Iodine Deficiency Disorder and Clinical Practice

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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...
normally excreted in the urine is 100–200μg/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 Pendrin, an 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 66104. 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-monoiiodotyrosine 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.
IODINE DEFICIENCY DISORDERS

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.

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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 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 90 \( \mu \text{g} \) for preschool children, 120 \( \mu \text{g} \) for schoolchildren, 150 \( \mu \text{g} \) for adults, and 200 \( \mu \text{g} \) 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**


