The Yin and Yang of Iodine in Human Physiology

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ABSTRACT

To prevent iodine deficiency disorders (IDDs), the universal salt iodization (USI) program has been initiated in many such regions, including several environmentally iodine-sufficient regions ignoring iodine status; as a consequence, thyroid dysfunctions, namely hyperthyroidism, hypothyroidism, autoimmune thyroid diseases, endemic goiter and even thyroid cancer including infertility, stillbirths, abortions, and embryotoxicity are found common among the excess iodine-induced population. In other words, the consequences of iodine deficiency and excess are almost 'U'- shaped. Chronic intake of low iodine affects the overall physiological functions of humans; however, such effects are also observed when excess iodine is consumed. This article will provide novel information regarding the deficiency and excess of iodine or, in other words, The Yin and Yang of Iodine in human physiology.

Keywords: Iodine excess, Iodine deficiency, Thyroid, Goitre, Salt iodization, Iodine prophylaxis, Iodine deficiency disorders (IDD).

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INTRODUCTION

Iodine is an essential nutrient for mammals, required as a structural and functional element of thyroid hormones. Through these hormones, iodine has an important role in energy-yielding metabolism and in the expression of genes that impart many physiological functions, including embryogenesis and growth, reproduction, and the development of neurological and cognitive functions. In addition to its role as a substrate for thyroid hormone biosynthesis, it participates in many clinically important interactions with the thyroid.[1] The primary function of the thyroid is the production of the hormones thyroxine (T4), triiodothyronine (T3), and calcitonin. Nearly 80% of the T_4 is converted to T_3 by peripheral organs such as the liver, kidney, and spleen. T_3 is about ten times more active than T_4.[2]

Thyroid hormones are phylogenetically very old molecules that are synthesized by most multicellular organisms and which even have some effect on unicellular organisms. Thyroid hormones play a basic role in biology, acting on gene transcription to regulate the basal metabolic rate. The total deficiency of thyroid hormones can reduce basal metabolic rate up to 50%, while in excessive production of thyroid hormones, the basal metabolic rate can be increased by 100%. T_4 acts largely as a precursor to T_3, which is (with minor exceptions) the biologically active hormone. Thyroid hormones (THs) are known to be essential regulators of post-implantation embryo development.[3]

Humans require iodine for proper physical, reproductive, and mental development. In an adult with sufficient iodine intake, approximately 15 to 20 mg of iodine is concentrated in the tissues of the thyroid gland (Table 1). However, only 30% of the body's iodine is concentrated in the thyroid tissue and thyroid hormones. The remaining non-hormonal iodine is found in various tissues, including mammary tissue, eye, gastric mucosa, cervix, prostate, reproductive organs (testis and ovary), and salivary glands. Except for mammary tissue, the function of iodine in these tissues is largely unknown.[4]

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Dietary Sources of Iodine

Iodine is found in various foods, the richest sources being fish and dairy products. Seaweed is a concentrated source of iodine, but it can provide excessive amounts (particularly so in the case of brown seaweed such as kelp), and therefore, eating seaweed more than once a week is not recommended, especially during pregnancy. Milk and dairy products are the main sources of iodine for most people. Research has shown that organic milk has a 40% lower iodine content than conventional milk. In many countries, iodine is added to table salt to give "iodized salt." Iodized salt is not only widely available in different countries but can be found in some branches of several supermarket chains. As government recommendations are to reduce salt intake for health reasons, one should not rely on iodized table salt as a means of increasing the iodine intake. The actual amount of iodine in food varies according to the iodine content of the soil, farming practice, fish species and season. This makes it difficult to estimate iodine per portion. Therefore, it is always important to follow Government advice on foods to avoid during pregnancy.

Iodine is found in nature in various forms, such as inorganic sodium and potassium salts (iodides and iodates), inorganic diatomic iodine (molecular iodine or I_2), and organic monoatomic iodine. Iodides (I^-) are absorbed via a transport

Table 1: Recommended daily dietary intake of iodine (RDA)[4]

RDA for men: 110–150 µg	RDA for infants: 40 µg
RDA for women: 80–115 µg	RDA for pregnancy: 125 µg
RDA for child/adolescent: 60–110 µg	RDA for lactation: 150 µg

protein in the gastric mucosa called the sodium-iodide symporter, a molecule found in a variety of tissues in the body that utilize and concentrate iodine – the thyroid, mammary tissue, salivary gland, and cervix.[5] The Na/I symporter is present in brush border membranes of salivary glands, gastric mucosa, kidney, placenta, testis, ovaries, and mammary glands, which mediate active iodine accumulation. Genetic expression of the symporter is down-regulated by iodide.

Iodine Physiology and Metabolism

Intestinal absorption

Ingested iodine in forms other than iodide is reduced to iodide in the gut. Iodide is almost completely absorbed by the small intestine, whereas the absorption and metabolism of iodized oils are not entirely known. The absorption efficiency of oral inorganic iodide and T_3 is > 90%; that of oral T_4 is around 70 to 80%.[6] Iodide absorption is reduced in the presence of humic acids in drinking water,[7] and of thiocyanates, isothiocyanates, nitrates, fluorides, calcium, magnesium and iron in food and water.[8]

Transport in blood

In blood, inorganic iodide and organic iodine are found. Total plasma iodine concentrations (inorganic and organic iodine) in euthyroid subjects range from 40 to about 80 µg/L[1]. Concentrations between 80 and 250 µg/L are generally associated with hyperthyroidism, whereas concentrations above 250 µg/L generally result from iodine overload with iodinated drugs. Most organic iodine is present as T_4, which accounts for more than 10 times the iodine content of T_3, reverse T_3 (rT_3), mono-iodotyrosine (MIT), and di-iodotyrosine (DIT).[9] T_4 occurs in either free (fT_4) or bound to proteins, mainly to thyroxine-binding globulin (TBG) and to a lower extent to transthyretin (TTR or pre-albumin) and albumin. Less than 1% of T_3 and T_4 are free in plasma. The concentration of plasma inorganic iodide is proportional to dietary intake and ranges from 2 to 6 µg/L for usual intakes below 200 µg/day.[10]

Distribution to tissues

Plasma iodide is actively taken up through the basal membrane of the thyroidal follicular cells using the Na/I symporter and concentrated 20 to 50 times in these cells. It is then transferred to the follicle lumen at the apical membrane by pendrin and possibly by an additional human apical iodine transporter. The activity of the Na/I symporter is sensitive to inhibition by the contaminant's perchlorate, thiocyanates, isothiocyanates, and nitrates, to an extent that might be relevant at the population level when iodine intake is low.[11]
Extra-renal clearance of iodide is assumed to represent thyroid clearance, corresponding to the capture of iodine by the thyroid gland. It is in the range of 3 to 40 mL of serum/minute in euthyroid subjects, which corresponds to a capture by the thyroid of an average of 33% (range 12–68%) of the administered dose. There is an inverse relationship between thyroid uptake and dietary iodine intake or urinary excretion. The percentage of capture by the thyroid can change within 12 to 14 weeks, and sometimes faster, in response to changes in iodine intake in euthyroid subjects.[12]
Other tissue sites for iodide uptake from plasma are the salivary glands, the choroid plexus, the mammary gland, the kidneys, and the gastric mucosa. Within the range of usual intakes, iodine flux in saliva is up to 10 µg/hour, depending on the intake level.[13]

Storage

In adults with adequate iodine status, average total body iodine amounts to about 10 to 20 mg, of which 70 to 80% is found in the thyroid containing, on average, 8 to 15 mg of iodine. In Germany, a mean thyroid iodine content of 10 mg was found in the thyroid glands of 20 euthyroid subjects at autopsy. A study using X-ray fluorescence in 37 subjects aged 60 to 65 years who had lived in an area of adequate iodine supply throughout their lives (average UI concentration 210 ± 50 µg/L) indicated that a wide variation in thyroid iodine content from 0.9 to 20.2 mg (mean 5.2 mg) is compatible with euthyroidism. These figures for thyroid iodine content are similar to thyroid iodine contents of 2 to 16 mg observed in Belgium. The thyroid iodine content at birth is around 100 to 300 µg, increasing progressively to around 0.8 to 1 mg at four to six years.[13]

Metabolism

In the thyroid, the follicular cells synthesize the glycoprotein Tg intracellularly, which is then transferred to and stored in the colloidal follicle lumen. At the cell-colloid interface, iodide is oxidized and attached to the phenyl ring of Tg tyrosyl residues. This so-called organification is catalyzed by thyroid peroxidase (TPO), an iron-containing enzyme, and results in the formation of MIT and DIT. Further action of TPO leads to the coupling of two DITs to give T4 or of MIT and DITs to give T_3. All these iodothyronines remain attached to the Tg. About one-third of the iodine present is in the form of T_3 and T_4; the rest is present as MIT and DIT. When needed, T_3 and T_4 are released into the circulation from Tg by endosomal and lysosomal cellular proteases. Released MIT and DIT are deiodinated by an iodotyrosine deiodinase, providing efficient intra-thyroidal recycling of iodide.[14]
A feedback process regulates thyroid function - in response to a decrease in circulating T_3 and T_4 concentrations, TRH is secreted by the hypothalamus and stimulates the secretion of thyrotropin (or TSH) by the anterior pituitary gland. Within 15 to 20 minutes, TSH stimulates the secretion of thyroid hormones and causes an increased iodide uptake by the thyroid and an increased Tg breakdown. The thyroid gland is also controlled by the interaction between growth factors, their receptors, and signal transduction pathways. Epidermal

and insulin-like growth factors may stimulate follicular cells to synthesize Tg. Persistent action of TSH causes hypertrophy and hyperplasia of the thyroid gland and reduces the colloid and the stored iodine. TRH secretion is also stimulated by -noradrenergic impulses and inhibited by dopaminergic impulses. Apart from these, autonomous regulation of thyroidal iodine metabolism also occurs independent of TSH. T_4 is produced only by the thyroid gland, whereas T_3 is primarily produced by extra-thyroidal deiodination of T_4 in the liver and kidney, brain, pituitary gland, and brown fat tissue, with some (20% in humans) deiodination taking place also in the thyroid. Removal of iodine occurs via specific iodothyronine deiodinases.[8] Deiodinases show reduced activity in selenium deficiency, with consequently impaired activity of thyroid hormones. The deiodinases forming the active hormone T_3 are inhibited by some drugs (thiouracil, propylthiouracil, propranolol, and glucocorticoids).

The iodine liberated when T_4 is enzymatically deiodinated to its active form, T3, enters the plasma pool as iodide and is either re-used by the thyroid or excreted in the urine. T_3, which is less tightly bound to proteins, enters the cells more easily.

Elimination

Urine

The kidney is the main route of excretion of iodine. In adults with adequate iodine intake, the excess iodine not taken up by the thyroid is excreted in the urine (more than 90% of dietary iodine),[15] with partial re-absorption occurring in the renal tubules. The renal iodide clearance is 30 to 36 mL/minute in euthyroid subjects and is significantly decreased either in impaired renal function or in myxoedema. Compared with habitual fluid intakes, an increase in fluid volume intake can lead to additional iodine losses: for an increase in the urinary volume of one liter, additional iodine losses of around 15 µg/day were predicted for adolescents and adult women, respectively.

Feces

The amount of iodine measured in feces varies, with most values between 10 and 30 µg/day. A part of fecal iodine consists of thyroid hormones metabolized in the liver to glucuronide or sulfate conjugates that are excreted in the bile (enterohepatic circulation).[11]

Sweat

Early studies were in disagreement about the extent of iodine losses via sweat. It has been found that an iodine concentration in sweat of around 9.5 µg/L, which increased to 31.8 µg/L after a single dose of 2 mg potassium iodide, whereas some workers concluded that iodine elimination in sweat was negligible (average 1.67 µg/L).[16]

Breast milk

The expression of the Na/I symporter is up-regulated in the lactating mammary gland, allowing a preferential uptake of iodine and, thereafter, secretion in breast milk, with the concentration in milk being 20 to 50 times higher than in plasma.[16] More than 80 % of iodine is in the form of inorganic iodide, whereas T_4 is < 2 µg/L and T_3 is < 0.05 µg/L.

Health consequences of iodine deficiency and excess

According to their thyroid function, individuals are classified as euthyroid (*i.e.*, having normal thyroid function), hypothyroid, or hyperthyroid. Various mechanisms can lead to thyroid disorders, and hypo- and hyperthyroid status can be observed in cases of both insufficient and excessive iodine intakes.[17]

Iodine deficiency disorders (IDDs)

The clinical effects of iodine deficiency, referred to as iodine deficiency disorders (IDDs), are the result of insufficient intake leading to insufficient thyroid function (hypothyroidism). The latter can also be induced by thyroiditis and exposure to anti-thyroid compounds. Chronic iodine deficiency may lead to compensatory thyroid hypertrophy/hyperplasia with goiter (enlarged thyroid gland). Goitre is initially diffuse but later may become nodular with the appearance of autonomous nodules, which may subsequently cause hyperthyroidism. Goitre also increases the risk of thyroid cancer. A large goiter may cause obstruction of the trachea and the esophagus. Mild iodine deficiency is associated with goiter in 5–20% of school children in the world,[16] appearing more frequently in girls.

The goal of eliminating iodine-deficiency disease due to iodine deficiency has been achieved since the universal salt iodization policy has been widely carried out in many nations, including India, China, and several other Asian countries. On the other hand, reports are now increasingly appearing on the toxic effects caused by high amounts of iodine intake in iodine-sufficient areas.

Iodine excess

Chronic excessive iodine supply can also lead to goiter, as has, for example, been observed following chronic excessive iodine intakes through water in China. An increase in the iodine consumption of people living in the coastal areas of Sunderban districts of West Bengal, India, is also reported[13]. In this epidemiological cross-sectional study, there was a strong correlation with iodine sufficiency in soil and water along with iodized salt supplementation induced the prevalence of miscarriages (18.26%) and stillbirth (4.26%) among the people living in those areas. Long-term follow-up suggests that chronic excessive iodine intakes may accelerate the development of sub-clinical thyroid disorders to overt hypothyroidism or hyperthyroidism, increase the incidence of autoimmune thyroiditis, and increase the risk of thyroid cancer. Some organizations adopted the value of 600 µg/day as a tolerable upper intake level (UL) for adults, including pregnant and lactating women (*i.e.* approximately half of the value of 1100 µg/day adopted by WHO, based on dose-response studies of short duration (two weeks) and in a small

Table 2: Epidemiological criteria for assessing iodine nutrition by median urinary iodine

Median urinary iodine (ng/mL)	*Iodine intake*	*Iodine status*
< 20	Insufficient	Severe iodine deficiency
20–49	Insufficient	Moderate iodine deficiency
50–99	Insufficient	Mild iodine deficiency
100–199	Adequate	Adequate iodine nutrition
200–299	Above requirements	Likely to provide adequate intake for pregnant/lactating women but may pose a slight risk of more than adequate intake in the overall population
> 300	Excessive	Risk for adverse health consequences (e.g., iodine-induced hyperthyroidism, autoimmune thyroid diseases)

Concentrations of school-age children ≥ 6 years.[13]

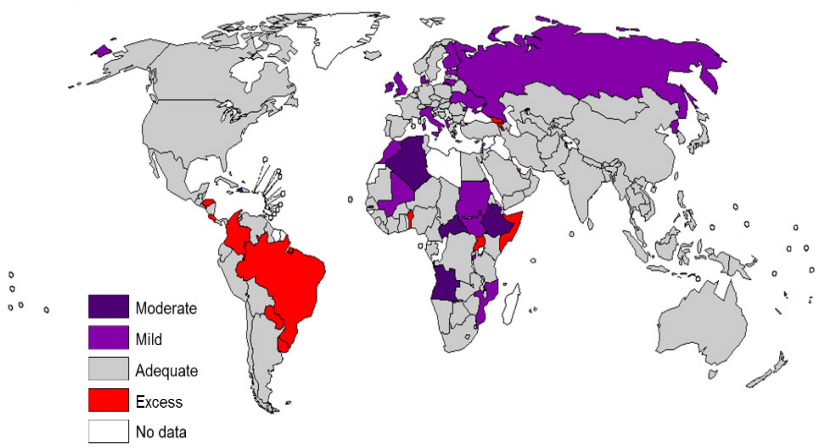

Figure 1: Global iodine map 2014-15 after successful iodization phase showing most of the countries are adequate in iodine nutritional status, but still, iodization policies are going on with incidences of excess iodine in future [Source: Global iodine network].[18]

number of subjects (n = 10–32). For iodine intakes of about 1,700 to 1,800 µg/day, the studies showed an increased response of TSH concentrations to thyrotropin-releasing hormone (TRH) provided intravenously,[17] but these changes were considered marginal and not associated with any clinical adverse effects. Some studies covering a five-year exposure to approximately similar iodine intakes in which no clinical thyroid pathology occurred were also considered, and an uncertainty factor of 3 was selected to derive the UL for adults. The ULs for children were derived by adjustment of the adult UL based on metabolic weight (Table 2).

Exposure to excessive iodine occurs via food, drinking water, medication and iodized salt or iodinated oil. Long-term ingestion of iodine in amounts that exceed dietary requirements may lead to iodism which is likely to be the scenario of the post-salt iodization phase. Prolonged intake of very large amounts of iodine (approximately ten times the recommended daily dietary allowance) can lead to enlargement of the thyroid, a condition called goiter.[14]

Sources of Iodine Excess

Iodine supplementation

Iodine is put into table salt to ensure that everyone has enough iodine to form essential thyroid hormones. Iodine has been administrated as iodized oil orally and intramuscularly, introduced into the water supply, used in crop irrigation, incorporated into animal fodder, and introduced into food through salt iodization, bread iodophores, and other products. Fortified micronutrient biscuits have also been successfully used to raise the median UICs of schoolgirls (aged 10–15 years) in India.[8]

Vitamins and supplements

Several cases of congenital hypothyroidism caused by ingestion of excess maternal iodine tablets during pregnancy have been reported. Similarly, hypothyroidism in neonates born to mothers who ingested excessive amounts of seaweed or seaweed soup during both pregnancy and lactation has been reported.[3]

Medications

Amiodarone, an iodine-rich medication used in the management of ventricular and supraventricular tachyarrhythmias, is probably the most important and common source of medication-induced thyroid dysfunction. Amiodarone is 37% iodine by weight and has some structural resemblance to the thyroid hormones T_3 and T_4.[1] Thus, one 200 mg tablet of amiodarone contains 75 mg iodine, which is several hundred-fold higher than the recommended daily intake of 150 µg in adults.

Table 3: Portion size of different foods with their iodine content

Food	*Portion (actual iodine content will vary)*	*Average iodine/ portion (µg)*
Cow's milk	200 mL	50–80*
Organic cow's milk	200 mL	30–65*
Yogurt	150 g	50–100*
Eggs	1 egg (50 g)	20
Cheese	40 g	15
Whitefish	100 g	115
Oily fish	100 g	50
Shellfish	100 g	90
Meat	100 g	10
Poultry	100 g	10
Nuts	25 g	5
Bread	1 slice (36 g)	5
Fruits and vegetables	1 portion (80 g)	3

*Depending on the season, higher value in winter [18,19]

Diet

Diet is considered one of the most effective forms of iodine nutrition (Table 3). Some examples are given – The iodine content of foods is highly variable between food categories as well as within each category. The richest sources are marine products (such as fish, shellfish, mollusks, and seaweed), eggs, and milk, as well as their derivatives and iodized salt. Feeding and hygienic practices influence the iodine content of milk and eggs.

Radiologic contrast media

The use of iodinated contrast agents in diagnostic radiologic studies is a common source of excess iodine exposure in many patients. Following exposure to an iodinated contrast agent, iodine stores in the body remain raised and provide a continuous pool that can potentially induce thyroid dysfunction, which is ultimately deleterious to the human body.

Other sources of iodine supplementation

Other sources of iodine include topical iodine supplementation, which is frequently done in hospitals for neonates. Other sources of potential excess iodine exposure include various expectorants, food preservatives, prescribed medications, parenteral nutrition preparations, mouthwashes, and vaginal douches.

Potential Hazards of Excess Iodine Exposure

Excess iodine and thyroidal adaptation

The acute Wolff-Chaikoff effect was described in 1948 by Drs Jan Wolff and Israel Lyon Chaikoff at the University of California Berkeley, USA.[19] They observed a transient reduction (lasting ~24 hours) in the synthesis of thyroid hormones in rats exposed to high amounts of iodide administered intraperitoneally. The mechanism for the acute Wolff–Chaikoff effect is not completely understood but is thought to be at least partially explained by the generation of several inhibitory substances (such as intra-thyroidal iodolactones, iodoaldehydes and/or iodolipids) on TPO activity.[20] Several mechanisms are involved in maintaining normal thyroid hormone secretion, even when iodine intake exceeds physiologic needs by a factor of 100.[17] Thyroidal adaptation to excess iodine fails only when the doses of iodine exceed 100 times its physiological daily dose.

Immunological effects

Excess iodide intake may be a contributing factor in the development of autoimmune thyroid disease in susceptible individuals, which can result in hypothyroidism or hyperthyroidism (associated with Graves' disease). Autoimmune thyroiditis is an inflammation of the thyroid gland that can lead to gland fibrosis, follicular degeneration, follicular hyperplasia, and hypothyroidism. IgG auto-antibodies to thyroglobulin (Tg) and, more frequently, TPO is a consistent feature of the disorder.[16]

Gastrointestinal effects

Ablative treatment of thyroid cancers with ^{131}I has been associated with inflammation of the salivary glands (sialadenitis) in humans. Salivary glands express a transport protein, the sodium-iodine symporter (NIS), which is present in high concentrations in the thyroid gland, where it functions to transport iodide into the gland for hormone synthesis. Exposures of ^{131}I-induced sialadenitis (inflammation of salivary glands) are reported within a few days or weeks of exposure.[16]

Neurological effects

An iodine-induced hypothyroid state can result in delayed or deficient brain and neuromuscular development of the newborn. Iodine-induced hypothyroidism in an older child or adult would be expected to have little or no deleterious effects on the neuromuscular system. Exposure of a fetus to large amounts of radioiodine would result in thyroid tissue ablation and in similar delayed brain and neuromuscular development if the hypothyroid state was not corrected (*e.g.*, with hormone replacement therapy) after birth.[12]

Developmental effects

Although iodine excess may result in hypothyroidism, iodine deficiency is far more likely to cause prenatal and postnatal hypothyroidism and be associated with neurologic injury leading to cretinism, a developmental effect.[13,21] Thyroid hormone deficiency from any cause at critical times of development may result in severe mental retardation, neurologic abnormalities, growth retardation, or abnormal pubertal development.

Excess iodine and cancer

Several large-scale epidemiology studies have examined the relationship between iodide intake and thyroid cancer.

Dietary iodine has been related to the development of ovarian, endometrial, and breast cancer.

Excess iodine and reproductive effects

Oral exposure to excess stable iodine may produce hypothyroidism or hyperthyroidism and may cause disruption of reproductive function secondary to thyroid gland dysfunction. Hypothyroidism can produce changes in the menstrual cycle in humans, including menorrhagia (excessive uterine bleeding) and anovulation (no ovulation).[3] Abortions, stillbirths, and premature births have also been associated with hypothyroidism.[22–25] Reproductive impairments associated with hyperthyroidism include amenorrhea, alterations in gonadotropin release and sex hormone-binding globulin (SHBG), and changes in the levels and metabolism of steroid hormones in both females and males.[26]

Excess iodine and apoptosis

Excess molecular iodide, generated by the oxidation of ionic iodine by endogenous peroxidases, induces apoptosis in thyroid cells through a mechanism involving the generation of free radicals. It has been shown that this type of apoptosis is p53 independent, does not require protein synthesis, and is not induced by modulation of Bcl-2, Bcl-XL, or Bax protein expression.[5]

Comprehensive studies on iodine deficiency led to the implementation of universal salt iodization (USI) policy in many countries, including India. With rapid global progress in correcting iodine deficiency, excessive iodine intake is emerging as a new concern (Figure 1). Iodine excess is associated with a spectrum of thyroidal effects, including birth defects and congenital abnormalities. Also, the effects of excess iodine on targeted thyroid hormone target organs like male and female reproductive physiology are very evident and need more focus in the times to come. Thus, consumption of iodine needs to be regulated as iodine can be a double-edged sword because too much iodine can cause the same symptoms as iodine deficiency in overall human physiology.

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