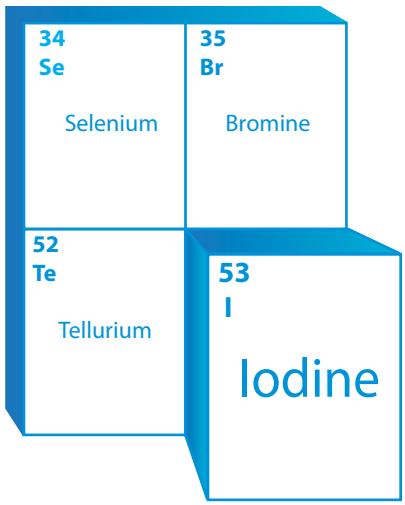
Iodine Monograph



Introduction

Iodine is a non-metallic element discovered by French chemist, Bernard Courtois, in 1811.[1] Its name is derived from the Greek "iodes" meaning violet or purple, the color of iodine in its gaseous phase. An essential trace mineral in humans, iodine is necessary for the synthesis of thyroid hormones. In addition, iodine plays a significant role in maintaining breast health.[2-5] Furthermore, animal studies suggest iodine may possibly benefit adrenal and immune function.[6,7] Dietary sources of iodine include iodized salt, seafood, seaweed, cow's milk, navy beans, and potatoes.

Most of the earth's iodine is found in oceans; by comparison iodine content in soil is low and varies by region. For instance, older, exposed soil surfaces are more likely to have iodine leached away by erosion. Major mountain ranges (e.g., Himalayas, Andes, Alps) and flooded river valleys (e.g., the Ganges) are among the most severely iodine-deficient areas in the world.[8] Not surprisingly, iodine deficiency is a significant health problem throughout much of the world.

Biochemistry

Iodine takes on various forms in nature. In the oceans, seaweed, algae, and seawater itself are rich with iodine as inorganic salts (e.g., sodium and potassium iodides), inorganic diatomic iodine (molecular iodine or I_2), and organic monoatomic iodine. Iodine in soil tends to be in the form of inorganic salts (e.g., sodium iodate, sodium periodate). Seaweeds, such as wakame, nori, or mekabu, are excellent sources of dietary iodine in several chemical forms, including I_2 and iodine organified to proteins. Intestinal absorption of iodine occurs via two possible processes depending on the form of iodine. Molecular iodine (I_2) is transported by facilitated diffusion and iodides (I^-) are absorbed via a transport protein in the gastric mucosa called the sodium-iodide symporter. The latter is a molecule found in a variety of tissues in the body that utilize and concentrate iodine – the thyroid, mammary tissue, salivary gland, and cervix.[9]

Pharmacokinetics

Iodine, when applied topically, is slightly absorbed through intact skin.[10] Absorption occurs more readily through broken skin, such as wounds, abrasions, and decubitus ulcers, or via mucosal surfaces with high absorptive capacity such as the vagina. Application of iodine to large areas of intact skin can increase absorption potential.[11-14]

When taken orally, iodine preparations are rapidly converted from iodine to iodide. The thyroid gland actively absorbs iodine from the blood, incorporating it into the thyroid hormones that are stored and released into circulation when needed. Triiodothyronine (T3), the physiologically active thyroid hormone, binds to thyroid receptors in the nuclei of cells in the liver and brain and regulates gene expression. Thyroxine (T4), the most abundant circulating thyroid hormone, is converted in target tissues to T3 via selenium-containing enzymes called deiodinases. Iodides not taken up by the thyroid are excreted primarily through the urine, with smaller amounts appearing in feces, saliva, and sweat. During pregnancy and lactation, iodides cross the placenta and are excreted in breast milk.[10]

Mechanisms of Action

The most understood role of iodine is its association with thyroid function and the synthesis of thyroid hormones, T3 and T4. Thyroid hormones help regulate several physiological processes, including growth, development, metabolism, and reproduction.[8,15]

The regulation of thyroid function relies on a negative feedback loop involving the hypothalamus, pituitary gland, and thyroid gland. The

hypothalamus secretes thyrotropin-releasing hormone (TRH), prompting the pituitary gland to secrete thyroid-stimulating hormone (TSH). As the name implies, TSH stimulates the production of T3 and T4 by the thyroid gland. These hormones are made by the addition of condensation products of the amino acid tyrosine and are stored prior to release in an iodine-containing protein called thyroglobulin. T3 and T4 contain three and four atoms of iodine per molecule, respectively. The thyroid gland actively absorbs iodide from the blood to make and release these hormones into circulation. The presence of adequate circulating T3 and T4 then feeds back to the hypothalamus and pituitary, decreasing TRH and TSH production.

Iodine deficiency results in inadequate production of T4, which spurs the pituitary gland to increase its output of TSH. A persistently elevated TSH level can lead to hypertrophy of the thyroid gland, also known as goiter.[16]

In an iodine-sufficient adult, only 30 percent of total iodine in the body, approximately 15-20 mg, is concentrated in the thyroid tissue and thyroid hormones. The remaining non-hormonal iodine is dispersed throughout the body within a variety of tissues, including mammary tissue, eye, gastric mucosa, cervix, and salivary glands.[15] Whereas iodine's role in mammary tissue is related to fetal and neonatal development, its role in the other tissues is largely unknown.[15] Research suggests iodine may act as an antioxidant in these tissues.[17-20]

Iodide acts as an electron donor in the presence of hydrogen peroxide, peroxidase, and some polyunsaturated fatty acids, decreasing damage by free oxygen radicals.[17,18] Iodine-deficient glands contain increased amounts of malondialdehyde, a product of lipid peroxidation that can occur as a result of inadequate iodine stores.[19] Concentrations of iodine as low as 15 micromolar (achievable in human serum) have the same antioxidant activity as ascorbic acid.[20] This antioxidant effect may explain the therapeutic effects of seaweed baths or iodine-rich solutions known as thalassotherapy used historically to treat ocular diseases, thyroid disease, diabetes, cardiac and respiratory disease, and arteriosclerosis.[20]

Animal studies have shown iodine normalizes elevated adrenal-corticosteroid hormone secretion related to the stress response and reverses the effect of hypothyroidism on the ovaries, testicles, and thymus in thyroidectomized rats.[6,21] Iodine may also have a role in immune function; when placed in a medium containing 10^{-6}M iodide, human leukocytes synthesize thyroxine.[7]

Deficiency States and Symptoms

According to the World Health Organization, over 30 percent of the world's population (2 billion people) suffers from insufficient iodine intake.[22] Iodine deficiency is generally considered to be the most common cause of preventable brain damage globally. Also known as iodine deficiency disorders (IDD), iodine deficiency can be detrimental in any stage of human life, but it is most damaging to the developing brain. Besides regulating many aspects of growth and development, thyroid hormone is important for myelination of the central nervous system, which is most active before and shortly after birth.[15,23]

A U.S. retrospective study assessing maternal hypothyroidism and subsequent IQ deficits in children ages 7-9 years found iodine deficiency may cause fetal brain damage and other neurological defects, including lowered IQ, spasticity, ataxia, and deaf-mutism.[24] Evidence also indicates autoimmune thyroiditis occurring during pregnancy appears to be the result of iodine deficiency.[25] Iodine intake is crucial during lactation to provide continuing neurological development of the infant.[26] Breast-milk iodine levels in a recent study of lactating mothers revealed 47 percent had levels insufficient to provide adequate iodine to meet infant requirements.[27] An estimated 31.5 percent of school-age children (6-12 years old) worldwide (266 million total children) are iodine deficient.[22]

Urinary iodine is an indicator of iodine status. Insufficient iodine is measured as urinary iodine excretion below 100 mcg/L.[22]

Thyroid enlargement, or goiter, is one of the earliest and most visible signs of iodine deficiency. Iodine supplementation can generally reduce the size of goiters, but the reversibility of the effects of hypothyroidism depends to a degree on the individual's stage of development.

During the 1990s, international efforts addressed global dietary iodine insufficiency primarily through the use of iodized salt in iodine-deficient countries.[23] As a result, 70 percent of households in the world today use iodized salt.[28]

Clinical Indications

Note: The following contains excerpts from Patrick L.[29] See this article for a more complete review of clinical indications.

Fibrocystic Breast Disease

Studies utilizing rat models observed that breast hyperplasia due to iodine deficiency responded to iodine repletion at a dose of 0.1 mg/kg body weight – an amount equivalent to a 5-mg dose in a 50-kg (110-pound) female.[3] It was further determined that molecular iodine is the active form of iodine in breast tissue in animal models, and it is less thyrotoxic than iodide due to higher levels of molecular iodine being selectively concentrated in breast tissue versus thyroid tissue. A significant amount of data shows the mammary gland is more efficient in capturing and concentrating molecular iodine than the thyroid gland.[3]

Three clinical trials were conducted to examine efficacy and toxicity of iodine repletion in women diagnosed with fibrocystic breast disease (FBD), using different forms of iodine – sodium iodide, protein-bound iodide (iodine caseinate), and molecular iodine.[4] Using weight-based dosing extrapolated from animal models, an uncontrolled study of 233 women with FBD compared sodium iodide to protein-bound iodide for a period of 2-5 years. Of those treated with sodium iodide, 70 percent experienced clinical improvement of their breast tissue versus 40 percent of the patients taking a protein-bound iodide. However, all participants experienced some side effects, such as acne, coryza, weakness, and foul breath.

The second trial was a prospective, controlled, crossover study comparing iodides (sodium iodide/protein-bound iodide) to molecular iodine. Patients (n=1,365), including those who did not respond to either form of iodide, were switched to molecular iodine using a 0.07-0.09 mg/kg dose. The researchers concluded molecular iodine was more effective and had a significantly lower side effect profile than the iodide forms. Both subjective and physician-evaluated clinical improvements were noted in 74 percent of women on a weight-based dose of 3-6 mg molecular iodine. No subjects treated with molecular iodine had thyroid-related side effects, and no changes were noted in thyroid lab values or on physical examination.

In the third study, 56 women with FBD were randomized to either molecular iodine or placebo for six months. They were assessed by physician examination and subjective evaluation every two months and followed with thyroid blood tests and mammography at the beginning and end of the trial.[4] After six months, 65 percent of the treatment group experienced significant improvement. By contrast, in the placebo group 33 percent experienced improvement while three percent demonstrated worsening on physician examination.

Another human study evaluating iodine and FBD examined the effect of an iodine compound of sodium iodide and iodate.[30] Based on animal studies showing molecular iodine is less thyrotoxic than iodide, this particular formulation was used because it generates molecular iodine as a result of dissolution in stomach acid. The randomized, double-blinded, placebo-controlled study evaluated the safety and efficacy of three dosages – 1.5, 3.0, and 6.0 mg – in 111 women. Patients were assessed by physicians and reported pain based on a standardized scale. The greatest reduction in pain, evident by the third month, occurred at the 6.0-mg dose. By the sixth month, 51.7 percent of study participants on 6.0 mg reported at least a 50-percent pain reduction, while the placebo group reported an 8.3-percent reduction. The efficacy of this iodine compound appeared to be dose-related, with a 6.0-mg dosage resulting in a greater level of pain reduction in a greater number of patients than the 3.0-mg dose. Due to the small number of women in the study, however, the p value did not reach significance.

Breast Cancer

The studies on iodine and breast cancer in humans and in animal models point to a close association with iodine and malignant cell growth. Iodine deficiency has been shown to alter the structure and function of the mammary glands of rats, especially alveolar cells. I_2 is distinctly more effective than I^- in diminishing ductal hyperplasia and perilobular fibrosis in mammary glands, using the same total iodine doses in both treatments.[3] A clinical study of breast cancer patients found breast tissue levels of iodine were significantly lower in women with diagnosed breast cancer than in women with either normal breasts or benign fibroadenoma.[31]

Animal and human studies show that in iodine-deficient states the breast parenchyma in rodents and women show atypia, dysplasia, and even neoplasia.[32] It has been observed that iodine-deficient breast tissue in animals is more susceptible to the effect of carcinogens, and breast lesions occur in greater numbers and earlier in the process of neoplasia. Metabolically, iodine-deficient breasts show pathological changes in RNA/DNA ratios, estrogen-receptor proteins, and cytosol iodine levels that lead to neoplasia.[33] Women with hyperplastic breast tissue have been shown to have significantly higher radioactive iodine uptake than women with normal breast tissue. This may be a

result of inadequate breast tissue iodine levels.[34]

Supplementation with iodine alone or in combination with progesterone has been shown to shrink breast tumors in animals. Lugol's solution (1 g iodine and 2 g potassium iodide in 100 mL water) and medroxyprogesterone acetate given to rats with chemically-induced breast tumors resulted in a significant reduction of tumor growth compared to the control group (that received no intervention).[35] The most effective dose of iodine was the lowest given – 0.0025 mg daily. The weight-based dose equivalent of Lugol's solution would be 5.0 mg inorganic iodine for a 50-kg female. This dose correlates with previous research finding 0.1 mg/kg body weight per day inorganic iodine promotes sufficiency in the rat necessary to improve signs and symptoms of FBD.[3]

Another study of chemically-induced mammary cancer in rats found molecular iodine is more effective at inhibiting mammary cancer than iodide or thyroxine.[36] The iodine used in the study was a 0.05-percent molecular iodine compared to 0.05-percent potassium iodide or thyroxine (3 mcg/mL), all in drinking water. Rats receiving molecular iodine demonstrated greater than 50-percent reduction in incidence of mammary cancer (30%) compared to controls (72.7%). Iodine-treated rats exhibited a strong and persistent reduction in mammary cancer, and only the I_2 treatment was capable of diminishing basal lipoperoxidation in mammary glands – the theoretical mechanism for iodine's action in mammary cancer reduction. Reactive oxygen species, specifically lipoperoxides, are involved in initiation and promotion of carcinogenesis, where specific mutations of certain genes occur.[20] No toxic effects of iodine on thyroid function or other side effects at effective dosages were noted in either study. Both authors recommend the initiation of human breast cancer trials with iodine.[35,36]

Drug-Nutrient/Nutrient-Nutrient Interactions

The anti-arrhythmic medication, amiodarone, contains high levels of iodine and may contribute to goiter, hypothyroidism, elevated TSH levels, and ocular damage.[37] Use of lithium in combination with pharmacological doses of potassium iodide may result in hypothyroidism. Use of pharmacological doses of potassium iodide in conjunction with warfarin (coumarin) may interfere with its anticoagulant effect.[23,38]

Selenium is required for the production of deiodinase selenoenzymes. Clinical investigators in selenium- and iodine-deficient populations conclude the coexisting deficiencies cause increased TSH levels and contribute to goiter development.[39] One French study found an inverse relationship between selenium status and thyroid volume.[40] Co-existing deficiencies become problematic in areas where iodine supplementation is promoted on a population-wide basis. Selenium supplementation may be necessary to prevent potential thyroid damage from iodide supplementation in selenium-deficient individuals.[41,42]

Side Effects and Toxicity

Iodine is generally considered to be safe when taken in amounts normally found in the diet and when used as recommended by a qualified clinician. However, sensitive individuals may experience allergic reactions even within these normally acceptable dose ranges. Symptoms of iodine hypersensitivity include bleeding and/or bruising, fever, joint pain, lymphadenopathy, urticaria, and severe allergic reactions such as angioedema and anaphylaxis.[43,44] Side effects associated with iodine repletion, as noted by some clinical trials, include acne, coryza, weakness, and foul breath.[4]

It is uncommon to see acute iodine toxicity, as this usually occurs only with doses of multiple grams. Symptoms of acute iodine poisoning include burning of the mouth, throat and stomach, fever, nausea, vomiting, diarrhea, a weak pulse, and even coma.[23]

Population studies have shown excessive iodine intake may increase the prevalence of autoimmune thyroiditis in animals and humans, increasing the risk of overt hypothyroidism.[45,46] Consequently, this may result in a goiter presentation. Some reports of iodine repletion, causing hyperthyroidism in individuals with prior severe iodine deficiency, have shown reversion to baseline in the continued presence of iodine repletion 3-5 years later.[47] Another study of a large population in China did not show a return to baseline after five years, and those authors suggest maintaining serum TSH levels in iodine-supplemented patients between 1.0 and 1.9 mIU to maintain the lowest incidence of abnormal thyroid function during iodine supplementation.[46] Children with cystic fibrosis may be more susceptible to the adverse effects of excess iodine.[38]

Dosage

Natural iodine content in the Western diet is typically no more than 2,000 mcg/day, with most diets supplying less than 1,000 mcg/day. However, certain Japanese populations whose diets contain large amounts of seaweed have iodine intakes ranging from 50,000 to 80,000 mcg (50-80 mg) of iodine/day.[8]

The Institute of Medicine's Food and Nutrition Board's recommended daily allowance (RDA) of iodine ranges from 150 mcg for adults to 290 mcg for lactating women.[23] The thyroid gland requires only 70 mcg/day to synthesize the needed amounts of T4 and T3. However, the higher iodine RDA levels are provided for optimal function of other body systems, including lactating breast, gastric mucosa, salivary glands, oral mucosa, thymus, epidermis, and choroid plexus.[48-50]

The safe upper limit has been set at 1,000 mcg (1 mg) as a result of studies assessing TSH levels with supplementation.[23]

For treatment of FBD, 3-6 mg of molecular iodine was used for up to five years with no associated thyroid abnormalities observed.[4,5] It is important to note, however, that patients with pre-existing autoimmune thyroid pathologies were excluded from participating in these studies.

Warnings and Contraindications

Daily iodine supplementation over 1,000 mcg (1 mg) has been shown to potentially contribute to underlying thyroid pathology in those with Hashimoto's thyroiditis or Graves' disease. Exacerbation of nodularities in euthyroid individuals may occur if daily intake exceeds 20 mg iodine or iodide.[51-53]

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