IODINE AND IODINE DEFICIENCY DISORDERS

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Summary

Iodine is an essential component of hormones produced by the thyroid gland. Thyroid hormones, and therefore iodine, are essential for mammalian life. Optimal dietary iodine intakes for healthy adults are 150–250 μg/day. In regions where iodine in soils and drinking water is low, humans and animals may become iodine deficient. Iodine deficiency has multiple adverse effects in humans due to inadequate thyroid hormone production that are termed the iodine deficiency disorders. Assessment methods for iodine deficiency include urinary iodine concentration, goiter, newborn thyroid-stimulating hormone, and blood thyroglobulin. Globally, it is estimated that 2 billion individuals have an insufficient iodine intake, many in developing countries. However, iodine deficiency also affects industrialized countries—50% of continental Europe remains mildly iodine deficient, and iodine intakes in other industrialized countries, including the United States, the United Kingdom, and Australia, have fallen sharply in recent years. Iodine deficiency during pregnancy and infancy may impair growth and neurodevelopment of the offspring and increase infant mortality. Deficiency during childhood reduces somatic growth and cognitive and motor function. In most countries, the best strategy to control iodine deficiency in populations is carefully monitored iodization of salt, one of the most cost-effective ways to contribute to economic and social development.

Introduction

In 1811, Courtois discovered iodine as a violet vapor arising from seaweed ash while manufacturing gunpowder for Napoleon's army. Gay-Lussac identified it as a new element, and named it iodine (atomic weight 126.9 g/atom), from the Greek word meaning "violet" (Zimmermann, 2008b). The Swiss physician Coindet, in 1813, hypothesized that the traditional treatment of goiter with seaweed was effective because of its iodine content and successfully treated goiterous patients with iodine. In 1851, the French chemist Chatin published the hypothesis that iodine deficiency was the cause of goiter, and, in 1896, Baumann and Roos discovered iodine in the thyroid

(Zimmermann, 2008b). In the first two decades of the twentieth century, pioneering studies by Swiss and American physicians demonstrated the efficacy of iodine prophylaxis in the prevention of goiter and cretinism. Today, control of the iodine deficiency disorders is an integral part of most national nutrition strategies.

I am satisfied. I have seen the principal features of Swiss scenery – Mount Blanc and the goiter – and now for home. Mark Twain, 1880

Ecology and Dietary Sources

Iodine (as iodide) is widely but unevenly distributed in the Earth’s environment. In many regions, leaching from glacial, flooding, and erosion have depleted surface soils of iodide, and most iodide is found in the oceans. The concentration of iodide in seawater is ~50 μg/L. Iodide ions in seawater are oxidized to elemental iodine, which volatilizes into the atmosphere and is returned to the soil by rain, completing the cycle (Kipper et al., 2011). However, iodine cycling in many regions is slow and incomplete, leaving soils and drinking-water iodine depleted. Crops grown in these soils will be low in iodine, and humans and animals consuming food grown in these soils become iodine deficient. In plant foods grown in deficient soils, iodine concentration may be as low as 10 μg/kg dry weight, compared with ~1 mg/kg dry weight in plants from iodine-sufficient soils.

Iodine-deficient soils are common in mountainous areas (e.g., the Alps, Andes, Atlas, and Himalaya ranges) and areas of frequent flooding, especially in South and Southeast Asia (for example, the Ganges River plains of north-eastern India). Many inland areas, including central Asia and Africa, the Midwestern Region of North America, and central and eastern Europe, are iodine deficient. Iodine deficiency in populations residing in these areas will persist until iodine enters the food chain through addition of iodine to foods (e.g., by iodization of salt) or through dietary diversification via introduction of foods produced outside the iodine-deficient area.

The native iodine content of most foods and beverages is low. In general, commonly consumed foods provide 3–80 μg per serving (Pearce et al., 2004; Haldemann et al., 2005). Foods of marine origin have higher iodine content because marine plants and animals concentrate iodine from seawater. Iodine in organic form occurs at high levels in certain seaweeds. Inhabitants of the coastal regions of Japan, whose diets contain large amounts of seaweed, have remarkably high iodine intakes amounting to 50–80 mg/day. In the United States the median intake of iodine from food in the mid-1990s was estimated to be 240–300 μg/day for men and 190–210 μg/day for women (Institute of Medicine, 2001). Major dietary sources of iodine in the United States are bread and milk (Pearce et al., 2004). In Switzerland, based on direct food analysis, mean intake of dietary iodine is ~140 μg/day, mainly from bread and dairy products (Haldemann et al., 2005). In many countries, use of iodized salt in households for cooking and at the table provides additional iodine. Boiling, baking, and canning of foods containing iodized salt cause only small losses (<10% of iodine content (Chavasiti et al., 2002).

Iodine content in foods is also influenced by iodine-containing compounds used in irrigation, fertilizers, and livestock feed. Iodophors used for cleaning milking machines and transport containers can increase the native iodine content of dairy products. Traditionally, iodate was used in bread making as a dough conditioner, but it is being replaced by non-iodine-containing conditioners. Erythrosine is a red coloring agent high in iodine that is widely used in foods, cosmetics, and pharmaceuticals. Dietary supplements often contain iodine. Based on data from the Third National Health and Nutrition Examination Survey (NHANES III), 12% of men and 15% of non-pregnant women took a dietary supplement that contained iodine, and the median intake of iodine from supplements was ~140 μg/day for adults (Institute of Medicine, 2001). Other sources of iodine include water purification tablets, radiographic contrast media, medicines (e.g., amiodarone, an antiarrhythmic drug, contains 75 mg/tablet), and skin disinfectants (e.g., povidone-iodine contains ~10 mg/mL).

Absorption, Metabolism, and Excretion

Iodine is ingested in several chemical forms. Iodide is rapidly and nearly completely absorbed in the stomach and duodenum. The sodium/iodide symporter (NIS), a transmembrane protein on the apical surface of enterocytes, mediates active iodine absorption (Nicola et al., 2009). Iodate, widely used in salt iodization, is reduced in the gut and absorbed as iodide. In healthy adults, the absorption of iodide is ~90% (Institute of Medicine, 2001). Organically bound iodide is typically digested and the released iodide absorbed, but some forms may be absorbed intact. For example, >75% of an oral dose of thyroxine, the thyroid hormone, is absorbed intact.
Iodine deficiency is the main cause of endemic goiter (see later in this chapter), but other dietary substances that interfere with thyroid metabolism can aggravate the effect and they are termed goitrogenes (Gaithan, 1990). A well-known example is linamarin, a thioglycoside found in cassava, which is a staple food in many developing countries. If cassava is not adequately soaked or cooked to remove the linamarin, it is hydrolyzed in the gut to release cyanide, which is metabolized to thiocyanate. Thiocyanate blocks thyroid uptake of iodine. Other goitrogenic substances are found in millet, sweet potato, beans, and cruciferous vegetables (e.g. cabbage). Unclean drinking water may contain humic substances that block thyroid iodination. Industrial pollutants, including resorcinol, perchlorate, and phthalic acid, may also be goitrogenic. Most of these substances do not have a major clinical effect unless there is coexisting iodine deficiency.

Deficiencies of selenium, iron, and vitamin A exacerbate the effects of iodine deficiency. Glutathione peroxidase and the deiodinases are selenium-dependent enzymes. In selenium deficiency, accumulated peroxides may damage the thyroid, and deiodinase deficiency impairs thyroid hormone synthesis (Zimmermann and Kohle, 2002). These effects have been implicated in the etiology of myxedematous cretinism (see next section). Iron deficiency reduces heme-dependent thyroxine oxidase activity in the thyroid and impairs production of thyroid hormone. In goitrous children, iron deficiency anemia blunts the efficacy of iodine prophylaxis while iron supplementation improves the iodine uptake of thyroid and circulating iodized salt (Zimmermann, 2006). Vitamin A deficiency in iodine-deficient children increases TSH stimulation and risk for goiter, probably through decreased vitamin A-mediated suppression of the pituitary TSHβ gene (Zimmermann et al., 2007).

The distribution space of absorbed iodine in the body is nearly equal to the extracellular fluid volume. Iodine is cleared from the circulation mainly by the thyroid and kidney (Figure 36.1), and whereas renal iodine clearance is fairly constant, thyroid clearance varies with iodine intake. In conditions of adequate iodine supply, ≥10% of absorbed iodine is taken up by the thyroid. In chronic iodine deficiency, this fraction can exceed 80%. During lactation, the mammary gland concentrates iodine and secretes it into breast milk to provide for the newborn. Iodine in the blood is turned over rapidly; under normal circumstances, plasma iodine has a half-life of ~10 hours, but this is shortened if the thyroid is overactive as in iodine deficiency or hyperthyroidism.

The body of a healthy adult contains up to 20 mg of iodine, of which 70–80% is in the thyroid. In chronic iodine deficiency, the iodine content of the thyroid may fall to <1 mg. In iodine-sufficient areas, the adult thyroid traps 60–80 μg of iodine per day to balance losses and maintain thyroid hormone synthesis. An NIS in the basolateral membrane transfers iodide into the thyroid at a concentration gradient 20 to 50 times that of plasma (Eskandari et al., 1997). The NIS concentrates iodine by an active transport process that couples the energy released by the inward translocation of sodium down its electrochemical gradient to the simultaneous inward translocation of iodide against its electrochemical gradient. Thyroglobulin (Tg), a large glycoprotein (molecular weight 660 000), is the carrier of iodine in the thyroid. At the apical surface of the thyrocyte, the enzymes thyroperoxidase (TPO) and hydrogen peroxide oxidize iodide and attach it to tyrosyl residues on Tg, to produce monoiodotyrosine (MIT) and diiodotyrosine (DIT), the precursors of thyroid hormone (Figure 36.2). TPO then catalyzes the coupling of the phenyl groups of the iodotyrosines through a di-ether bridge to form the thyroid hormones. Linkage of two DIT molecules produces tetraiodothyronine or thyroxine (T4), and linkage of an MIT and a DIT produces triiodothyronine (T3). Thus, T3 is structurally identical to T4 but has one less iodine (at the 5' position on the outer ring) (Figure 36.3). Iodine comprises 65% and 59% of the weights of T4 and T3, respectively. In the thyroid, mature Tg, containing 0.1 to 1.0% of its weight as iodine, is stored extracellularly in the luminal colloid of the thyroid follicle. After endocytosis, endosomal and lysosomal processes digest Tg and release T4 and T3 into the circulation. MIT and DIT are not normally released into the blood. Iodine is removed from their thyroxines by a selenium-dependent deiodinase and is then recycled for use within the thyroid, conserving iodine (Kohle and Gartner, 2009).

In the circulation, thyroid hormone is bound non-covalently to carrier proteins, mainly thyroxine-binding globulin, but also to transthyretin and albumin. In target tissues – liver, kidney, heart, muscle, pituitary, and the developing brain – T4 is deiodinated to T3. T3 is the main physiologically active form of thyroid hormone and binds to nuclear receptors. The thyroid hormone receptors have been cloned and regulatory DNA elements identified in thyroid hormone responsive genes (Ten.

FIG. 36.1 Over 90% of dietary iodide is absorbed in the duodenum. Iodine (as iodide) is cleared from the circulation mainly by the thyroid and kidney. Thyroid clearance varies with iodine intake. Above: in iodine-sufficient individuals with adequate thyroid iodide stores, about 35% of circulating iodide is taken up by the thyroid to balance losses and maintain thyroid hormone synthesis. Below: in chronic iodine deficiency, the fraction of circulating iodide cleared by the thyroid increases to about 65% but the iodine content of the thyroid is depleted and hypothyroidism develops.
Iodine pathway in the thyroid cell. Iodide (I) is transported into the thyrocyte by the sodium iodide symporter (NIS) at the basal membrane and migrates to the apical membrane. The I is oxidized by the enzymes thyroxine peroxidase (TPO) and hydrogen peroxidase (H₂O₂), and attached to tyrosyl residues in thyroglobulin (Tg) to produce the hormone precursors iodothyronines (MIT and DIT) and diiodothyrosine (DTT). The residues then couple to form thyroxine (T₄) and triiodothyronine (T₃) within the Tg molecule in the follicular lumen. Tg enters the cell by endocytosis and is digested. T₄ and T₃ are released into the circulation, and non-hormonal iodine on MIT and DIT is recycled within the thyrocyte.

2001). Hormone-receptor interactions stimulate several pathways, including the adenylate cyclase (ATP) and inositol phosphate-Ca²⁺ cascades, which in turn stimulate or inhibit protein synthesis.

Both T₄ and T₃ are degraded through a complex series of pathways, and their turnover is relatively slow: the half-lives of T₄ and T₃ are about 5 days and 1–3.5 days (Hypothenimer et al., 1975). The released iodine enters the plasma iodine pool and can be taken up again by the thyroid or excreted by the kidney. However, more than 90% of ingested iodine is ultimately excreted in the urine, with only a small amount appearing in the feces.

The principal regulator of thyroid hormone metabolism is thyroid-stimulating hormone (TSH), a protein hormone (molecular weight ~ 28,000) secreted by the pituitary. TSH secretion is controlled through negative feedback by the level of circulating thyroid hormone, modulated by TSH-releasing hormone from the hypothalamus. In the thyroid, TSH increases iodine uptake through stimulation of NIS expression. TSH exerts its action at the transcription level of the NIS gene through a thyroid-specific enhancer that contains binding sites for the transcription factors Pax8 and a CAMP response element-like sequence (Takai et al., 2002). TSH also stimulates breakdown of Tg and release of thyroid hormone into the blood. Because the primary stimulus to TSH secretion is circulating thyroid hormone, an elevated serum TSH concentration generally indicates primary hyperthyroidism, while a low concentration indicates primary hypothyroidism.

Physiologic Function and Deficiency Disorders

Thyroid hormone regulates a variety of physiologic processes, including reproductive function, growth, and development. During pregnancy, thyroid hormone crosses the placenta to the fetus early in the first trimester, before the fetal thyroid is functioning. In the developing brain, it influences cell growth and migration (Morreale de Escobar et al., 2004a). It also promotes growth and maturation of peripheral tissues and the skeleton. Thyroid hormone increases energy metabolism in most tissues, and raises the basal metabolic rate.

Iodine deficiency has multiple adverse effects on growth and development in animals and humans. These are collectively termed the iodine deficiency disorders (IDD) (Table 36.1), and are one of the most important and common human diseases (WHO, 2007). They result from inadequate thyroid hormone production due to lack of sufficient iodine.

Thyroid enlargement (goiter) is the classic sign of iodine deficiency (Figure 36.4A). It is a physiologic adaptation to chronic iodine deficiency. As iodine intake falls, secretion of TSH increases in an effort to maximize uptake of available iodine, and TSH stimulates thyroid hyperplasia and hyperplasia. Initially, goiters are characterized by diffuse, homogeneous enlargement, but over time thyroid follicles may fuse and become encapsulated, a condition termed nodular goiter. Large goiters may be cosmetically unattractive, can obstruct the trachea and esophagus, and may damage the recurrent laryngeal nerves and cause hoarseness.

Although goiter is the most visible effect of iodine deficiency, the most serious adverse effect is damage to the developing brain. Severe iodine deficiency during pregnancy is associated with a greater incidence of stillbirths, abortions, and congenital abnormalities. Iodine prophylaxis with iodized oil in pregnant women in areas of severe iodine deficiency reduces fetal and neonatal mortality (Zimmermann et al., 2009). The fetal brain is particularly vulnerable to iodine deficiency. Normal levels of thyroid hormones are required for neuronal migration and myelination of the central nervous system (Azzou et al., 2004). The most severe form of neurological damage from fetal hyperthyroidism is termed cretinism. It is characterized by gross mental retardation along with varying degrees of short stature, deaf mutism, and spasticity (Zimmermann et al., 2009) (Figure 36.4B). Up to 10% of populations with severe iodine deficiency may be cretinous. Iodine prophylaxis has completely eliminated the appearance of new cases of cretinism in previously severely iodine-deficient Alpine regions in Switzerland, Austria, and Italy.
Although new cases of cretinism are now rare, iodine deficiency still affects approximately one-third of the global population (see later) and can impair cognitive development. A meta-analysis concluded that moderate-to-severe iodine deficiency (severity of iodine deficiency was defined by the cut-off values for median urinary iodine concentrations shown in Table 36.4) reduces mean IQ scores by 13.5 points (Bleichrodt et al., 1996). Iodine deficiency is one of the most common causes of preventable mental impairment worldwide. Even in areas of mild to moderate iodine deficiency, cognitive impairment in school-age children is at least partly reversible by administration of iodine (Zimmermann et al., 2006a; Gordon et al., 2009).

Only a few countries — Switzerland, the Scandinavian countries, Australia, United States, and Canada — were completely iodine sufficient before 1990. Since then, widespread introduction of iodized salt has produced dramatic reductions in iodine deficiency. The World Health Organization recently estimated the worldwide prevalence of iodine deficiency, defined as a UI <100 mg/L, at just over 2 billion individuals who have inadequate iodine nutrition, of whom 266 million are school-age children (Table 36.2). The prevalence of iodine deficiency in school-age children is 31.5% (de Benoist et al., 2008). In Australia, the United Kingdom, and the United States, three countries previously iodine sufficient, iodine intakes are falling. Australia and the United Kingdom are now mildly iodine deficient, and in the United States the median UI in women is 130 mg/L, still adequate but less than the median value of 321 mg/L found in the 1970s (Perrine et al., 2010).

**TABLE 36.2 Prevalence of iodine deficiency in general population (all age groups) and in school-age children (6–12 years), by WHO region, in 2007**

<table>
<thead>
<tr>
<th>WHO region</th>
<th>General population</th>
<th>School-age children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>312.9 (41.5%)</td>
<td>57.7 (40.8%)</td>
</tr>
<tr>
<td>Americas</td>
<td>98.6 (11.0%)</td>
<td>11.6 (10.6%)</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>259.3 (47.2%)</td>
<td>43.3 (48.8%)</td>
</tr>
<tr>
<td>Europe</td>
<td>459.7 (52.0%)</td>
<td>38.7 (52.4%)</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>503.8 (40.0%)</td>
<td>73.1 (30.3%)</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>374.7 (21.2%)</td>
<td>41.6 (27.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>2008.8 (30.0%)</td>
<td>266.0 (31.5%)</td>
</tr>
</tbody>
</table>

*193 WHO Member States.  
*Based on population estimates for 2006 (see also United Nations, 2011). Data from de Benoist et al. (2008).

Dairy products are an important iodine source in US diets, and women who do not consume dairy products may be at risk for iodine deficiency (Perrine et al., 2010). These changes emphasize the importance of regular monitoring of iodine status in countries throughout the world.

**Requirements and Status Assessment**

The US Food and Nutrition Board of the National Academy of Sciences has set an adequate intake (AI) for iodine in infancy and a recommended dietary allowance (RDA) for children, adults, and pregnant and lactating women (Institute of Medicine, 2001) (Table 36.3). The WHO has estimated recommended nutrient intake for iodine (World Health Organization, 2007) (Table 36.3). Iodine requirements for different age and population groups have been established based on studies of radioiodine uptake by the thyroid, balance studies, and factorial estimates (Institute of Medicine, 2001).

Several methods are available for assessment of iodine status. The most commonly used are measurement of thyroid size and concentration of urinary iodine (UI) (World Health Organization, 2007). Additional indicators include newborn thyroid test (TSH), and blood concentrations of thyroglobulin, thyroid hormone (T4), or triiodothyronine (T3). As discussed below, UI is a sensitive indicator of recent iodine intake (days), and serum Tg shows an intermediate response (weeks to months), whereas changes in the goiter rate reflect long-term iodine nutrition (months to years).

Two methods are available for measuring goiter: neck palpation and, and thyroid ultrasonography. Goiter surveys are usually done in school-age children. By palpation, a thyroid is considered goitrous when each lateral lobe has a volume greater than the terminal phalanx of the thumb of the subject being examined. In the classification system of WHO, grade 0 is defined as a thyroid that is not palpable or visible, grade 1 is a goiter that is palpable but not visible when the neck is in the normal position (i.e. the thyroid is not visibly enlarged), and grade 2 is a thyroid that is clearly visible when the neck is in a normal position.

In areas of mild to moderate iodine deficiency, where goiters are small, measurement of thyroid size by ultrasonography is a more objective and precise method and is preferable to palpation. Portable ultrasound equipment can be used in the field, and goiter classified according to international reference criteria for iodine-deficient children by age, gender, and body surface area (Zimmermann et al., 2004a). The total goiter rate is used to define severity using the following criteria: <5%, iodine sufficient; 5.0–19.9%, mild deficiency; 20.0–29.9%, moderate deficiency; and >30%, severe deficiency (World Health Organization, 2007).

In areas of endemic goiter, although thyroid size predictably decreases in response to increases in iodine intake, thyroid size may not return to normal for months or years after correction of iodine deficiency (Zimmermann et al., 2003a). During this transition period, the goiter rate is difficult to interpret because it reflects both a population’s history of iodine nutrition and its present status. Despite this long period, a sustained salt iodization program will decrease the goiter rate to <5% in school-age children, and this indicates disappearance of iodine deficiency as a significant public health problem (World Health Organization, 2007).

**TABLE 36.3 Recommendations for iodine intake (ug/day) by age or population group**

<table>
<thead>
<tr>
<th>Age or population group</th>
<th>US Institute of Medicine*</th>
<th>Age or population group</th>
<th>World Health Organization*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAR</td>
<td>110–130</td>
<td>Children 0–5 years</td>
<td>90</td>
</tr>
<tr>
<td>AI or RDA</td>
<td></td>
<td>Children 6–12 years</td>
<td>120</td>
</tr>
<tr>
<td>Infants 0–12 months</td>
<td>65</td>
<td>Children 6–12 years</td>
<td>120</td>
</tr>
<tr>
<td>Children 1–8 years</td>
<td>73</td>
<td>Adults &gt;12 years</td>
<td>150</td>
</tr>
<tr>
<td>Children 9–13 years</td>
<td>95</td>
<td>Adults &gt;12 years</td>
<td>250</td>
</tr>
<tr>
<td>Adults 14 years</td>
<td>160</td>
<td>Pregnancy</td>
<td>250</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>200</td>
<td>Lactation</td>
<td>250</td>
</tr>
</tbody>
</table>

*AI, adequate intake; EAR, estimated average requirement; RDA, recommended daily allowance; RNI, recommended nutrient intake.

*Data from Institute of Medicine (2001).

*Data from World Health Organization (2007).
Because >90% of ingested iodine is excreted in the urine, UI is an excellent indicator of recent iodine intake. Most methods of measuring UI are based on the Sandell-Kolthoff reaction, in which iodine catalyzes the reduction of yellow ceric ammonium sulfite to the colorless cerous form in the presence of arsenious acid (Bier et al., 1998). UI can be expressed as a concentration (µg/L), in relation to creatinine excretion (µg iodine/g creatinine), or as 24-hour excretion (µg/day). To estimate iodine intakes in individuals, 24-hour collections may be preferable. For populations, it is impractical to collect 24-hour samples in field studies. UI can be measured in spot urine specimens from a representative sample of the target group, and expressed as the median, in µg/L (World Health Organization, 2007) (Table 36.4). Variations in hydration and individual excretion may occur in a large number of samples, so that the median UI in spot samples correlates well with that from 24-hour samples. Creatinine may be unreliable for estimating daily iodine excretion from spot samples, especially in malnourished subjects where creatinine concentration is low. Spot UI measurements in population studies are often misinterpreted. Although the median UI is a population indicator, it is a common mistake to assume that all subjects with a spot UI <100µg/L are iodine deficient, but, even in iodine-sufficient regions where intrathyroidal iodine stores are adequate, individual spot UI concentrations are highly variable from day to day.

Daily iodine intake for population estimates can be extrapolated from UI, using estimates of mean 24-hour urine volume and assuming an average iodine bioavailability of 92%. This can be done using the following formula (Institute of Medicine, 2001):

\[
\text{Urinary iodine (µg/L) × 0.0235 × body weight (kg) = daily iodine intake}
\]

**TABLE 36.4 Epidemiological criteria from the World Health Organization for assessment of iodine nutrition in a population based on median or range of urinary iodine concentrations**

<table>
<thead>
<tr>
<th>Population group</th>
<th>Iodine intake</th>
<th>Iodine nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>School-age children</td>
<td>&lt;20µg/L</td>
<td>Insufficient</td>
</tr>
<tr>
<td>20-49µg/L</td>
<td>Insufficient</td>
<td>Moderate iodine deficiency</td>
</tr>
<tr>
<td>50-99µg/L</td>
<td>Insufficient</td>
<td>Mild iodine deficiency</td>
</tr>
<tr>
<td>100-199µg/L</td>
<td>Adequate</td>
<td>Optimum</td>
</tr>
<tr>
<td>200–299µg/L</td>
<td>Adequate</td>
<td>Risk of iodine-induced hyperthyroidism in susceptible groups</td>
</tr>
<tr>
<td>&gt;300µg/L</td>
<td>Excessive</td>
<td>Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid disease)</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>&lt;150µg/L</td>
<td>Insufficient</td>
</tr>
<tr>
<td>150–249µg/L</td>
<td>More than adequate</td>
<td></td>
</tr>
<tr>
<td>250–499µg/L</td>
<td>Excessive</td>
<td></td>
</tr>
<tr>
<td>≥500µg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactating women*</td>
<td>&lt;100µg/L</td>
<td>Insufficient</td>
</tr>
<tr>
<td>≥100µg/L</td>
<td>More than adequate</td>
<td></td>
</tr>
<tr>
<td>Children less than 2 years of age</td>
<td>&lt;100µg/L</td>
<td>Insufficient</td>
</tr>
<tr>
<td>≥100µg/L</td>
<td>More than adequate</td>
<td></td>
</tr>
</tbody>
</table>

*The term “excessive” means in excess of the amount needed to prevent and control iodine deficiency. There may be an increased risk of adverse effects at this level of intake.

In lactating women, the numbers for median urinary iodine are lower than the iodine requirements, because of the iodine excreted in breast milk.

Data from World Health Organization (2007).

Using this formula, a UI of 100µg/L in an average adult corresponds roughly to a daily intake of 150µg.

Because serum TSH is determined mainly by the level of circulating thyroid hormone, which in turn reflects iodine intake, TSH can be used as an indicator of iodine nutrition. However, in older children and adults, although serum TSH may be slightly increased by iodine deficiency, values often remain within the normal range. TSH is therefore a relatively insensitive indicator of iodine nutrition in adults. In contrast, TSH is a sensitive indicator of iodine status in the newborn period. Compared with the adult, the newborn thyroid contains less iodine but has higher rates of iodine turnover. Particularly when iodine supply is low, maintaining high iodine turnover requires increased TSH stimulation. Serum TSH concentrations are therefore elevated in iodine-deficient infants for the first few weeks of life, a condition termed transient newborn hyperthyroidism. In areas of iodine deficiency, an increase in transient newborn hyperthyroidism, indicated by >3% of newborn TSH values above the threshold of 5mU/L whole blood, suggests iodine deficiency in the population (Zimmermann et al., 2005a). TSH is used in many countries for routine newborn screening to detect congenital hypothyroidism. If already in place, such screening offers a sensitive indicator of iodine nutrition.

Newborn TSH is an important measure because it reflects iodine status during a period when the developing brain is particularly sensitive to iodine deficiency. Thyroglobulin (Tg), which is synthesized only in the thyroid, and is the most abundant intrathyroidal protein. In iodine deficiency, small amounts of Tg are secreted into the circulation, and serum Tg is normally <10µg/L. In areas of endemic goiter, serum Tg increases due to greater thyroid cell mass and TSH stimulation, and is a sensitive indicator of iodine status (Zimmermann et al., 2003b; Vejhøj et al., 2009). Tg can also be assayed on dried blood spots taken by a finger pricker, simplifying collection and transport (Zimmermann et al., 2006b), and Tg in school-age children is now recommended to assess iodine status in populations (World Health Organization, 2007).

In contrast, thyroid hormone concentrations are poor indicators of iodine status. In iodine-deficient populations, serum T3 increases or remains unchanged, and serum T4 usually decreases. However, these changes are often within the normal range, and the overlap with iodine-sufficient populations is large enough to make thyroid hormone levels an insensitive measure of iodine nutrition.

**Prophylaxis and Treatment**

There are two methods commonly used to correct iodine deficiency in a population: iodized oil and iodized salt. In nearly all regions affected by iodine deficiency, the most effective way to control iodine deficiency is through salt iodization (World Health Organization, 2007). All salt for human consumption, including salt used in the food industry, should be continuously iodized. In Switzerland, previously affected by endemic goiter and cretinism, a monitored national program, in place for over half a century, has effectively eliminated iodine deficiency (Zimmermann et al., 2005a). Iodine can be added to salt in the form of potassium iodide (KI) or potassium iodate (KIO3). Because KIO3 has higher stability in the presence of soil and salt irritants, humidity, and moisture (Diosady and Mannan, 2000), it is the recommended form. Iodine is usually added at a level of 20–40µg iodine/kg salt, depending on local salt intake (World Health Organization, 2007). But in industrialized countries, because 80–90% of salt consumption is from purchased foods (Sanchez-Castillo et al., 1987; Andersen et al., 2009), if only household salt is iodized it will not supply adequate iodine. Thus, although it is critical that the food industry use iodized salt, in many countries it is not added to processed foods. Food producers are often reluctant to add iodized salt because of the widespread misperception that iodine can precipitate adverse sensory changes in their products. However, this does not occur, as the iodine is added in only minute amounts; fortified salt has only parts-per-million concentrations. The current push to reduce salt consumption to prevent chronic diseases and the policy of salt iodization to eliminate iodine deficiency do not conflict: iodization methods can fortify salt to provide recommended iodine intake even if per capita salt intakes are reduced to <5g/day (World Health Organization, 2008).

As a result of a major international effort led by WHO, the United Nations Children's Fund (UNICEF) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDDD), more than 120 countries have implemented salt iodization programs and ~70% of people worldwide have access to iodized salt in 2006, compared with <10% in 1990 (United Nations Children’s Fund, 2008). However, when coverage is not complete, iodized salt use is often lowest in the poorest socioeconomic classes, typically the population most affected by iodine deficiency. For a national program to succeed, >95% of salt for human consumption should be iodized, with 2% to 3% of the population consuming iodized salt to maintain optimal iodine status.
consumption should be iodized according to government standards at the production or importation site. Worldwide, sustainability of iodized salt programs has become a major focus. These programs are fragile, and require a long-term commitment from national governments, donors, consumers, and the salt industry. In several countries where iodine deficiency had been eliminated, salt iodization programs fell apart, and iodine deficiency recurred (Dunn, 2000). Children in iodine-deficient areas are vulnerable to even short-term lapses in iodized salt programs (Zimmermann et al., 2004b).

In some regions, iodization of salt may not be practical for control of iodine deficiency, at least in the short term. This may occur in remote areas where communications are poor or where there are numerous very small-scale salt producers. In these areas, other options for correction of iodine deficiency should be considered, such as iodized oil (World Health Organization, 2007). Iodized oil is prepared by esterification of the unsaturated fatty acids in seed or vegetable oils, and addition of iodine to the double bonds. It can be given orally or by intramuscular injection. The intramuscular route has a longer duration of action (up to 2 years), but oral administration is more convenient because it is simpler. Iodized oil is recommended for populations with moderate to severe iodine deficiencies that do not have access to iodized salt, and may be targeted at women of child-bearing age, pregnant women, and children. The recommended dose is 400 mg iodine per year for women and 200 mg iodine per year for children 7–24 months of age (World Health Organization, 2007). Iodine can also be administered in the form of iodinated milk or as drops or tablets, and in drinking or irrigation water (Squarrito et al., 1986). Iodine supplements (~150 μg/day) are recommended for pregnant and lactating women residing in areas of mild to moderate iodine deficiency. In the United States, because it is uncertain if dietary iodine intakes are adequate in pregnancy, expert groups have recently called for iodine supplementation of this group (Becker et al., 2006). In countries where iodized salt programs supply sufficient iodine to older children and pregnant women, women, children, particularly those not receiving receiving iodine-containing infant formula milk, may be at risk of iodine deficiency (Anderson et al., 2010).

Excess and Toxicity

Acute iodine poisoning caused by ingestion of many grams causes gastrointestinal irritation, abdominal pain, nausea, vomiting, and diarrhea, as well as cardiovascular symptoms, coma, and cyanosis (Pennington, 1990). Most people are remarkably tolerant of high dietary intakes of iodine. The US Food and Nutrition Board of the National Academy of Sciences has set a tolerable upper intake level (UL) for iodine (Institute of Medicine, 2001). The UL is the highest level of daily intake that is likely to pose no risk of adverse health effects in almost all individuals. The UL is 200 μg/day for ages 1–3 years, 300 μg/day for ages 4–8 years, 600 μg/day for ages 9–13 years, 900 μg/day for ages 14–18 years, and 1100 μg/day thereafter. Individuals with autoimmune thyroid disease or chronic iodine deficiency may respond adversely to intakes lower than these (Zimmermann, 2008a).

In iodine-sufficient individuals, the earliest effect of high iodine intakes is typically an increase in serum TSH without a decrease in serum T4 or T3, a condition termed subclinical hypothyroidism. Large excesses of iodine inhibit thyroid hormone production, leading to increased TSH stimulation, thyroid growth, and goiter. A clinical trial in healthy adults found TSH concentrations were increased by oral iodine intakes of 2750 μg/day (Chow et al., 1991). In children, chronic intakes of 2500 μg/day are associated with increased thyroid volume, an early sign of thyroid dysfunction (Zimmermann et al., 2005b). Iodine-induced goiter and hypothyroidism can occur in newborns due to maternal intakes, or through exposure to excess iodine at delivery from the use of antiseptics containing beta-iodine (Nishiyama et al., 2004). Prospective studies in China have suggested chronic excess iodine intake is associated with increased incidence of subclinical hypothyroidism and autoimmune thyroiditis, but not overt hypo- or hyperthyroidism (Teng et al., 2006).

A rapid increase in iodine intake of populations with chronic iodine deficiency may precipitate iodine-induced hyperthyroidism (IHI) (Delange et al., 1999). This is more likely to occur if the iodine is given in excess, e.g. if the iodine content of iodized salt is too high, or when iodine-containing medication is given. IHI occurs mainly in older people with nodular goiter. Thyrotoxins in nodules often become insensitive to TSH control, and, if iodine supply is suddenly increased, these autonomous nodules may overproduce thyroid hormone (Corvilain et al., 1998). Symptoms of IHI include weight loss, tachycardia, muscle weakness, and skin warmth, without the ophthalmopathy of Graves’ disease. IHI is dangerous when superimposed on underlying heart disease, and may be lethal. Introduction of iodine prophylaxis has been associated with increased hospitalizations for IHI in Europe, the United States, and several African countries. The incidence tends to gradually subside, but may rise again when the level of iodine in salt is increased. Its occurrence should not be an argument against salt iodization, as the underlying cause of most autonomous nodules is chronic iodine deficiency. To reduce risk for IHI, the iodine level in salt should be monitored and reduced if too high.

Future Directions

Future research priorities in iodine nutrition should include correlation of community iodine intake with thyroid disease, the role of iodine in fibrocystic breast disease and the immune response, and interactions with other nutrients, particularly vitamin A, iron, and selenium. In the field of IDD, efforts should focus on ensuring adequate iodine during pregnancy and infancy. Monitoring indicators for these key target populations need to be developed and tested. More research on the effects of high intakes of iodine from iodized salt and/or other sources could lead to better estimates of the UL for iodine in different ages and populations. Globally, the elimination of iodine deficiency is within reach, but effort and is needed to cover the remaining populations at risk and to ensure quality control and sustainability of existing iodized salt programs.

Suggestions for Further Reading


References


Iodine and Iodine Deficiency Disorders


