (most frequently reduced or abnormal sense of taste) has been on the increase.\(^1,2\) It has been estimated that about 140,000 new patients with such complaints are registered annually,\(^3\) and that about 30% of these patients have dietary zinc deficiency.\(^1,2\)

Zinc is known to serve as the active center of about 300 enzymes, and is an essential trace element in humans (Table 1).\(^1\)

It has been reported that the amount of zinc ingested per day may be insufficient relative to the daily requirement in some groups of individuals (children, elderly people, young women on weight-reducing diets, and some other groups). These individuals may develop quasi-deficiency or true deficiency of zinc.\(^1,2\) In
Acquired zinc deficiency is often attributable to extreme deficiency of nutrients including zinc, or extremely unbalanced diets (insufficient ingestion of animal proteins rich in zinc). The most frequent causes of zinc deficiency are prolonged high-calorie parenteral therapy and enteral nutrition. Long-term high-calorie parenteral therapy inevitably induces zinc deficiency. To avoid its occurrence, IV solution additives containing 5 trace elements (iron, zinc, copper, manganese, and selenium) are induced by post-natal factors (Table 2).1) Acquired zinc deficiency is often attributable to extreme deficiency of nutrients including zinc, or extremely unbalanced diets (insufficient ingestion of animal proteins rich in zinc).

The most frequent causes of zinc deficiency are prolonged high-calorie parenteral therapy and enteral nutrition. Long-term high-calorie parenteral therapy inevitably induces zinc deficiency. To avoid its occurrence, IV solution additives containing 5 trace elements (iron, zinc, copper, manganese, and selenium) are induced by post-natal factors (Table 2).1)

Table 1 Zinc and Its Functions

<table>
<thead>
<tr>
<th>Essential trace element</th>
<th>Target</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>Carbonic anhydrase, peptidase, alcohol dehydrogenase, alkaline phosphatase, polymerase, superoxide dismutase (SOD), angiotensin-converting enzyme, collagenase, δ-aminolevulinic acid anhydrase, protein kinase C, phospholipase C, aspartate transcarbamylase, nucleotide phosphorylase (5′-nucleotidase), RNase, etc.</td>
<td>Cell division, nucleic acid metabolism, co-enzymes</td>
</tr>
</tbody>
</table>


Table 2 Major Causes of Zinc Deficiency

1. Inadequate intake
   1) Low-zinc-containing diets: Foods poor in animal protein (vegetarians)
   2) Loss of zinc during food processing (desalting during production of artificial milk)
   3) Prolonged intravenous alimentation, enteral alimentation
   4) Shortage of nutrient intake
2. Malabsorption
   1) Congenital: Acrodermatitis enteropathica (very rare)
   2) Acquired
      1) Ingestion of absorption inhibitors: Phytic acid, edible fibers
      2) Malabsorption syndrome: Liver dysfunction, pancreatic dysfunction, inflammatory bowel disease, short bowel syndrome
      3) Drugs, chelating agents: EDTA, penicillamine
3. Excessive loss
   1) Loss into digestive fluid: Child intractable diarrhea, intestinal fistula, gastrointestinal disease associated with diarrhea
   2) Increased urinary elimination: Liver cirrhosis, diabetes mellitus, renal disease, hemolytic anemia, intravenous alimentation, enhanced catabolism (surgery, trauma, infection, etc.), diuretics, sodium polyphosphate
   3) Others: Burns, hemodialysis
4. Increased demand
   Pregnancy, neonates (premature babies), enhanced anabolism (during intravenous alimentation, etc.)
5. Unexplained Congenital thymus defect, Mongolism

*Underlined = particularly important

In this paper, we shall briefly discuss the etiology, clinical symptoms, and the methods of diagnosis and treatment of zinc deficiency, a condition that has recently drawn much attention.

Etiology

Zinc deficiency can be divided into congenital and acquired types of zinc deficiency. Acrodermatitis enteropathica, an inherited abnormality of zinc absorption, is rare. Most cases are induced by post-natal factors (Table 2).1) Acquired zinc deficiency is often attributable to extreme deficiency of nutrients including zinc, or extremely unbalanced diets (insufficient ingestion of animal proteins rich in zinc).

The most frequent causes of zinc deficiency are prolonged high-calorie parenteral therapy and enteral nutrition. Long-term high-calorie parenteral therapy inevitably induces zinc deficiency. To avoid its occurrence, IV solution additives containing 5 trace elements (iron,
zinc, copper, manganese, and iodine), that have recently become available commercially (including Elemenmic® (Ajinomoto Pharma Co., Ltd.) and Mineralin® (Nihon Pharmaceutical Co., Ltd. and Takeda Chemical Industrials, Ltd.), may be used. The use of these additives has reduced the apparent incidence of zinc deficiency. Although these 5 trace elements are also contained in preparations used for enteral nutrition, zinc deficiency can develop if the amount of zinc in the diet is insufficient relative to the requirement, or if the patients have such conditions as malabsorption, diarrhea, or intestinal fistula. Furthermore, zinc deficiency can be induced by continued use of low-mineral purified foods (minerals are lost during purification), foods containing additives with chelating activity (sodium polyphosphate, phytic acid, or EDTA [which is also used as a drug]), and drugs which can disturb the sense of taste (about 170 such drugs are known, and many of them have chelating activity\(^2\)).\(^1,2\)

Regarding the relationship of zinc deficiency with age, the deficiency is more likely to develop during childhood, when the daily requirement of zinc is higher, in adult women (especially young women on weight-reducing diets), and in elderly people whose dietary consumption of nutrients is poor. In a survey in the United States, a reduced serum level of zinc was seen in 2–3% of the population.\(^1\)

### Clinical Symptoms

While the symptoms of zinc deficiency are common irrespective of the causative factors (Table 3),\(^1\) they may vary depending on the severity of zinc deficiency.

Mild cases of zinc deficiency may present with such features as a reduced sense of taste, reduced sperm counts, reduced serum testosterone level, and non-fat weight loss. Moderate cases of zinc deficiency, which may develop in association with deficient nutrient intake, unbalanced nutrition, chronic liver disease, chronic renal disease, malabsorption syndromes, may present with growth retardation, delayed gonadal development, skin abnormalities, anorexia, somnolence, reduced dark adaptation, delayed wound healing, hypogeusia, and hyposmia. In severe zinc deficiency, which may be associated with acrodermatitis enteropathica, prolonged high-calorie parenteral therapy, or penicillamine therapy, features such as bullous or pustular dermatitis, diarrhea, balding, mental abnormalities (depression, etc.), and recurrent infections due to compromised immune function may be seen.

Of the aforementioned symptoms, subjects with hypogeusia, in particular, and hyposmia

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Symptoms and Diseases Caused by Zinc Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>Hypogeusia/Hyposmia</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>Pica</td>
</tr>
<tr>
<td>Skin symptoms</td>
<td>Depression/Emotional instability</td>
</tr>
<tr>
<td>· Extension from mucocutaneous junctions (mouth, eyes, anus, etc.) to the periphery</td>
<td>Ataxia</td>
</tr>
<tr>
<td>· Bullous or pustular dermatitis, erosive eczema, hyperkeratosis, skin atrophy</td>
<td>Dementia (hypothesis)</td>
</tr>
<tr>
<td>Alopecia/baldness</td>
<td>Reduced glucose tolerance</td>
</tr>
<tr>
<td>Gonadal hypofunction</td>
<td>Increased incidence of cataracts</td>
</tr>
<tr>
<td>Delayed wound healing</td>
<td>Disturbed dark adaptation (night blindness)</td>
</tr>
<tr>
<td>Susceptibility to infections (compromised immune function)</td>
<td>Increased incidence of ischemic heart disease</td>
</tr>
<tr>
<td></td>
<td>Increased carcinogenesis</td>
</tr>
<tr>
<td></td>
<td>Abnormal pregnancy</td>
</tr>
</tbody>
</table>

are often encountered at outpatient clinics. In hospitals for elderly patients, erosive eczema spreading from mucocutaneous junctions (e.g., mouth, eye, anus, etc.) towards the periphery, as well as bullous or pustular dermatitis, are often noted as the first symptoms of zinc deficiency. In recent years, it has been suggested that zinc deficiency may be associated with carcinogenesis, senility, and the onset or progression of some lifestyle-related diseases (Table 3).1)

The authors recently reported that zinc deficiency may lead to exacerbation or progression of renal disease (especially diseases of the glomeruli) through inducing the expression of endothelin-1 (a potent vasoconstrictor) which stimulates the renin-angiotensin system,4–6) and also to exacerbation of hypertension through increasing the oxidative stress associated with the production of superoxides.4,7)

**Diagnosis**

Many methods of diagnosis of zinc deficiency have been attempted.3) At present, measurement of the serum (plasma) zinc level (Table 4), and confirmation of a deficient state by administering a zinc load are considered to be the most reliable methods of diagnosing zinc deficiency.1–3) However, since the intracellular level of zinc is higher than its serum level, it is quite plausible that the serum zinc level may not faithfully reflect the nutritional state of an individual. It must be borne in mind that the serum zinc level may fall at the lower end of the normal range even in the presence of zinc deficiency. The serum zinc level may also show circadian variations (high level in the morning and low level in the afternoon) and changes related to the contents of meal. It can also be affected by some drugs (Table 5). Therefore, when checking for zinc deficiency on the basis of the serum zinc levels, in addition to consideration of the clinical symptoms, it would be essential to take these aforementioned factors also into account.

Zinc is absorbed primarily from the small
ZINC DEFICIENCY

In the presence of zinc deficiency, absorption of copper is enhanced. As a result, a reduced serum zinc level, elevated serum copper level, and an elevated serum copper/zinc ratio are noted in the presence of zinc deficiency. Thus, measurement of the serum copper level may be a helpful auxiliary test in the diagnosis of zinc deficiency. Like the authors, Tomita et al. proposed that diet therapy and oral zinc replacement therapy must be started in individuals who satisfy all of the following criteria of zinc deficiency: (1) serum zinc level lower than the quasi-deficiency level (Table 4) and (2) serum copper level over 120μg/dl as a reference value, i.e., a serum copper/zinc ratio of 1.5 or higher. Confirmation of the diagnosis using a zinc load is advisable in suspected cases of zinc deficiency in whom the serum zinc level is normal.

### Table 5 Changes in Serum Zinc Levels

<table>
<thead>
<tr>
<th>Condition</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>Increase</td>
</tr>
<tr>
<td>Food ingestion</td>
<td>Decrease (2–3 hours later)</td>
</tr>
<tr>
<td>Stress</td>
<td>Increase</td>
</tr>
<tr>
<td>Ingestion of marine products</td>
<td>Increase (oyster, etc.)</td>
</tr>
<tr>
<td>Neonates and infants</td>
<td>Decrease</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Decrease (gradually)</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Decrease</td>
</tr>
<tr>
<td>Thiazides</td>
<td>Increase</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Increase</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>Increase</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>Decrease</td>
</tr>
<tr>
<td>Oral contraceptive pills</td>
<td>Decrease</td>
</tr>
</tbody>
</table>


### Treatment

In cases of zinc deficiency associated with high-calorie parenteral therapy, Elemenmic® or Mineralin® (trace element preparations) may be added to parenteral nutritional formulas. If zinc deficiency is seen during enteral nutrition, zinc compounds such as zinc sulphate, zinc gluconate, or zinc picolinate may be added to the enteral preparations. If oral ingestion is possible, these zinc compounds may be administered orally mixed with juices, or in the form of enterosoluble capsules.

In adults, a daily zinc dose of 150–200mg (as the zinc compound) is usually sufficient. In Japan, the anti-ulcer agent polaprezinc (Promac®, ZERIA Pharmaceutical Co., Ltd.) is commercially available as a zinc preparation. The daily dose of polaprezinc includes 34mg of zinc load, which is sufficient for the treatment of zinc deficiency, although only its use in the treatment of gastric ulcer is covered by the National Health Insurance in Japan.

Recently, health promotion foods and OTC drugs containing zinc have been marketed in Japan. The amounts of these foods or drugs taken per day often contain 20–30mg of zinc. Therefore, it is possible to use these foods or OTC drugs for zinc replacement therapy. Usually, zinc replacement therapy is continued for 3–4 months. If initiated within 6 months after the onset of zinc deficiency, the response rate to this therapy (the percentage of cases where the therapy is effective or markedly effective) is 70% or higher. The response rate decreases, especially in elderly people, if the therapy is started later than 6 months after the onset of zinc deficiency. In cases responding to therapy, the zinc replacement therapy may sometimes have to be continued for about 6 months.

### Conclusion

The etiology, clinical symptoms, and methods of diagnosis and treatment of zinc deficiency
are described in this paper. Although no optimum dose level for zinc replacement therapy has been established, daily doses of about 30 mg zinc seem to be relatively safe. It would be desirable for additional studies on the safety and adverse effects of zinc therapy to be conducted, and for new zinc preparations for the treatment of zinc deficiency to be developed.

REFERENCES

Copper Deficiency and the Clinical Practice

Tsugutoshi AOKI

President, Toho University

Abstract: In 1993, the candidate genes for Menkes disease and Wilson disease were cloned, and remarkable progress has been made in the study of copper metabolism during the past 10 years. The proteins induced by the ATP7A and ATP7B genes are highly homologous. Both are P-type ATP-related copper-transporter membrane proteins, and control cellular copper transport. Recently, three chaperones supplying copper to the intracellular copper-requiring enzymes were discovered, and the physiology of intracellular copper metabolism is becoming more and more clear. Numerous copper-requiring enzymes are present in the body, therefore, copper deficiency may lead to various disorders. Menkes disease is well-known as an inherited disorder of copper transport from the intestine resulting in copper deficiency. In regard to acquired copper deficiency, nutritional deficiency is probably the most common cause, and may be seen in malnourished low-birth-weight infants, newborns, and small infants. Copper deficiency has also been reported to develop after gastrointestinal surgery, intractable diarrhea, and prolonged parenteral or enteral nutrition. In this article, I present a review of copper deficiency and its treatment.

Key words: Copper deficiency; Copper metabolism; Menkes disease

Introduction

Copper is one of the essential trace elements in humans, and disorders associated with its deficiency and excess have been reported. Menkes (kinky-hair) disease is well-known to be associated with copper deficiency due to an inherited disorder of copper transport from the intestine metabolism, and Wilson disease (hepatolenticular degeneration) is a well-known inherited disorder of cellular copper transport resulting in copper accumulation. Acquired copper deficiency is mainly attributable to nutritional deficiency, and may be seen in malnourished low-birth-weight infants, newborns, and small infants. Copper deficiency has also been reported to develop after gastrointestinal surgery, intractable diarrhea, and prolonged parenteral or enteral nutrition. However, since copper supplementation of intravenous and enteral nutritional formulas was made mandatory, the incidence of copper deficiency...
Table 1 Major Copper-requiring Enzymes and Their Actions

<table>
<thead>
<tr>
<th>Name of major enzymes</th>
<th>Major action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceruloplasmin</td>
<td>Oxidase activity, Fe(^{2+})→Fe(^{3+})</td>
</tr>
<tr>
<td>Lysyl oxidase</td>
<td>Elastin cross-linkage, collagen formation (cross linking)</td>
</tr>
<tr>
<td>Superoxide dismutase (SOD)</td>
<td>Superoxide radical metabolism ((O_2^- + O_2^- + 2H^+ \rightleftharpoons O_2 + H_2O_2))</td>
</tr>
<tr>
<td>Tyrosinase</td>
<td>Melanin synthesis</td>
</tr>
<tr>
<td>Monoamine oxidase</td>
<td>Oxidative deamination</td>
</tr>
<tr>
<td>Dopamine (\beta)-hydroxylase</td>
<td>Epinephrine synthesis</td>
</tr>
<tr>
<td>Cytochrome c oxidase</td>
<td>Complex of cytochrome a and a(_s), respiratory chain terminal enzyme (mitochondria)</td>
</tr>
<tr>
<td>Ascorbate oxidase</td>
<td>Oxidation of vitamin C, etc.</td>
</tr>
</tbody>
</table>

Fig. 1 Physiological copper transport system in hepatic cells (image)

Intracellular copper-transport proteins (Wilson ATPase: ATP7B) and ceruloplasmin are expressed via an intracellular copper-importing protein (Ctr), intracellular copper-storing protein (Metallothionein: MT), intracellular copper-transporting protein chaperones (Cu or metallo-chaperones: (1) HAH1, (2) Ccs, (3) Cox17) and TGN (trans-Golgi network). ER: endoplasmic reticulum, Golgi: Golgi body, ●: Cu, ➡️: Wilson ATP7B. Copper is taken up from capillary blood across the hepatic cell membrane via Ctr. It is then taken transported to the cellular organelles by three chaperones, consisting of recently discovered intracellular copper-transport proteins, with specific functions. The first is the HAH1-chaperone, which carries copper to the Golgi bodies; the second is the Ccs-chaperone, which carries copper to the Cu/Zn superoxide dismutase (SOD) enzyme; the third is the Cox17-chaperone, which carries copper to cytochrome oxidase (Cco). Metallothionein (MT) works against the stored copper. Holo-ceruloplasmin is secreted from the hepatic cells into the capillary blood. The excess copper in the Golgi body is transported to the intracellular vesicular compartments (lysosomes, endosomes, etc.). After assisting in copper excretion into the biliary canaliculi and executing its role, ATP7B returns to the Golgi body (this is called the trans-Golgi network).

(Quoted with Harris, Z.L., Gitlin, J.D.: Genetic and molecular basis for copper toxicity. Am J Clin Nutr 1996; 63 (5): 836s–841s with modification by the author.)
has decreased dramatically. An acquired copper excess state has been described in cases of Indian childhood cirrhosis, non-Indian childhood cirrhosis, excessive copper intake, and parenteral bolus administration of copper for the treatment of copper deficiency.

Many aspects regarding the physiological roles of copper in the body remain unknown. However, remarkable progress in the understanding of copper metabolism has been made since the cloning of the candidate genes for Menkes disease (ATP7A) and Wilson disease (ATP7B). It has been revealed that the proteins induced by these genes (ATP7A and ATP7B) are highly homologous, and that both are P-type ATP-related copper-transporter membrane proteins that control cellular copper transport. Furthermore, the mechanism by which copper is transported into cells and the chaperones (three kinds) supplying copper to the copper-requiring enzymes have been discovered, and the physiology of cellular copper metabolism is being gradually elucidated.

For lack of space, the physiological roles of copper in humans are not discussed here. Table 1 lists the major copper-requiring enzymes in the body, and Fig. 1 shows a chart of the various steps in copper metabolism in hepatocytes. See cited references for further details.

The discussion in this article is mainly focused on copper deficiency in humans.

General Symptoms of Copper Deficiency

The clinical symptoms associated with copper deficiency are extremely diverse. The most common features include anemia, leucopenia, bone lesions (scorbutic-like bone changes and occipital horn), and vesical diverticula. In children, some commonly noted findings are hypotonia, psychomotor retardation, and hypothermia.

1. Hematological abnormalities

(1) Microcytic hypochromic anemia:
This is attributable to a decrease in the ferrooxidase activity of ceruloplasmin (Cp) and reduced iron oxidation. When anemia is noted in low-birth-weight infants, patients with chronic diarrhea, and patients receiving prolonged enteral or parenteral nutrition, copper deficiency must be suspected in addition to iron deficiency.

(2) Neutropenia:
Granulocyte maturation disorder in the bone marrow and vacuolation in neutrophils are observed.

2. Bone lesions in copper deficiency states

Rachitic-like or scorbutic-like changes (enlargement of the epiphyseal area and changes in the margin) are observed in the bones of extremities. They may be accompanied by osteoporosis and occipital horn formation after adolescence. These are attributable to functional impairment of copper-requiring enzymes, such as ascorbate oxidase and lysyl oxidase, associated with copper deficiency.

3. Vascular lesions

Menkes disease is characterized by tortuosity and winding of arteries and increased capillary fragility. Caution must be exercised to avoid prolonged copper deficiency in humans, since this may lead to abnormal vascular tortuosity and increased capillary fragility.

4. Central nervous system disorder and convolution

Reports of central nervous system disorder and convolution associated with secondary copper deficiency are rare, but they are characteristic features of Menkes disease. Progressive Menkes disease can be fatal. Prolonged copper deficiency may cause degeneration of the cerebrum and cerebellum (numerous copper-requiring enzymes are present in the brain, such as dopamine β-hydroxylase and cytochrome c oxidase), associated with slowing of mentation and muscular rigidity, as well as hemorrhagic changes due to increased capillary
In children, hypotonia is often observed.

5. Hair abnormalities

Change of hair texture, namely, kinky-hair, may be observed in children with Menkes disease. Hair changes are, however, considered rare in cases with secondary copper deficiency. On the other hand, the possibility of changes in the hair should be borne in mind in cases of prolonged copper deficiency. The copper content of the hair and nail is decreased in cases of copper deficiency.

6. Others

Attention should be paid to the development of hypothermia, achromoderma, splenomegaly, and susceptibility to infections in copper deficiency states.

Diagnosis and Evaluation of Copper Deficiency States and Indicators

The above-described clinical findings are important pointers for the diagnosis of copper deficiency. In addition, when copper deficiency is suspected, the following tests must be conducted. The most important indicators of the status of copper deficiency are the serum ceruloplasmin (Cp) level and the serum copper level. Caution must be exercised in interpreting their values, because newborns and low-birth-weight infants often have physiological hypoceruloplasminemia and hypocupremia, which make the diagnosis and assessment of copper deficiency difficult in these cases.

1. Serum Cp level

Except in newborns, low-birth-weight infants, and small infants, serum Cp levels may be interpreted as follows: 10 to 20 mg/dl, mild decrease; 5 to 10 mg/dl, moderate decrease; 5 mg/dl or less, marked decrease.

2. Serum copper level

Except in newborns, low-birth-weight infants, and small infants, serum copper levels may be interpreted as follows: 60 to 80 mg/dl, mild decrease; 40 to 60 mg/dl, moderate decrease; 40 mg/dl or less, marked decrease.

In addition, information regarding the copper content of the hair and nails, and a study of the urinary copper excretion and copper balance would be useful.

Treatment of Copper Deficiency

1. Treatment of copper deficiency in low-birth-weight infants and newborns

When copper is administered intravenously, the amount of copper accumulating is proportional to the amount administered, and a large amount of non-Cp copper in the blood may induce toxicity. Therefore, oral administration is recommended, where possible. Intravenous administration may become necessary if no improvement in the clinical condition is observed after oral administration for about a week. However, this should be avoided as far as possible during the first 3 weeks after

<table>
<thead>
<tr>
<th>Segment</th>
<th>Oral dose</th>
<th>Parenteral/intravenous dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-birth-weight infants</td>
<td>100–200 µg/kg/day</td>
<td>20–30 µg/kg/day</td>
</tr>
<tr>
<td>Newborns</td>
<td>2.5–5.0 mg/day</td>
<td>20–35 µg/kg/day</td>
</tr>
<tr>
<td>Infants/children</td>
<td>5.0–10.0 mg/day</td>
<td>15–20 µg/kg/day</td>
</tr>
<tr>
<td>Adolescents and adults</td>
<td>5.0–10.0 mg/day</td>
<td>900–1,500 µg/day</td>
</tr>
</tbody>
</table>
birth, when copper supplementation should be conducted gradually.

2. Treatment of copper deficiency in infants and children

As a general rule, oral administration should be employed. When oral administration is impossible, treatment should be provided by either intravenous or subcutaneous injection.

3. Treatment of copper deficiency in adolescence and adulthood

The doses are shown in Table 2. The route of administration is the same as that for infants and children.

Menkes Disease

Menkes disease is a genetic disorder of copper transport in the body, and disorder of copper absorption and excretion is noted in the intestinal tract and uriniferous tubules. The Menkes disease gene is located on the long arm of the X chromosome (Xq 13.3). The protein induced by this gene is an intracellular copper-transport membrane protein called ATP7A. The Menkes disease gene is predominantly expressed in the duodenum, upper part of the small intestine, and renal proximal tubules, while no expression is noted in hepatocytes (the Wilson disease gene is strongly expressed in the hepatocytes). Therefore, this disease is transmitted by X-linked recessive inheritance and develops in boys, at an estimated incidence of about 1 in 100,000–200,000. In this disease, copper absorption from the intestine is impaired, resulting in a copper deficiency state. Central nervous system disorder, collagen metabolism disorder, bone lesions, vascular lesions, hair abnormalities, abnormality of pigmentation, vesical diverticula, and decreased skin elasticity may be noted. However, hematological abnormalities, which are commonly seen in cases of nutritional copper deficiency are rare. Hypothermia and weak breast-feeding may be noted during the neonatal period in some cases, but many of the infants grow normally until 3 or 4 months of age, when the disease often manifests by features such as convulsion, etc. The central nervous symptoms are progressive, may become serious even during the early stages, and then regress. Typically, kinky hair (nodules, trichorrhaxis, and kinky) is noted and the hair is rough, brittle and breaks easily. However, this may not be evident in some cases. Hypoceruloplasminemia and hypocupremia are seen on blood biochemical tests. Copper absorption is noted to be poor in the oral copper sulfate tolerance test, with no increase in the serum Cp level or serum copper level.

The typical form of this disease is called classic Menkes disease, which is a serious condition. In addition, mild Menkes disease and extremely mild Menkes disease (occipital horn syndrome and Ehlers-Danlos syndrome, type IX) may also be seen, and abnormality of the Menkes disease gene has been confirmed in both cases. The mild type develops between 6 and 24 months after birth, and the extremely mild type is often discovered from the age of 5 or 6 years through adolescence.

There is no radical cure for this disease. Parenteral copper administration (intravenous or subcutaneous injection) may be administered, but it is ineffective against advanced cerebral disorder. Parenteral copper administration is believed to resolve the systemic condition, bone and hair changes, and the susceptibility to infection, and to prolong patients’ lives. It is considered effective against mild and extremely mild cases.

Conclusion

The clinical aspects of copper deficiency in humans are discussed in this article, including the characteristic clinical features, methods of diagnosis and evaluation, and treatment. In addition, Menkes disease has been reviewed briefly.
REFERENCES


Iodine Deficiency Disorder and Clinical Practice

Makoto IITAKA

Associate Professor, Fourth Department of Internal Medicine, Saitama Medical School

Abstract: Most iodine is present in marine sediment, and large amounts are contained in marine algae and saltwater fish. Thus, there is a risk of iodine deficiency in the interior of continents and in countries where marine products are not consumed. Because of the large amounts of algae consumption, iodine deficiency never develops in Japan. According to the World Health Organization, however, the iodine deficiency disorders (IDD) are observed in 130 countries throughout the world, and 2.2 billion people live in iodine-deficient regions. The minimum daily requirement for iodine is 100–150 μg, and almost all of it is used to synthesize thyroid hormone. In iodine-deficiency states, the decrease in thyroid hormone leads to an increase in thyroid-stimulating hormone (TSH) resulting in the development of goiter. Goiter due to iodine deficiency affects 740 million people worldwide, accounting for 13% of the world’s total population. Severe neurological disorders and developmental delay due to cretinism are observed in newborn infants in severely iodine-deficient regions. Cretinism is classified into a myxedematous type, a neurological type, and a mixed type based on the clinical manifestations. Although intensive efforts have been made by many countries to eliminate IDD, it still remains the most common endemic disease in the world.

Key words: Iodine deficiency disorder; Hypothyroidism; Endemic goiter; Cretinism

Introduction

Chemically, iodine is a halogen. It has an atomic number of 53 and is an amphoteric element with an atomic mass of approximately 127. Iodine possesses both positive and negative valences. At ordinary temperatures it exists in the form of purplish-black scale-like crystals with a metallic sheen, and it is volatile and has a characteristic odor. Iodine is an essential trace element and iodine deficiency causes serious metabolic disorders.

Distribution of Iodine in the Natural World

Most of the iodine in nature exists in the form of iodine salts. Since many iodine salts are

Trace Elements
water-soluble, they are flushed out by rainwater and rivers to the sea. There are various opinions as to the total amount of iodine present in the earth’s crust, which covers the surface of the globe, but the total amount is estimated to be 8.7 trillion tons, with the majority present in marine sediment and sedimentary rock, and approximately 0.8%, 70 billion tons, is presumed to be present in seawater. The iodine content of soil is approximately 0.2–12 mg/l, but because iodine salts are water-soluble, clayish soil contains relatively large amounts, and sandy soil contains little. Moreover, the soil in mountainous regions previously covered by glaciers contains hardly any iodine after the glaciers melted, and there is also little iodine in soil around rivers that have repeatedly flooded. Since natural water contains very small amounts of iodine, there is extremely little iodine in regions far from the sea.

In the biological world, marine algae contain large amounts of iodine, and a wide range of sea-dwelling animals also contain iodine, but freshwater fish and land animals contain little. Expressed as amounts of their dry weight, kelp contains 200–300 mg/100 g, wakame seaweed contains 7–24 mg/100 g, hijiki seaweed (Hizikia fusiforme) contains 20–60 mg/100 g, and saltwater fish contain 0.1–0.3 mg/100 g. The iodine content of cereals and vegetables is about 2–40 μg/100 g.

Because of the iodine distribution described above, there is a risk of iodine deficiency occurring in the interior of continents and in countries where few sea products are consumed. According to World Health Organization (WHO) statistics, iodine deficiency occurs in 130 countries around the world, and 2.2 billion people, or approximately 38% of the world’s population, live in iodine-deficient areas.

The bodies of healthy persons contain 15–20 mg of iodine. The minimum daily requirement is 100–150 μg, and almost all of it is taken up by the thyroid gland and used to synthesize thyroid hormone. The remaining iodine is excreted in the urine, and the amount of iodine normally excreted in the urine is 100–200 μg/l. However, because Japanese people consume large amounts of kelp and other marine algae, their daily intake is 1–3 mg, and their urinary iodine excretion is much greater than that of people in other countries.

**Iodine and Thyroid Hormone Synthesis**

The follicular epithelial cells of the thyroid gland convert iodine into organic iodine compounds and synthesize thyroid hormone. Iodine is taken up by the follicular epithelial cells via the Na+/I− symporter (NIS) on their basement membrane. When a mutation is present in the NIS, iodine uptake is impaired, and hypothyroidism develops. The iodine that has been taken up is excreted into the follicular lumen by the I−/Cl− transporter present in the apical membrane facing the follicular lumen. Abnormalities of the Pendrin gene (PDS) are observed in Pendred syndrome patients, and they develop hypothyroidism or sensory deafness as a result of impaired conversion of iodine into organic iodine compounds.

Conversion of iodine into organic iodine compounds is performed on thyroglobulin (Tg) in the follicles. Tg is a large molecule with a molecular mass of 66×10⁴. Each molecule contains 120–130 tyrosine residues, and about 25% of them function as iodine acceptors. Tg synthesis is modulated by TSH (thyroid-stimulating hormone). The iodine taken up is oxidized in the follicular lumen by H₂O₂ and thyroid peroxidase (TPO), and it binds to Tg’s tyrosine residues. 3-moniodotyrosine residues (MITs) and 3,5-diiodotyrosine residues (DITs) are synthesized as a result. MITs and DITs are then coupled to form T₃ residues on Tg, and pairs of DITs are coupled to form T₄ residues. Tg in the follicular lumen is taken up by the epithelial cells in the form of colloid droplets, and Tg is hydrolyzed by proteases to form T₃ (triiodothyronine) and T₄ (thyroxine). T₃ and T₄ are then secreted into the blood.
Goiter due to iodine insufficiency was observed in ancient times in China and India, and in the Greek and Roman era. The oldest description is a statement in China around 2700 BC that marine algae are an effective treatment for goiter, and in the 4th to 5th centuries AD, the thyroid glands of animals were shown to be useful in treating goiter. The obvious goiter of a person in a Buddhist frieze in Gandhara Pakistan in the 2nd–3rd century is thought to be the first goiter ever depicted graphically.

Goiter was commonly seen in the Alpine region of Switzerland. Even today 97 million people in Europe are reported to have goiter due to iodine insufficiency, and huge goiters caused by iodine deficiency are seen in the mountainous zones of the Himalayan and Andean regions and deep in the African continent.

Several times more people with latent hypothyroidism who have elevated serum TSH values but normal T4 values are presumed to exist in iodine-deficient regions than those who have overt hypothyroidism with T4 levels below the reference range.

### Table 1 Epidemiological Statistics for the Iodine Deficiency Disorders (1999)

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of IDD-affected countries</th>
<th>Population affected by goiter (in millions)</th>
<th>Proportion of the total population (%)</th>
<th>Percentage of households with access to iodized salt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>44</td>
<td>124</td>
<td>20</td>
<td>63</td>
</tr>
<tr>
<td>The Americas</td>
<td>19</td>
<td>39</td>
<td>5</td>
<td>90</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>9</td>
<td>172</td>
<td>12</td>
<td>70</td>
</tr>
<tr>
<td>Europe</td>
<td>32</td>
<td>130</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>17</td>
<td>152</td>
<td>32</td>
<td>66</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>9</td>
<td>124</td>
<td>8</td>
<td>76</td>
</tr>
<tr>
<td>Total</td>
<td>130</td>
<td>741</td>
<td>13</td>
<td>68</td>
</tr>
</tbody>
</table>


### Endemic Goiter

Iodine insufficiency induces an increase in thyroid-stimulating hormone (TSH) in response to decreased production of thyroid hormone, and goiter develops as a result of the stimulating action of TSH. Because of the high intake of seaweed, iodine deficiency never develops in Japan. The WHO, however, estimates that 500–850 million people worldwide have goiter caused by iodine deficiency. According to the statistics for 1999, a survey of WHO member states revealed that 130 countries were in iodine-deficient regions and that 740 million people had goiter secondary to iodine deficiency, amounting to 13% of the total population (Table 1). If the incidence of goiter in schoolchildren age 6–12 years is 5% or more, the region is considered to be an iodine-deficient region. The WHO defines regions with a goiter incidence of 5–19.9% as a mild iodine-deficiency region, an incidence of 20–29.9% as moderate iodine-deficiency regions, and an incidence of 30% or more as severe iodine-deficiency regions.

Iodine excretion in the urine is also used as an index of the severity of iodine deficiency, with median values of 50–99 μg/l classified as mild, 49–20 μg/l as moderate, and less than 20 μg/l as severe.

Goiter due to iodine insufficiency was observed in ancient times in China and India, and in the Greek and Roman era. The oldest description is a statement in China around 2700 BC that marine algae are an effective treatment for goiter, and in the 4th to 5th centuries AD, the thyroid glands of animals were shown to be useful in treating goiter. The obvious goiter of a person in a Buddhist frieze in Gandhara Pakistan in the 2nd–3rd century is thought to be the first goiter ever depicted graphically.

Goiter was commonly seen in the Alpine region of Switzerland. Even today 97 million people in Europe are reported to have goiter due to iodine insufficiency, and huge goiters caused by iodine deficiency are seen in the mountainous zones of the Himalayan and Andean regions and deep in the African continent.

Several times more people with latent hypothyroidism who have elevated serum TSH values but normal T4 values are presumed to exist in iodine-deficient regions than those who have overt hypothyroidism with T4 levels below the reference range.
Endemic Cretinism

Many of the cases of cretinism in newborn infants in Japan are attributable to thyroid gland anomalies (aplasia, hypoplasia, ectopic thyroid). However, in regions where iodine deficiency is severe, pregnant women often experience spontaneous abortion and stillbirths because of placental hypofunction, and children manifest irreversible physical and intellectual developmental delay due to the effects of hypothyroidism beginning in the fetal period. Reduced thyroid hormone levels caused by iodine deficiency lead to brain damage in the fetal and neonatal period, when sensitivity to thyroid hormone is particularly high. Moreover, because their resistance is weak, mortality in the neonatal period and in childhood is also high.

Based on its clinical manifestations, cretinism due to iodine deficiency is classified into a myxedematous type (myxedematous cretinism), a neurological type (neurological cretinism), and a mixed type, in which the two are mingled in various degrees. Manifestations of myxedema due to hypothyroidism predominate in myxedematous cretinism, and there are marked delays or decreases in growth, mental development, and secondary sex characteristics, but there are few neurological manifestations, such as paralysis. Patients have no goiter, and the serum T4 values are reduced. In neurological cretinism, neuropsychiatric manifestations are prominent, and patients exhibit decreased intelligence, deaf-mutism, strabismus, and spastic quadriplegia, but there are few manifestations of hypothyroidism. In the neurological type, patients have a goiter, and the serum T4 values are sometimes normal.

The neurological type is more common in China although the myxedematous type is also seen. The distribution of endemic cretinism in China is characterized by the neurological type being more common in the southeastern part and the myxedematous type being more common in the northwestern part. The thyroid gland is atrophied in the myxedematous type. Although an autoimmune mechanism has also been proposed, developmental disorders of the nervous system due to the decrease in thyroid hormone beginning in the fetal period are the main cause of both types. The difference between them seems to be related to the degree and period of hypothyroidism after birth.

Prevention and Treatment of Iodine Deficiency

In response to calls by the WHO, UNICEF, and the International Council for Control of Iodine Deficiency Disorders (ICCIDD) over the past 20 years, iodine salts have been added to the table salt in countries where iodine deficiency exists, and iodine deficiency is now being prevented. There are also countries where iodine has been added to drinking water, bread, etc. The WHO is verifying a daily iodine intake of 90μg for preschool children, 120μg for schoolchildren, 150μg for adults, and 200μg for pregnant and breast-feeding women. As shown in Table 1, it has now become possible to use iodized salt in an average of 68% of households worldwide. However, no measures have yet been adopted in 30 of the 130 countries where iodine deficiency exists. Moreover, without quality control of the iodized salt or proper control of intake, there is the risk of inability to consume a sufficient amount of iodine, as well as the opposite, that is, inducing hyperthyroidism by taking excessive amounts of iodine, and these issues represent a future task.

Japan accounts for approximately 40% of the world’s iodine production. In addition to being used as a radiographic contrast medium, 6.2% (1,140 tons) of the total iodine produced worldwide is used in the form of iodized salt. Use of iodine to treat cretinism induced by iodine deficiency is often effective in restoring thyroid function in children up to 4 years of age, but the prospects for normal function decrease with age. Neuropsychiatric improvement cannot be expected in response to treat-
ment with thyroid hormone, and thyroid function fails to recover in children after puberty and in adults even when given iodine. To avoid damage to the cranial nervous system, hypothyroidism needs to be prevented in the fetus, and pregnant women must not be allowed to develop iodine deficiency. In other words, prevention of iodine deficiency is the most important means of eliminating endemic cretinism.

Since thyroid hormone supplementation is immediately started whenever cretinism is diagnosed on the basis of neonatal screening tests in Japan, there are very few cases of serious sequelae.

Conclusion

In Japan there is a tendency toward excessive iodine intake instead of iodine deficiency. However, iodine deficiency disorders are the most common endemic disease in the world. Iodine deficiency causes goiter and serious neurological damage as a result of hypothyroidism. The WHO, UNICEF, and the ICCIDD are actively attempting to eradicate it. Since iodine deficiency can be prevented by iodine supplementation, sustained government commitment and motivation are essential to eliminate IDD.

REFERENCES

Trace Element Deficiency in Infants and Children
—Clinical practice—

JMAJ 47(8): 376–381, 2004

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Abstract: Trace element deficiencies commonly encountered in Japanese infants and children are discussed. Premature birth infants have a high likelihood of developing deficiency of trace elements such as iron, zinc, and selenium, during the period of rapid growth from 2 months to 6 months of age. Breast-fed infants, in particular, are prone to develop trace element deficiency, and alopecia and dermatitis attributable to zinc deficiency have been reported. Furthermore, “follow-up milk” formulas (milk-substitute nutritional supplement for infants) in Japan contain practically no zinc or copper. Dependence on follow-up milk formulas as the main source of nutrition is associated with a high risk of zinc and copper deficiency. In one study, 60% of short-statured children without any endocrine disease were found to have zinc deficiency, and zinc administration was associated with an increase of body height. About 20 to 30% of adolescent and young women exhibit iron and zinc deficiency due to dieting. Excessive iodine intake by mothers during pregnancy has been suggested to be the cause of hyper-TSH-emia detected during the mass screening of neonates. Many enteral formulas in Japan do not contain selenium and iodine, and long-term administration of such formulas has been reported to be associated with deficiency of these elements.

Key words: Premature birth infants; Short-statured children; Infantile iron deficiency; Infantile zinc deficiency

Introduction

Deficiency of trace nutrients is more likely to be encountered in children and pregnant women, who have a larger demand per unit body weight. On a global level, the trace element deficiency status in the population is particularly serious in Southeast Asia and Africa, and 41 to 99% of children in these regions have been reported to be suffering from deficiency of vitamin A, iodine, iron, or zinc. In Japan, trace element deficiency is seldom encountered.
in healthy infants and children. However, it poses a problem in premature birth infants and children with poor nutritional intake, patients receiving enteral formulas for prolonged periods, and patients with various chronic diseases.

In this article, we discuss trace element deficiency of the type most commonly encountered in Japanese infants and children. “Trace elements,” in general, do not include iron. However, since iron is a trace element and iron deficiency is a particularly important problem in children, iron deficiency is also discussed here.

### Iron Deficiency Anemia

1. **Diagnosis and treatment of iron deficiency**

Iron deficiency anemia occurs more commonly in premature infants (premature birth infants), infants between 6 months and 2 years of age, and adolescent women. In these age groups, the iron demand is particularly high due to the rapid growth of body height. Table 1 shows the symptoms of iron deficiency anemia in children, the diagnostic criteria, and the treatment strategies.

#### Table 1  Symptoms, Diagnosis, and Treatment of Major Iron Deficiency in Infants

<table>
<thead>
<tr>
<th>Major symptoms</th>
<th>Diagnostic criteria</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Premature birth infants</strong>&lt;br&gt;Latent anemia (16 months or later after birth)</td>
<td>Facial pallor, inanition, dysphoria, anorexia, poor weight gain</td>
<td>Hb ≤ 10 g/dl</td>
</tr>
<tr>
<td><strong>Delayed weaning, between 6 months to 2 years after birth</strong>&lt;br&gt;(Milk anemia)</td>
<td>Facial pallor, inanition, dysphoria, anorexia, poor weight gain</td>
<td>Hb ≤ 11 g/dl</td>
</tr>
<tr>
<td><strong>Adolescent women</strong></td>
<td>Indefinite complaints (malaise, fatigability, palpitation, shortness of breath), facial pallor, decreased attentiveness, asthenia</td>
<td>Hb ≤ 12 g/dl</td>
</tr>
<tr>
<td><strong>Athletes</strong> (Sports anemia)</td>
<td>Same as in adolescent anemia, failure to achieve better records, inability to muster the last spurt</td>
<td>Hb ≤ 12 g/dl</td>
</tr>
</tbody>
</table>

Note 1) Administer ferric pyrophosphate (Incremin syrup®) to infants and small children, and ferrous sulfate (Ferro-Gradumet®), ferrous fumarate (Ferrum®) or ferrous citrate (Ferromia®) to older children.


2. **Premature infants**

The amount of iron delivered from the maternal body to the fetus via the placenta increases during the late gestation period, therefore, iron deficiency is more likely to be encountered in premature infants. Anemia in premature birth infants can be divided into...
early anemia developing around 8 weeks after birth, and late anemia developing 16 weeks or later after birth. Since early anemia is attributable to a decline in hemopoiesis in neonates, iron supplements are not effective, while blood transfusion and erythropoietin injection are effective. The late anemia represents iron deficiency anemia due to depletion of iron stores. Its incidence is high among breast-fed infants and iron supplements are effective in the treatment of this condition.

3. Milk anemia
Anemia occurring between late infancy and early childhood in children with delayed weaning who drink a lot of milk is well known as milk anemia. This has been attributed to insufficient iron intake. It may be associated with protein-losing enteropathy and gastrointestinal bleeding.

4. Adolescent women
Anemia in adolescent women is caused by iron loss due to menstruation, unbalanced diets, and dieting for weight loss. It occurs at a high incidence, and about 8 to 10% of adolescent women are reported to have iron deficiency anemia. When taking iron deficiency without anemia also into account, one out of about four adolescent patients with indefinite complaints is thought to have iron deficiency.

5. Athletes
Iron deficiency anemia in athletes is considered to be caused by insufficient iron intake, iron loss, intestinal bleeding, and erythroclasis. This type of anemia is particularly important to be borne in mind when adolescent women, who are already susceptible to anemia, engage in intensive sports activities.

**Zinc Deficiency** (Table 2)

1. Diagnosis and treatment of zinc deficiency
Zinc deficiency in children is characterized mainly by dermatitis and alopecia during infancy, and by short stature during childhood. Zinc deficiency in children is not rare in Japan. Evaluation of age-related variations of serum zinc levels shows that the levels are low because of physiological factors between 2 months to 6 months after birth. However, there are as yet no diagnostic criteria specifically established for zinc deficiency in children. Perhaps the same criteria as for adults are applicable (serum zinc level under 65 µg/dl).

For the treatment of zinc deficiency, zinc sulfate is administered at the dose of 5 mg/kg/day (1 mg/kg/day of zinc) b.i.d or t.i.d after meals. However, zinc sulfate is not yet approved for use as a drug. Polaprezinc (Promac®) is a zinc-containing preparation that can be taken orally, however, only treatment of gastric ulcer with this drug is covered by the National Health Insurance in Japan.

2. Premature infants
Infants born prematurely and/or breast-fed are particularly prone to develop zinc deficiency between 2 months to 6 months after birth.

<table>
<thead>
<tr>
<th>Symptoms of deficiency</th>
<th>Factors related to the onset of zinc deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Symptoms of acute deficiency&lt;br&gt; Eruptions around the mouth, on the pubis, and extremities, skin erosion, alopecia, susceptibility to infections, poor weight gain&lt;br&gt; • Symptoms of chronic deficiency&lt;br&gt; Stagnation of growth of body height, anemia, dysgeusia, susceptibility to infections</td>
<td>Between 2 months and 6 months of age in premature birth infants (especially breast-fed infants), unbalanced diets, short stature, young women, long-term administration of large amounts of iron, chronic diarrhea, diabetes mellitus, nephrotic syndrome, cirrhosis, Crohn’s disease, Down’s syndrome</td>
</tr>
</tbody>
</table>
Since premature infants have only small stores of trace nutrients in the body, they tend to develop trace element deficiency during the period of rapid growth when the demand for these elements increases. Moreover, since the zinc concentration in breast milk is lower than that in milk formulas, breast-fed infants are more likely to develop zinc deficiency.

Fortified human milk products are available commercially for premature infants fed on breast milk. The appearance of symptoms of acute zinc deficiency, such as alopecia and dermatitis, has been reported even in infants receiving fortified human milk products between 2 months and 6 months of age, when marked increase in the body weight is observed; this is because even though fortified human milk products contain zinc, they are not present in sufficient amounts to satisfy the requirements associated with the rapid increase of body weight.

3. Infants depending on “Follow-up milk” formulas as the main source of nutrition

“Follow-up milk” formulas (milk-substitute nutritional supplement for infants), which are used from 9 months after birth, contain practically no zinc or copper. Although there have been no reports yet, dependence on follow-up milk formulas as the main source of nutrition can lead to zinc and/or copper deficiency.

4. Short-statured children

Out of 30 short-statured Japanese children who did not have any endocrine disease, 18 (60%) had latent zinc deficiency and 11 (37%) showed serum zinc levels below the standard level (under 70 μg/dl). Zinc administration is associated with an increase of body height in many cases. The increase is particularly marked in boys receiving zinc supplementation; (Fig. 1). Children with short stature due to zinc deficiency usually do not exhibit other symptoms of zinc deficiency, such as alopecia and dermatitis.

Therefore, when children of short stature are investigated as to the cause, examination for zinc deficiency is essential, and zinc administration may be attempted to improve the height of the children.

5. Young women

About a half of female college students are reported to show serum zinc levels below the standard, and extremely poor nutritional intake of zinc due to dieting and intake of unbalanced diets has been suggested to be the cause.

6. Other patient groups susceptible to zinc deficiency

Children with Down’s syndrome, serious psychosomatic disorders, diabetes mellitus, or nephrotic syndrome have a relatively higher likelihood of developing zinc deficiency. Acr-o-dermatitis enteropathica is a congenital zinc absorption disorder, and symptoms of zinc deficiency are typically observed during infancy.

Copper Deficiency

Copper deficiency, like zinc deficiency, is also more likely to develop in premature infants,
but it usually does not cause any clinical problems and copper supplementation is unnecessary. Menkes disease is a congenital abnormality of copper metabolism characterized by severe copper deficiency, but the incidence of this condition is extremely low, and it is rarely encountered in ordinary pediatric practice.

**Selenium Deficiency**

Selenium deficiency, like iron and zinc deficiency, is also more likely to occur in premature birth infants between 2 months to 6 months of age when they show rapid growth, but it is not associated with any clinical abnormalities. Children taking enteral formulas with little selenium content exhibit marked selenium deficiency. Also, children with conditions such as serious psychosomatic disorders who have lower daily caloric intake than the caloric requirement for age are more prone to develop deficiency of selenium and other trace elements.

**Iodine Deficiency**

Since Japanese people consume marine products in relatively large quantities, iodine excess may be more of a problem than iodine deficiency. However, some enteral formulas have extremely low iodine content (Ensure Liquid®, Twinline®, Racol®, etc.). Dependence on such enteral formulas as the only source of nutrition is associated with the risk of iodine deficiency. Iodine deficiency may cause goiter and/or hypothyroidism.

**Conclusion**

This article discusses trace element deficiencies that are relatively commonly encountered in Japanese infants and children. Particularly in the following cases, aggressive examination and treatment are necessary (see the respective sections for treatment).

1) Premature birth infants have a greater likelihood of developing deficiency of trace elements such as iron, zinc, and selenium during the period of rapid growth between 2 months and 6 months of age. Breast-fed infants are particularly susceptible to trace element deficiency.

2) The incidence of latent zinc deficiency is high among children of short stature without endocrine disease, and zinc administration is often associated with an increase in the body height.

3) Deficiency of iron and zinc is often noted in adolescent and young women.

4) Prolonged use of enteral formulas in children is associated with the risk of trace element deficiency, such as selenium and iodine deficiency. Children with serious psychosomatic disorders are particularly likely candidates to develop trace element deficiency. One of the countermeasures is to avoid usage of the same type of enteral formula over prolonged periods of time.

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Deficiencies of Trace Elements among the Aged and Clinical Aspects

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Abstract: A survey was conducted on the aged individuals at health care facility for the elderly to investigate problems associated with the intake of minerals and trace elements among the aged Japanese. In addition, the literature was reviewed to the effects of trace elements that are involved in diseases common among the aged. The results indicated that although aged individuals consume the same amount as young people, the plasma concentration of calcium of the former was lower, indicating that their capacity to utilize this metal (e.g., intestinal absorptive capacity) has been compromised. Furthermore, consumption of magnesium and zinc is very low among the aged and their plasma concentrations of these elements are frequently far below the normal threshold. These facts indicate that aged individuals suffer from a very poor nutritional state. A review of the literature revealed that magnesium and selenium are involved in circulatory diseases; and not only iron but also copper and zinc play a role in the development of anemia. Iron and zinc are related to the pathogenesis of decubitus ulcers; zinc and lithium in psychiatric disorders; and chromium and vanadium related to the cause of diabetes mellitus. Generally speaking, aged individuals consume less than optimum amounts of trace elements and their capacity to utilize them is limited. Thus it is possible that the lack of an adequate supply of these trace elements may explain why many of the diseases normally attributed to old age develop.

Key words: Trace elements; The aged; Nutritional status; Mineral

Introduction

Various physiological changes related to nutrition take place in old age.

First, the deterioration in the capacity for digestion and absorption results in a need for intake of nutrients in excess of what an average adult requires per unit weight. In the aged, the capacity to retain nutrients in the body appears also to be reduced. Because the intracellular fluid volume is reduced, a large quantity of nutrients (e.g., potassium and magnesium) that
have been dissolved in this fluid also tend to be lower. The gustatory sensation is compromised and the sensation for sweet or salty flavors becomes exaggerated in comparison with that they had when they were younger. The deterioration in the masticatory function results in a preference for softer food; and a reduced intake of dietary fibers may lead to the development of constipation.

The present study was conducted to investigate how the physiological changes and the status of mineral and trace element nutrition in the aged — such as that described above — are related to their health and affect the development of diseases.

### Status of Mineral Nutrition in the Aged

First, a study was conducted to discover the status of mineral nutrition among the aged.\(^1\)

For the subjects, 10 male and 10 female inpatients were selected (average age, 77.4 years). The prerequisites used for the selection were that they were suffering from conditions such as arteriosclerosis and osteoporosis (common among the aged) but were at a relatively mild stage of the disease; and they still retained a certain level of independence in their daily activities. For the controls, 10 male and 10 female students or hospital employees (average age, 24.6 years) were selected. The participants were asked to fill out a dietary survey sheet on 3 consecutive days. The amounts of calcium, magnesium, zinc, and copper consumed were computed by using a nutrient computing program prepared for use on a personal computer and which was based on a table of components of standard Japanese foods and several references. Blood specimens were collected from both patients and controls following fasting and their plasma mineral contents were computed. It was found that each of the 4 minerals cited exhibits a different pattern of consumption and absorption.

The amount of calcium consumed varied widely among individuals regardless of their age but the mean did not differ significantly between the two groups. However, the plasma calcium concentration of the aged individuals was significantly lower than that of the younger subjects, proving that although calcium consumption is similar in these two groups, its utilization is far less efficient among the elderly.

In Fig. 1, the relationship between magnesium intake and its concentration in the plasma is shown. The amount of magnesium consumed is evidently low and so is its plasma concen-
tration in the older population. Although the plasma magnesium concentration is not a sensitive indicator of magnesium balance in the body, the concentrations for 3 of the older individuals were below the normal level, suggesting that their state of magnesium deficiency was advanced.

Figure 2 shows the relationship between zinc intake and plasma zinc concentration. Zinc intake was generally low among the aged; the plasma zinc concentration was below the lower threshold of the normal level in many; and a correlation was noted between the intake of magnesium and zinc and their plasma concentrations.

Copper intake by the aged was very low, with an evident difference between the young and the aged. However, there was no difference in the plasma copper concentrations between these groups; neither was there any correlation between the intake and their plasma concentrations. It appears that there is a need to develop better evaluation indices for copper.

The study described above has a certain limitation — i.e., it was conducted on a unique group of aged individuals (e.g., inpatients). However, it is sufficient to suggest that among these older subjects, their intake of minerals and trace elements is reduced and their capacity to utilize them (e.g., their rate of intestinal absorption) has been compromised; thus their nutritional state vis-à-vis trace elements deteriorates as they grow older.

Diseases of the Aged and Trace Elements

1. Circulatory diseases

Although not included in the category of trace elements, magnesium is closely related to circulatory diseases. The antagonist-like action of magnesium prevents calcium from flowing into the vascular smooth muscle cells. Because of this action, magnesium has an effect to prevent myocardial and cerebral infarctions. As described above, its intake by the aged is low: special caution must be exercised in this area.

According to a report from China, Keshan disease, a heart disease prevalent there, is caused by a selenium deficiency. Starting around 1974, a special nutritional program was implemented to add selenium to the diet of inhabitants in those areas where this disease was endemic, which resulted in dramatic reductions in its mortality and prevalence. Selenium is incorporated in the form of a seleno-amino acid into glutathione-peroxidases, which plays an important role in preventing oxidation disorders. A selenium deficiency and a resultant increase in the lipid peroxide level invite the development of circulatory diseases such as arteriosclerosis. Known food sources of selenium include fish and grains, which are often favored by the aged. However, the overall intake of food decreases as one grows older and it is quite possible that some may suffer from a deficiency of this element.

2. Anemia

Figure 3 shows the frequency of the incidences of anemia at each age level, according to the National Nutrition Survey in Japan. Among women, peaks are noted in those in their 30s and 40s, which can be explained by heightened iron requirements due to menstruation. As men and women become older, the incidence of anemia also rises. However, aged individuals consume a greater amount of iron than their younger counterparts. One must look into other areas — e.g., reduced capacity to utilize this element — to explain the causes for iron deficiency anemia.

In the relationship with trace elements, copper plays a role in supplying iron to various tissues in the body. Thus even when the iron intake is adequate, a copper deficiency may cause anemia. Furthermore, it was found recently that anemia may also be caused by a zinc deficiency. As stated earlier, copper and zinc intake is low among the aged and it is possible that a deficiency of either of these
elements is involved in the development of anemia among the aged population.

3. Decubitus ulcer

A decubitus ulcer causes extreme pain to the bed-ridden elderly and markedly deteriorates their QOL. Tanaka et al.\(^4\) divided bed-ridden inpatients over 65-years of age into those with a decubitus ulcer and those without (the controls) and studied their nutrient intake. There was no significant difference between the two groups in the intake of iron and zinc; but it was slightly higher for the group with decubitus ulcers. Yet the iron and zinc concentrations in the serum were significantly lower in this group, suggesting a reduced rate of utilization of these trace elements. It is probable that for these aged bed-ridden patients, supplementation with trace elements — such as zinc, which restores the immune and tissue repair capacities and iron, which prevents the development of anemia — will lead to prevent decubitus ulcers.

4. Psychiatric disorders

Among autopsy cases, Kimura et al.\(^5\) selected 10 patients with hebephrenia (schizophrenia) and 10 who succumbed from other diseases and measured the zinc content in their brains. It was found that the zinc concentration in the brain of the former was significantly lower. Nishigori et al.\(^6\) in another study, reported that when health foods containing zinc were given to patients with hebephrenia (schizophrenia) their psychiatric symptoms ameliorated.

Schrauzer et al.\(^7\) reported that there is an inverse relationship between the lithium concentration in drinking water and the incidence of suicides and violent crimes, such as homicide, robbery, and rape; and they proposed that lithium probably has a sedative effect.

There is a possibility that these trace elements have an effect on the psychiatric condition of the aged. This subject will be investigated further.

5. Diabetes mellitus

There are many reports on diabetes mellitus and trace elements, among which chromium and vanadium are particularly worthy of attention. It has been reported that chromium restored glucose tolerance in young children who had been rendered glucose intolerant due to a nutritional disorder. In another report, glucose tolerance was reduced in patients who had been fed intravenously with an infusion fluid without the addition of chromium: the condition was refractory to insulin treatment and improved only when chromium was added to the infusion fluid. There are a number of reports on the beneficial effects of chromium...
on diabetes mellitus. Vanadium has frequently been cited for its contribution to improving glucose tolerance in rats with experimental diabetes mellitus. However, no detailed mechanisms by which these two elements act in combating diabetes mellitus have been given.

When these mechanisms are thoroughly explained and the safety and efficacy of these trace elements are established, it is possible that they will be used increasingly for the prevention and treatment of diabetes mellitus.

Conclusion

There are few studies that elucidate the metabolic state of trace elements in the aged; and only a limited number have been introduced to explain the effects of these elements on diseases. The present study was conducted on these limited data but one can be readily convinced that aged individuals take in reduced amounts of trace elements and their capacity to utilize them are also compromised. The aged suffer from diverse forms of illnesses, some of which are most likely to be caused by inadequate intake of these trace elements.

One hopes that progress will be made in studying this area so that many trace elements may be used to prevent and treat the diseases that afflict aged patients.

REFERENCES

Sensory Dysfunctions due to Trace Element Deficiencies and the Clinical Aspects
—Taste and olfactory disorders—

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Abstract: Among the trace elements known to be essential to human nutrition, zinc is typical in that the lack of it can cause sensory dysfunctions in human. It is known that a deficiency of zinc results in a wide variety of diseases with sensory (gustatory, olfactory, and visual) dysfunctions being only one type of them. In the present study, the focus is placed on the taste disorders as an example of a sensory dysfunction caused by trace element deficiencies; and on the etiological mechanism of the disorders that are associated with zinc deficiency. A reduced serum zinc level (below 70μg/dl) seen in cases of taste disorders has also been noted frequently in similar conditions that are putatively provoked by other causes (e.g., those caused by systemic or drug-induced dysfunctions). These findings suggest that zinc is likely to play a role in the development of many types of taste disorders. Supplementation by oral zinc preparations has been found to be effective in a number of double-blind tests on clinical cases with idiopathic or zinc deficiency-induced taste disorders, which substantiated the aforementioned possibility.

Key words: Zinc; Taste disorder; Olfactory disorder; Essential trace elements

Introduction

Among the trace elements essential to human nutrition, zinc is typical, the deficiency of which is known to cause sensory dysfunctions. Located at the center of a number of metalloenzymes, it is involved in many types of essential metabolic processes, thus considered to be a very important trace element for the body. It is known that a deficiency of zinc is responsible for a variety of disorders, sensory dysfunctions being one type.

For the sensory dysfunctions, gustatory, olfactory, and visual dysfunctions are known.1)
deficient feed, a taste disorder developed in 30% of the young animals and 70% of their older counterparts. These zinc deficient rats exhibited a decrease of microvilli at the ends of their taste cells where the receptors are located or breakage of these cells with their ends torn off. Many other abnormal features — e.g., a loss of electron dense substance, a reduction in the number of Golgi-originated dark granules that are distributed in the taste cells, and vacuolization of these cells — were also noted. These abnormalities involving the taste bud cells that were confirmed in animal experiments were also observed in human subjects who suffered from taste disorders caused by zinc deficiency. The taste cells of normal rats continuously undergo a fast turnover (requiring about 10 days) through generation followed by replacement of their epithelial cells to maintain the function as taste receptors. In zinc-deficient rats, however, this turnover time is prolonged: it is known that if the zinc is replaced, this delay in the turnover is corrected, while improving also the symptoms of taste disorder. The current study focuses on the first two, which come under the heading of sensory disorders in the field of otorhinolaryngology.

**Zinc Deficiency and Taste Disorders**

Table 1 lists diverse causes for taste disorders. Some develop as a direct consequence of the dysfunctions of the peripheral or central nervous system related to taste sensation; but many are considered to be caused by dysfunctions at the peripheral receptor level. Taste disorder caused by zinc deficiency belongs to the category of peripheral receptor level dysfunctions.

1. **Taste disorder in animal experiments**

In the living body, zinc is abundantly distributed in epithelial tissues and their appendages (about 20% in organs, such as the skin, hair, and nails). The lingual epithelium is also known for its rich zinc content. In particular, zinc is localized in many sites at the base of the filiform papillae and the epithelium section, including the taste buds of the vallate papillae. Furthermore, the area within the taste buds (in particular, around the taste pores) is richly endowed with zinc enzymes (e.g., alkaline phosphatase, acid phosphatase, ATPase, adenylate cyclase, and cyclic AMP phosphodiesterase), which suggests a significant correlation between the taste organ and zinc.

Of the rats that have been raised on zinc-deficient feed, a taste disorder developed in 30% of the young animals and 70% of their older counterparts. These zinc deficient rats exhibited a decrease of microvilli at the ends of their taste cells where the receptors are located or breakage of these cells with their ends torn off. Many other abnormal features — e.g., a loss of electron dense substance, a reduction in the number of Golgi-originated dark granules that are distributed in the taste cells, and vacuolization of these cells — were also noted. These abnormalities involving the taste bud cells that were confirmed in animal experiments were also observed in human subjects who suffered from taste disorders caused by zinc deficiency.

The taste cells of normal rats continuously undergo a fast turnover (requiring about 10 days) through generation followed by replacement of their epithelial cells to maintain the function as taste receptors. In zinc-deficient rats, however, this turnover time is prolonged: it is known that if the zinc is replaced, this delay in the turnover is corrected, while improving also the symptoms of taste disorder.

2. **Zinc deficiency-induced taste disorder in human**

The low serum zinc level (below 70µg/dl) seen in cases of a taste disorder is also frequently observed in those patients suffering from a similar affliction that is caused by a systemic disease or incurred by drug actions. It is suspected that in many instances of taste
disorders ostensibly from other causes, zinc deficiency is also involved in their etiology. Even those cases of an idiopathic taste disorder that yield normal results in clinical tests (including analysis of serum zinc level), oral zinc administration has been found to be as effective as in those suffering from zinc deficiency. It is suspected that in these cases of idiopathic taste disorders, a latent zinc deficiency that cannot be detected by ordinary serum chemical analyses exists and participates in the development of taste disorder.

For the pathogenesis of zinc deficiency in human, various causes have been put forth; but no organized studies have been conducted on what causes this deficit in patients who ultimately develop a taste disorder. Tomita\(^9\) suggested the low zinc content of the typical Japanese diet and the high intake of processed food that may contain a high content of food additives as the possible causes for the low blood zinc levels among Japanese.

**Treatment of Zinc Deficiency-Induced Taste Disorder**

1. **Zinc preparations used for treatment**

   Zinc sulfate has been used for a zinc preparation. In most instances, each capsule contains 100 mg of zinc sulfate (equal to 23 mg of zinc) and is administered 3 times a day (300 mg/day). This method is cumbersome because each capsule must be prepared by placing the right amount of zinc sulfate. The only zinc-containing pharmaceutical preparation that can be prescribed is polaprezinc (Promac\(^9\)), a product used to treat peptic ulcers. Its dosage is set at 150 mg/day, which is given twice a day (after morning and evening meals). If the serum zinc level does not rise sufficiently, it may be administered before meal.

2. **Therapeutic effect of zinc preparations on taste disorders**

   If stratified by the causes of taste disorders, the efficacy of zinc sulfate is 73.7% for a condition caused by zinc deficiency and 75.8% for that of an idiopathic nature. Thus the efficacy rate was about the same in the two disorders of different etiologies. For a taste disorder caused by systemic diseases or drug actions, the efficacy rate is slightly lower (65 to 67%), with an overall efficacy of 67%.\(^9\) Double-blind tests were conducted on the efficacy of zinc preparations on taste disorders by using zinc gluconate\(^10\) and zinc picolinate.\(^11\) Significant efficacy has been reported for those cases with zinc deficiency-induced and idiopathic taste disorders.

**Olfactory Disorders**

In rats with a zinc deficiency such as that described above, the zinc content in the olfactory epithelium also decreases markedly.\(^12\) The ultrastructure of the olfactory epithelium also undergoes changes: the entire epithelium becomes squamatized, intercellular space markedly increases, and most outstandingly, the olfactory cells undergo extreme degeneration. However, it has been reported that administration of zinc corrects these deformation and induces neurons to regenerate.\(^13\)

Reports such as these suggest that zinc deficiency may be one cause for olfactory disorders. At the moment, however, there have not been sufficient studies to prove the extent of involvement of a zinc deficiency in clinical cases of olfactory disorders. Future studies are awaited.

**Conclusion**

For an example of disorders of sensory organs caused by zinc deficiency, a taste disorder was described in detail with special reference to its relationship with a deficit of this trace element. As a cause of the taste disorder, zinc deficiency is clinically significant. Treatment with zinc preparations has been found to be highly effective in cases with idiopathic or zinc deficiency-induced taste disorders.
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Trace Elements and Cancer

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Abstract: In regard to iron, malignant neoplasms are often seen in various organs in idiopathic hemochromatosis, and complication by lung cancer is especially common. In regard to the carcinogenicity of copper, large amounts of copper and iron have been reported to accumulate in the liver and spleen of patients with cancer of the respiratory tract, urinary tract, and thorax. Increases in skin and pulmonary epithelial cancer, and the precancerous condition cutaneous keratosis (Bowen's disease) are seen as a result of chronic oral or airway exposure to arsenic. In addition, there is a report that leukemia has been observed in aplastic anemia and a report that arsenic causes cancer of the bladder, kidney, digestive tract, and liver, etc. Lung cancer is cited in associations between chromium and carcinogenesis. Nickel has been reported to be associated with lung cancer and nasal cavity cancer. High mortality from lung cancer in factories handling beryllium and increased tumors of the central nervous system have also been suggested.

Key words: Trace element; Cancer; Metal carcinogenicity

Introduction

Arsenic, chromium, and nickel are said to contribute to the development of cancer based on the epidemiologic evidence, and beryllium, cadmium, chromium, cobalt, lead, nickel, zinc, and iron have been found to be carcinogenic in experimental animals. In this paper, we will describe the carcinogenicity of a variety of metals.

Carcinogenicity of Metals

1. Iron

Sarcomas and skin cancers have been reported to have developed when animals were intramuscularly injected with iron dextran.1) Boyd et al.2) reported an association between iron ore miners and the incidence of lung cancer, but it also appeared that they may have been exposed to radon, which was also present, and
Various malignant neoplasms of different organs are often seen in idiopathic hemochromatosis, but liver cancer is an especially common complication. The mechanisms of the hepatocarcinogenesis are thought to be that iron bound to low-molecular protein in the liver generates hydroxyl radicals via the Fenton reaction that damage DNA, and a direct action of iron on the replication process of the DNA. In a study of iron deposits in the surrounding liver parenchyma in a group of HCV-positive liver cirrhosis patients with liver cancer and a group without liver cancer, the iron deposits were reported to be clearly more common in the group with liver cancer.

2. Copper

Accumulation of large amounts of copper and iron has been reported in the liver and spleen of patients with cancer of the respiratory tract, urinary tract, and thorax, and the copper content of benign tumors of the esophagus, bronchi, and intestine is said to be lower than in cancers.

LEC rats (Long-Evans rats with cinnamon-like color) are animal models of Wilson disease, in which copper accumulates in liver tissue. The animals develop hepatitis at 4 months of age and approximately 40% die, and at approximately 1 year of age those that survive develop liver cancer via cirrhotic change. Gel-filtration analyses have shown that the majority of the increased copper exists in the form of Cu-MT (copper-metallothionein), and it is thought that hydroxyl radicals are generated in the presence of hydrogen peroxide as a result of a Fenton-like reaction and cause hepatitis and hepatocarcinogenesis.

Liver tissue copper content increases in human chronic hepatitis C and liver cirrhosis as the liver disease progresses, and the copper content of well differentiated hepatocellular carcinoma becomes significantly greater than that of moderately or poorly differentiated hepatocellular carcinoma. According to the gel-filtration method, the increased copper in hepatocellular carcinoma also appears to exist in the form of Cu-MT and hydroxyl radicals are generated by a Fenton-like reaction, and similarities to LEC rats have been found. Hydroxyl radicals form the DNA damage marker 8-OHdG (hydroxydeoxyguanosine), and tissue 8-OHdG levels have been shown to be high in chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma.

3. Zinc

Zinc deficiency causes dermatitis, alopecia, and taste disorders, and excessive intake can cause acute poisoning. In experimental models, development of teratomas and cancers were observed when zinc chloride was injected into the testes of chicks and rats.

No epidemiologic evidence of any type of increased cancer incidence has yet been obtained in zinc factory workers or ordinary populations. Zinc is a component of SOD (superoxide dismutase), an enzyme that removes free radicals, and since it is also necessary for activation of DNA repair enzymes, zinc has the opposite effect and protects against carcinogenesis.

4. Arsenic

In a study in which carcinogenesis was observed when animals were exposed to arsenic, Yamamoto et al. reported that bladder, kidney, liver, and thyroid tumors were induced when rats were given another initiator at the same time as a dimethylarsinic acid solution, and the development of skin and pulmonary epithelial cancer, and the development of precancerous cutaneous keratosis (Bowen’s disease) are seen when chronically exposed orally or via the airway.

In addition, there have been reports of leukemia in aplastic anemia and of arsenic causing cancer of the bladder, kidney, digestive tract, liver, etc. The carcinogenetic mechanism is unknown, but there have been reports that arsenic compounds inhibit methyl thymidine
uptake by human skin cells in vitro and inhibit DNA synthesis. Chromosome abnormalities have been observed when human leukocytes or cutaneous fibroblasts were exposed, and there is a report that it is due to DNA binding becoming weaker as a result of substitution for phosphorus in DNA.

5. Chromium
An association between chromium and carcinogenesis has been pointed out in regard to lung cancer. A high incidence of lung cancer has been demonstrated as an occupational disease among workers engaged in the chromate production process in Germany and the United States. The risk of lung cancer among chromium workers compared to an ordinary population is very high, with a lung cancer prevalence rate 100,000 versus 578, and the relative risk from the standpoint of lung cancer deaths has reached from 3.6 to 29.1. Histopathologically, the most common chromium-related lung cancers are squamous cell carcinomas and small cell cancers.

6. Nickel
In experiments on rats, induction of rhabdomyosarcoma was reported as a result of intramuscular injection of nickel subsulfate, and development of sarcoma in various organs has been reported as a result of intravenous injection of nickel carbon. Lung cancer developed when cats were allowed to inhale nickel dust, and high rates of lung cancer and cancer of the nasal cavity have been found in nickel refinery workers. The principal carcinogens are thought to be inhaled nickel particles and nickel oxide.

7. Vanadium
Vanadium has been negative in many bacterial tests for mutagenicity. It is not recognized as possessing carcinogenic activity, and no association has been found with cancer in humans or animals. Nevertheless, vanadium promotes cell mutation in some cells, causes tyrosine kinase phosphorylation, and is said to possibly exert an effect on oncogenes. Since it also interferes with proper chromosome arrangement during cell division, the risk of carcinogenicity cannot be ruled out. An association is also said to exist between the vanadium concentration in air and lung cancer, but no clear causality has been established.

8. Beryllium
Lung tumors have been observed in carcinogenesis experiments in response to intratracheal administration, inhalation exposure, and intraperitoneal administration, and development of osteosarcoma has been reported after intravenous administration. Carcinogenicity in humans has been suggested by high mortality from lung cancer in factories handling beryllium and by increases in tumors of the central nervous system.

The carcinogenetic mechanism is thought to be inhibition of the enzymes required for DNA synthesis, such as thymidine kinase, thymidine synthase, and DNA polymerase.

9. Lead
Renal cancer has been reported in rats and mice subcutaneously injected with lead phosphate. There are also reports of lung cancer in hamsters after simultaneous intratracheal administration of lead oxide and benzpyrene, and of development of brain tumors when lead acetate was orally administered to rats. A slight association with the development of lung cancer, stomach cancer, and brain tumors has been reported in workers in a lead smelter, and in lead poisoning, but lead has not been definitely concluded to be carcinogenic in humans.

The carcinogenetic mechanism is assumed to be interference with the DNA repair process, but the details are currently unknown.

10. Cadmium
DNA fragmentation and chromosome mutations have been reported in cultured human cells, sarcoma and testicular interstitial cell
tumors have been reported as a result of injections in rats, and an association with prostate cancer has been reported in humans, but questions about the carcinogenicity of cadmium have arisen based on recent epidemiologic research.19)

11. Cobalt

The mechanism of gene mutations by cobalt is known to be DNA breaks and inhibition of DNA repair by cobalt, and gene mutations and carcinogenicity have been reported in cells and in experimental animals. However, no evidence is yet available in humans.20)

Conclusion

Metal carcinogenesis has recently been attracting attention not only in terms of occupational diseases but in ordinary environments. In humans, iron is said to cause liver cancer in hemochromatosis, copper to cause liver cancer, respiratory tract cancer, urinary tract cancer, and thoracic cancer, arsenic to cause skin cancer, liver cancer, respiratory tract cancer, and urinary tract cancer, chromium to cause lung cancer, nickel to cause lung cancer and cancer of the nasal cavity, beryllium to cause lung cancer and central nervous system tumors, lead to cause lung cancer, stomach cancer, and central nervous system tumors, and cadmium to cause prostate cancer, but many aspects of their carcinogenic mechanisms are unknown.

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Trace Elements and Nervous and Mental Diseases

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Abstract: Relationships between Al, Fe, and Mn and Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and parkinsonism are outlined. These diseases are thought to be multifactorial, and trace element abnormalities are suspected of being risk factors. Al and Fe are suspected of being involved in the formation of neurofibrillary tangles (NFT) and senile plaque in AD. The Kii Peninsula of Japan has been the focus of ALS, and an association between environmental factors and its occurrence is suspected. Environmental metal analyses in this area has revealed low contents of Ca and Mg and high contents of Al and Mn in the drinking water and soil. Al deposition has been observed in the brain tissue of patients from Kii Peninsula. Cell loss has been noted in the spinal cord and cerebrum of animals chronically given a low Ca/Mg high-Al diet, and an etiological association with these trace elements was suspected in ALS cases from this area. Mn is known to induce the development of extrapyramidal manifestations. Although the clinical manifestations of Mn-exposure parkinsonism and Parkinson's disease are different, involvement of environmental factors has been speculated in the onset of Parkinson's disease, and there is concern about air pollution by Mn. In addition, there are cases of Al encephalopathy in which an association with high-calorie infusion therapy and Al-containing medical materials is suspected.

Key words: Aluminum; Neurotoxicity; Amyotrophic lateral sclerosis foci; Amyotrophic lateral sclerosis; Iron; Manganese

Introduction

A variety of trace elements have been shown to be involved in nervous and mental diseases. In this article, the etiological associations will be described between iron (Fe), zinc (Zn), and aluminum (Al) and dementia, especially Alzheimer's disease; calcium (Ca)/magnesium (Mg) deficiencies and excessive trace elements, such as aluminum and manganese (Mn), in amyotrophic lateral sclerosis (ALS), parkinsonism induced by manganese poisoning; dialysis encephalopathy and aluminum; and aluminum poisoning by medical materials.

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Alzheimer’s Disease and Trace Elements

In 1965 Klazo et al.1) reported the development of abnormal intracellular accumulations of neurofilaments (NFs) when they administered aluminum phosphate into the brain of experimental animals. Since the changes closely resembled the neurofibrillary tangles (NFTs) of Alzheimer’s disease, attention was focused on an etiologic association. Epidemiologic surveys in the United Kingdom, the United States, Canada, and Norway have shown high prevalences of Alzheimer’s disease in regions where the aluminum concentration in tap water is high. Metal analyses have also shown higher aluminum concentrations in the brains of Alzheimer’s disease patients than in controls, and aluminum deposition has been demonstrated in NFTs and senile plaques.

In contrast, many reports about the association between aluminum and Alzheimer’s disease have been negative. Since aluminum displays an aggregating action in vitro, at least on cytoskeletal proteins such as NF, the possibility that it plays some sort of etiologic role cannot be ruled out, and further investigation appears to be needed.

Aluminum binds to the phosphate groups of DNA and cytoskeletal proteins in vitro and induces aggregation of amyloid protein and excessive phosphorylation of tau protein. It causes irreversible changes in the structure of these proteins, and hyperphosphorylated fibers are thought to cause cell death by accumulating and impairing axonal transport. The cytotoxic mechanism of aluminum is also suspected of being caused by the production of free radicals, such as hydroxyl radicals, as a result of a transition from Al2+ to Al3+.

Next, there is the neural cytotoxicity widely known to be caused by iron. The globus pallidus, red nucleus, substantia nigra, cerebellar dentate nucleus, and cerebral motor area contain large amounts of non-heme iron. The values are low in newborn infants, but rapidly increase until the late teens. They remain almost the same in the 30s to 50s, before slowly rising in the brain again in old age. The iron is specifically distributed in the oligodendrocytes in the central nervous system and in the Schwann cells in the peripheral nervous system, and it binds to ferritin. By storing iron in its molecules, ferritin plays a role in the intracellular utilization and inactivation of iron. As an essential element in tyrosine hydroxylase, the action of iron is important in the synthesis of dopamine, norepinephrine, serotonin, and GABA.

In contrast, iron ions cause peroxide-radical damage by changing from an oxidized to a reduced form. They also reversibly hyperphosphorylate and insolubilize tau protein and contribute to the formation of NFT.3) It has been reported that there is increased iron content in the brain tissue of Alzheimer’s disease patients as well as increased ferritin in senile plaques and microglia, increased iron and zinc content, and decreased selenium (Se) content (selenium is speculated to have a preventive effect against the cytotoxicity produced by toxic elements).3) In addition, there is increased Fe-binding protein P97 and melanotransferrin in the serum, spinal fluid, and brain tissue of Alzheimer’s patients; and glutathione transferase, which possesses lipid-peroxide-degrading activity, is decreased and there are changes in metallothionein. Cytotoxicity caused by metal elements, such as iron and aluminum, is suspected, and use of p97, etc., has been assessed as a serum biomarker for Alzheimer’s disease.4) It is hard to imagine that these abnormal findings of chemical elements are the sole cause of Alzheimer’s disease, but they appear to be associated as risk factors.

Superficial siderosis is known as another central nervous system disorder caused by iron, and chronic, repeated bleeding in notably chronic subarachnoid hemorrhages, dural lesions, cervical spinal root lesions, vascular tumors, and vascular malformations, results in deposition of iron in the dura mater and
the surface of the central nervous system. After an asymptomatic interval of 4 months to 30 years, it leads to sensory deafness (95%), cerebellar ataxia (88%), pyramidal disorders (76%), dementia (24%), and urination disorders (24%).

**Amyotrophic Lateral Sclerosis (ALS) and Calcium, Magnesium, and Aluminum**

ALS is a degenerative disease that systematically affects upper and lower motor neurons and is characterized by severe neuronal loss of Betz cells in the motor cortex, and motor neurons in the brain stem, and spinal anterior horn cells with degeneration of the pyramidal tracts. Its prevalence is almost the same in every region of the world, and it is said to be 0.8–6.4 per 100,000 people, with an annual incidence rate of 0.4–2.6. In the 1960s, the prevalence of ALS in the Kozagawa region and Hobara region of the Kii Peninsula and in the southern part of Guam Island reached levels of 10 to 100 times higher than in other regions. The incidence of new cases began to decline in the 1970s, and it dramatically decreased in the 1980s to only several times the level in other areas. A recent repeat survey showed that the regional differences in the Kii Peninsula as a whole have tended to disappear due to the movement of the population to other areas, but, the annual incidence of ALS in the southern part of the Kii Peninsula is still high.

The cause and pathogenetic mechanism of ALS are still unknown, but attention is being focused on the free-radical and excitatory-amino-acid cytotoxicity hypothesis, superoxide dismutase (Cu/Zn SOD) gene abnormalities, and ubiquitin-proteasome system damage. Involvement of environmental factors appears to be important in ALS foci, in addition to these factors.

Another area of focus for ALS lies above the Mariana volcano zone that runs geologically north to south through the Western Pacific. There is high annual rainfall, and the soil is strongly acidic in this region. The soil and the water used in daily living were characterized by low calcium and magnesium levels as well as high levels of toxic elements, including manganese and aluminum according to the survey findings obtained during the 1960s and the 1970s. In addition to the ordinary pathological findings in ALS, the autopsy brain and spinal cord tissue in Guam ALS/parkinsonism-dementia (PD) and Kii ALS is characterized by the presence of NFTs. Element analysis revealed deposition of calcium and aluminum at the sites of degeneration, and in the nuclei and nucleoli of degenerated neurons, Bunina bodies, and NFTs. In considering these combined findings, the neuronal degeneration of Kii ALS has been speculated to be due to these elements.5)

When aluminum was injected into the brains of experimental animals, extensive abnormal
intracellular accumulation of NFs (neurofibrillary change; NFC) was observed in the cerebrum and spinal cord, and numerous spheroids began to appear in the anterior horns of the spinal cord in the early stages. This abnormal accumulation of NFs strongly resembled the spheroids/chromatolysis, which are characteristic pathological findings in the early stages of ALS. NFC differs from NFTs at the electron microscopic level, but tau, ubiquitin, MAP-2, amyloid precursor protein, etc., have been observed immunohistochemically, and similarities between the two have been pointed out.6)

To explain the occurrence of NFTs in the ALS from the focused area, the author and colleagues investigated the cytotoxicity of aluminum due to metal ion interactions in the environment of the Kii area. More specifically, experimental animals were chronically administered a low-CA/Mg high-Al diet. Neuropathological examinations of these animals showed a decrease in the spinal cord anterior horn cells, and cerebral cortical neurons, an increase in spheroids, and an appearance of anti-PHF (abnormal phosphorylated tau)-antibody-positive neurons.7)

Aluminum is a toxic element, and only about 1% of the amount ingested is absorbed by the gastrointestinal tract. Approximately 80% of the aluminum in the blood binds competitively with iron to transferrin, and a portion of the remainder binds to low-molecular-mass molecules, such as citric acid, and is transported. Aluminum’s entry into the brain is mediated by transferrin receptors, and it is bound to glial transferrin. Aluminum absorption from the intestine is promoted under low-Ca/Mg conditions, and when aluminum is administered chronically, it is thought to accumulate in the brain and spinal cord and to have cytotoxic effects. Clinically, anemia, bone damage, and dialysis encephalopathy are known to develop in aluminum poisoning. As mentioned above, aluminum has been found to bind irreversibly to phosphate groups in vitro and to be widely neurotoxic, e.g., by inhibiting polymerization/depolymerization of tau and NF, inhibiting Ca-binding proteins, such as calmodulin, and Ca-dependent enzymes. A mechanism in which mild damage caused by microamounts of aluminum incorporated from the environment, food, etc., accumulates. It has been speculated that cell death occurs when it exceeds a certain level, and abnormalities in interactions between elements appear to be important in terms of assessing the pathogenesis of the ALS occurring in foci.

Parkinsonism and Manganese

The first mention of manganese toxicity was found in a report on manganese grinding workers in Glasgow by Couper et al. in 1837, and extrapyramidal symptoms were subsequently reported in manganese miners in various areas of Europe.

Manganese is an essential element in the body, and 2–9 mg/day is ingested in food. Absorption from the intestine increases in iron, calcium, and magnesium deficiency. Approximately 80% of the manganese in the blood is bound to transferrin, and the rest is bound to unidentifed ligands. It is a constitutive element of metalloproteins, including mitochondrial enzymes, Mn-SOD, pyruvate carboxylase, and glutamine synthetase. Manganese is incorporated by endocytosis mediated by cerebral vascular transferrin receptors, and approximately 80% is localized in astrocytes.

Convulsions are known to occur as a result of manganese deficiency. Decreased manganese content in whole blood has been reported in an epilepsy patient group regardless of whether they were on medication, and it appeared to have been due to a decrease in Mn-SOD and glutamine synthetase activity.8) Dermatitis, hair damage, and hypocholesterolemia have also been shown to occur. Inner ear damage and ataxia have been mentioned as a result of manganese deficiency during the fetal period in animals.

Toxicity due to excess manganese, in contrast,
causes irreversible psychological manifestations (locura manganica) and neurological manifestations. Pneumonia and bronchitis develop as a result of airway exposure, and excess manganese accumulated in the lungs is said to pass into the brain. Psychological manifestations, such as impaired orientation, memory disorders, compulsive and violent behavior, emotional hypersensitivity, hallucinations, etc., are said to occur in acute poisoning. Progressive neurological manifestations, i.e., akinesia, dystonia, and gait disturbances appear 1–2 months after the onset of mental symptoms, and mask-like facies, articulation disorders, low voice, and monotonous whispering voice develop. In chronic poisoning, symptoms of a nervous breakdown and blunted affect appear after several months to several years of exposure, and progressive akinesia, gait disturbances, language disorders, parkinsonism, dystonia, increased deep tendon reflexes in the lower extremities, excitement, etc., gradually develop.

Neuropathologically, cerebral atrophy, cerebral ventricle enlargement, and atrophy of the caudate nucleus, putamen, globus pallidus, and thalamus are observed in manganese poisoning patients, with the greatest damage occurring in the globus pallidus. Loss and demyelination of large neurons in the internal segment of the globus pallidus and astrocyte proliferation are seen, but the substantia nigra is said to be normal. Loss of pigmentation, although mild, is seen in the substantia nigra in chronic manganese poisoning. At the cellular level, manganese accumulation is seen especially at sites in the brain where there is a high content of nonheme iron, the caudate nucleus, putamen, globus pallidus, substantia nigra, and hypothalamic nuclei. Biochemically, there is said to be an increase in dopamine and norepinephrine in the brain in the early stage, and decreases in the late stage. Exogenous manganese is claimed to promote active oxygen production at sites of very active catecholamine metabolism, such as the substantia nigra, and cause cytotoxicity.

Parkinson’s disease and parkinsonism due to manganese exposure clearly differ both in terms of their clinical manifestations and pathological findings, but it has also been shown that environmental factors may be involved in the development of Parkinson’s disease. Air pollution by manganese as a result of the use of methylcyclopentadienyl manganese tricarbonyl (MMT) as an anti-knock compound has recently been demonstrated, and accumulation in the corpus striatum, cerebral cortex, and cerebellum and the development of extrapyramidal manifestations have been shown to occur as a result of administration of MnO2 and MnCl2 via the airway in animal experiments. There has been apprehension about low-concentration manganese content in the air as an environmental factor.8,9)

Aluminum and Neurotoxicity

In 1972 Alfrey et al. noted the onset of articulation disorders, aphasia, convulsions, myoclonus, and dementia symptoms in long-term dialysis patients, and they found high aluminum concentrations in the patients’ brains. Residual aluminum from the hemodialysis process was considered to be the cause, and as a result of removing the aluminum in the dialysis fluid and discontinuing oral administration of aluminum preparations, no new cases have been seen. Although rare, a tendency to have lower scores in neurologic development examinations using the Bayley Mental Development Index has been reported for premature infants and children who have received aluminum-contaminating high-calorie infusion therapy,10) and aluminum has been shown to be replaced by amino acids and to leak out in solutions stored in glassware.

Aluminum encephalopathy has been reported after oral administration of aluminum preparations to chronic renal failure patients. The serum aluminum concentration has been shown to increase to twice the normal upper limit as a result of intravenous alimentation even when
renal function is normal,\textsuperscript{11)} and there have also been reports of the occurrence of language disorders, consciousness disorders, or dementia after long-term occupational exposure, such as among workers in an aluminum refinery, an aluminum pot factory, etc. Similar manifestations have been observed as a result of ear-nose-throat (ENT) surgery in which aluminum-containing bone cement (Ionocap\textsuperscript{®}, Ionocem\textsuperscript{®}, Ionos GmbH & Co. KG, Seefeld, Germany) was used. This is thought to represent aluminum poisoning as a result of aluminum coming into direct contact with cerebrospinal fluid and eluted because aluminum-containing cement had been used at bone defect sites or because of accidental entry into the spinal fluid compartment after local CNS fistula formation or surgery.\textsuperscript{12)}

**Conclusion**

Associations between aluminum, iron, and manganese have been primarily outlined, where deficiencies and excesses are thought to cause irreversible changes in the nervous system as well as neurodegenerative diseases, notably Alzheimer’s disease, amyotrophic lateral sclerosis, and parkinsonism. These neurodegenerative diseases are suspected of having a multifactorial etiology and of being caused by environmental factors in addition to genetic factors. Although these trace element abnormalities are not thought to exert pathogenetic effects, the evidence suggests that they are involved as risk factors.

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