Severe iodine deficiency causes hypothyroidism that results in impaired somatic growth and motor development in children. Mild and moderate iodine deficiencies cause multifocal autonomous growth of thyroid, which results in thyrotoxicosis. On the other hand, iodine excess is associated with the development of hypothyroidism and thyroid autoimmunity. In areas of iodine deficiency, a sudden increase in iodine intake is associated with transient hyperthyroidism. Recent studies demonstrated that long-term thyroid function of subjects who experienced both iodine deficiency and iodine excess during childhood tended to be abnormal despite optimization of their current iodine intake. Iodine status in the Korean Peninsula is very unique because people in the Republic of Korea have been shown to have predominantly excessive iodine levels, whereas the Democratic People's Republic of Korea is known to be an iodine-deficient area. Further research is warranted to verify the optimal ranges of iodine intake and to clarify the effects of iodine intake on thyroid disorders in the Korean Peninsula.

Keywords: Thyroid, Iodine, Hypothyroidism

Introduction

Thyroid function is crucial to the metabolism of almost all tissues and is critical for the development of the central nervous system in the fetus and children. The effects of the thyroid come from two iodine containing-hormones, triiodothyronine (T3) and thyroxine (T4). Iodine (atomic number, 53; standard atomic mass, 126.9) is a rate-limiting element for the synthesis of thyroid hormones. At present, the only physiological role known for iodine in the human body is in the synthesis of thyroid hormones by the thyroid gland.

The relationship between iodine deficiency and thyroid disease was known since early in the twentieth century. Iodine deficiency has been regarded as one of the most important preventable causes of brain damage worldwide. In 2013, 30 countries remain iodine-deficient; 9 are moderately deficient, and 21 are mildly deficient by defined median urinary iodine (UI) in school-aged children. While the prevalence of severe iodine deficiency was reduced recently, the problems of iodine deficiency remerged in vulnerable populations, such as pregnant women and infants. Furthermore, some food or medications have very high iodine contents, which can result in thyroid dysfunction in some susceptible individuals.

The Republic of Korea (South Korea) is regarded as an iodine-sufficient area, while the Democratic People's Republic of Korea (DPRK) is known to be an iodine-deficient area, although there has been no nation-wide evaluation of iodine levels.

This paper reviews the physiologic role of iodine, methods to assess iodine nutrition, clinical implications of iodine deficiency or excess, and iodine-related thyroid problems in the Korean Peninsula.

Role of iodine in thyroid physiology

Iodine is a trace element in soil and water that is ingested in several chemical forms. Most...
forms of iodine are reduced to iodide in the gut. Iodide is nearly completely absorbed in the stomach and duodenum. Iodine is cleared from the circulation primarily by the thyroid and kidney. Under normal circumstances, plasma iodine has a half-life of approximately 10 hours, but this is shortened if the thyroid is overactive, as in iodine deficiency or hyperthyroidism. The mean daily turnover of iodine by the thyroid is approximately 60–95 μg in adults in iodine-sufficient areas. The body of a healthy adult contains from 15 to 20 mg of iodine, 70%–80% of which is in the thyroid. In the basolateral membrane of the thyroid cell, the sodium/iodine symporter (NIS) transfers iodide into the thyroid across a concentration gradient 20–50 times that of plasma by active transport.

Degradation of T4 and T3 in the periphery releases iodine that re-enters the plasma iodine pool. Most ingested iodine is eventually excreted in the urine. Only a small amount appears in the feces.

The mammary gland concentrates iodine and secretes it into breast milk to provide for the newborn. The salivary glands, gastric mucosa, and choroid plexus also take up small amounts of iodine. The NIS and pendrin have been reported in trophoblasts, and the placental iodine content is approximately 3% that of the thyroid.

Control of the thyroid by iodine

Iodide is known to control thyroid function. Its main effects are to decrease the response of the thyroid to thyrotropin (TSH); to acutely inhibit its own oxidation; to reduce its trapping after a delay; and, at high concentrations, to inhibit thyroid hormone secretion. Small changes in iodine intake are sufficient to reset the thyroid system at different serum TSH levels. This suggests that modulation of the thyroid response to TSH by iodide plays a major role in the negative feedback loop. In response to increasing doses of iodide, iodine organification increases initially and then decreases. This acute inhibition of organification, termed the Wolff-Chaikoff effect, results from a high concentration of inorganic iodide within thyroid cells. The mechanism responsible for inhibition of organification is unclear, but it may be caused by inhibitory effect of iodide on thyroid peroxidase or some other enzymes. In normal subjects who have been given iodide, the inhibition of organification is transient and this phenomenon is termed escape from the Wolff-Chaikoff effect or adaptation to the Wolff-Chaikoff effect.

In vitro, iodide has been reported to inhibit various metabolic steps in the thyroid cell. Iodide inhibits the cyclic adenosine monophosphate cascade and the Ca-phosphatidylinositol 4, 5-bisphosphate (PIP2) cascade. Iodide also activates H2O2 generation and thus protein iodination in the thyroid of some species, including humans. The down-regulation of NIS by iodide explains the adaptation to the Wolff-Chaikoff effect.

Assessment of iodine nutrition and measurement of iodine content

Most methods of measuring iodine sufficiency have focused on field studies of iodine deficiency, because elimination of iodine deficiency disorders (IDD) has been an integral component of many national nutrition strategies since 1990. Assessment of the size of the thyroid is the historical method to evaluate iodine nutrition because iodine deficiency is associated with an increased goiter rate. In areas of moderate to severe iodine deficiency, iodine status has been assessed by goiter palpation. In contrast, in areas of mild iodine deficiency, where goiters are smaller, palpation of goiters has poor sensitivity and specificity, so measurement of thyroid volume by ultrasound is preferable. In 1992, the World Health Organization (WHO), together with the United Nations International Children’s Emergency Fund (UNICEF) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD), simplified the previous goiter classification; grade 0 was defined as a thyroid that is not palpable or visible; grade 1 was defined as an enlarged gland that is palpable but not visible when the neck is in the normal position; and the previous stages 2 and 3 were combined into a single new grade 2, defined as a thyroid that is clearly visible when the neck is in the normal position.

Because 90% of ingested iodine is excreted through kidney within 24–48 hours, the median of spot UI concentrations is used as a biomarker for recent dietary iodine intake. Because it is impractical to collect 24-hour urine samples in field studies, UI concentrations (μg/L) are usually measured in spot urine collections. If a large number of samples are collected, variations in hydration among individuals and day-to-day variations in iodine intake generally balance each other, so that the median UI concentration of spot urine samples correlates well with the median from 24-hour samples and with the estimated UI excretion (μg/day) from creatinine corrected UI concentrations. However, UI concentration of spot urine should not be applied to individuals because of the significant day-to-day variation in iodine intake. Because of this variation, 10 repeat spot urine collections are needed to estimate an individual’s iodine intake with acceptable precision. Iodine nutrition can be assessed by dietary sources of iodine. Saltwater fish and seafood, and especially some types of seaweeds have high natural iodine content. Milk and dairy products are important iodine sources for children. Drinking water drawn from certain aquifers or water disinfected with iodine can also be rich in iodine. The large day-to-day variations make it difficult to quantify the usual iodine intake, and dietary assessment of iodine intake is not practical to determine.

In iodine sufficiency, small amounts of thyroglobulin (Tg) are secreted into the circulation, and serum Tg is normally < 10 mg/L. In areas of iodine deficiency, serum Tg increases due to greater thyroid cell mass and TSH stimulation. Serum Tg is well correlated with the severity of iodine deficiency. A new assay for Tg was developed that uses dried blood spots, thereby
simplifying collection and transport\(^{27}\).

There are several methods to measure iodine content in urine or food, as follows: colorimetry using a spectrophotometric procedure\(^{28}\), the iodine specific electrode\(^{29}\), neutron activation analysis\(^{30}\), and mass-spectrometry\(^{31}\). The most commonly used method is the sensitive spectrophotometric procedure based on the Sandell-Kolthoff reaction, in which iodide acts as a catalyst in the reduction of ceric ammonium sulfate (yellow color) to the cerous form (colorless) in the presence of arsenious acid\(^{26}\). A digestion or other purification step using ammonium persulfate (for urine) or chloric acid (for urine and food) is necessary before carrying out this reaction, to rid the urine of interfering contaminants\(^{32}\).

**Iodine deficiency disorders**

IDDs are defined as all the consequences of iodine deficiency in a population that can be prevented by ensuring that the population has an adequate intake of iodine.

Insufficient iodine during pregnancy and infancy results in neurological and psychological deficits in children. The intelligence quotient (IQ) of children living in severely iodine-deficient areas is, on average, 12 points lower than that of those living in iodine-sufficient areas\(^31\). Iodine deficiency remains the leading cause of preventable mental retardation worldwide\(^31\). In adults, mild-to-moderate iodine deficiency increases the incidence of hyperthyroidism due to toxic goiter\(^30\).

The iodine status of most premature infants worldwide is that of iodine deficiency\(^30\), whereas in South Korea a substantial proportion of premature infants have iodine excess\(^31\). In a longitudinal study, persistent decreases in TSH and increases in free T4 were observed in a previously iodine insufficient population, even though the present iodine status was adequate, suggesting that low iodine intake at young age leads to thyroid autonomy that persists despite normal iodine intake later in life\(^30\).

**Effect of excessive iodine on the thyroid**

Excessive iodine intake can alter thyroid function, although most individuals tolerate high dietary intakes of iodine remarkably well.

Following exposure to high iodine levels, the synthesis of thyroid hormone is normally inhibited by the acute Wolff-Chaikoff effect\(^{13-15}\). Administration of supplemental iodine to subjects with endemic iodine deficiency goiter can result in thyrotoxicosis. This response, termed iodide-induced hyperthyroidism or the Iod-Basedow effect (Iod is derived from the German word for "iodine"), occurs in only a small fraction of individuals at risk\(^35\). Patients with underlying, perhaps mild, autoimmune thyroid disease, such as Hashimoto's thyroiditis, are particularly susceptible to developing iodine-induced hypothyroidism during several weeks after the exposure\(^39\). The Wolff-Chaikoff effect dose not mature until 36–40 weeks' gestation; therefore, preterm infants are vulnerable to the effects of iodine overload\(^{39,41}\).

High iodine intake is associated with autoimmune thyroid disease\(^34\). A sudden increase in iodine intake in an iodine-deficient population may induce thyroid autoimmunity\(^{42}\). People with antithyroid antibodies have a higher risk of developing thyroid dysfunction when the iodine intake is high\(^43\). The overall incidence of thyroid carcinoma in populations does not appear to be influenced by iodine intake\(^{40}\). Excessive iodine intake in children in high iodine areas is associated with impaired thyroid function\(^45\).

**Iodine related health problem in Korean peninsula**

Although no nation-wide survey has estimated the iodine status in South Korea, several studies of iodine status in South Korean have revealed that the iodine nutritional state of South Koreans is more than adequate. In a cross-sectional study of 611 healthy South Korean preschool children, approximately two-thirds of subjects were found to have excessive iodine intake, and 3.9% of these children had insufficient iodine intake\(^{46}\). A study performed in 540 healthy adults showed that the median UI levels in a Korean urban population were more than adequate\(^7\). However, adverse effects of excess iodine were not apparent. In a study of 337 healthy South Korean adults, UI excretion had a weakly negative correlation with free T4 and showed a positive trend with TSH, whereas their levels of free T4 and TSH were within the normal ranges\(^{48}\). Iodine excess did not directly influence the risk of goiter in 69 Korean prepubertal children\(^{49}\).

Koreans consume excess iodine from seaweed, and iodine intake is strongly influenced by seaweed consumption. However, dose-response data derived from subjects who consume excess iodine frequently, but not continuously, during their lifetime are not available\(^{20}\). Further population-based studies are warranted to clarify the implications of iodine excess in South Korea.

In contrast, North Korea is geologically prone to iodine deficiency owing to its predominantly mountainous terrain. A national IDD survey was conducted from November 2009 to March 2010 by the ICCIDD in 6- to 12-year-old North Korean children throughout the country. The total goiter rate was 19.5%, 2.2% of which were visible goiters. The overall median UI concentration was 97 μg/L and the proportion with UI concentration below 100 μg/L was 51%. In the DPRK, a salt iodization program has been supported by UNICEF for more than 10 years; however, the amount of iodized salt remains limited because of issues related to the purchase of potassium iodate and the production capacity of the salt factories\(^{51}\). Health problems associated with iodine deficiency in North Korea might be public health concerns after unification of Korea.

**Conclusions**

Both iodine deficiency and iodine excess are associated
with an increased risk of thyroid disorders. Further research is warranted to verify the optimal ranges of iodine intake and to clarify the effects of iodine intake on thyroid disorders, considering the unique and divergent patterns of iodine status in the Korean Peninsula.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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