Iodine Supplementation and Monitoring to Ensure Patient Health and Safety

Jorge D. Flechas, MD[a]

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ABSTRACT

Iodine deficiency is a leading cause of thyroid disorders. Deficiency can manifest as hypothyroidism, goiter, or impaired mental function. Insufficient levels of iodine increase the risk of thyroid cancer and may be associated with risk of breast, ovarian, endometrial, stomach, and esophageal cancer. In an effort to address iodine deficiency, salt iodization was introduced. Yet, despite these efforts, iodine levels have decreased in recent years. Several tests may be used to determine iodine status including the iodine spot test, iodine loading test, bromide spot test, bromide loading test, fluoride spot test, fluoride loading test and sodium/iodide symporter (NIS) test. Iodine supplements are effective in preventing and treating iodine deficiency and in achieving whole-body iodine sufficiency. In order to avoid adverse effects such as hyperthyroidism, and goiter, iodine supplementation requires proper monitoring of thyroid hormones (TSH, serum total T4, and free T3), with more frequent assessments during the first year of supplementation. Adverse effects are usually avoided when adequate and regular monitoring of thyroid hormone levels and whole-body iodine levels is employed and when dosages are increased/decreased accordingly.

KEY WORDS

Iodine deficiency, iodine supplementation, hypothyroidism, thyroid hormones (TSH, T4, T3)

[a] Corresponding author: 80 Doctors Dr., Ste 3, Hendersonville, NC 28792, USA,
E-mail: otntg@msn.com

INTRODUCTION

Iodine is essential to life and is a component of hormones produced by the thyroid.[1] Because iodine cannot be synthesized by the body, it must be obtained through dietary sources.[2,3] Iodine content in foods and beverages is low and is affected by environmental factors such as climate and soil quality.[3] Seawater contains a low level of iodine, and as a result, marine plants (which can extract the iodine) and fish (which eat the plants) generally have an iodine content higher than most other foods.[4,5] Other dietary sources high in iodine content include iodized salt and some processed foods containing iodized salt.[6] Salt iodization was introduced in many countries around the world to combat iodine deficiency.[5] Daily recommended iodine intake values in the US are 150 ug/day for adults ≥14 years of age; 220 ug/day for pregnant women; and 290 ug/day for lactating women with actual dietary intake levels estimated to be 167 ug/day.[4] Dietary intake of iodine in Japan is estimated to range from 5.3 - 13.8 mg/day.[4]

Typical iodine levels in the total human body are between 15 and 20 mg with the thyroid gland containing approximately two thirds of this amount[7]. When whole-body iodine sufficiency is reached, total iodine content has been reported to reach as high as 1,500 mg.[8,9] Iodine is taken up via the sodium iodide symporter by the following tissues: pituitary gland, salivary glands, pancreas, testes, prostate gland, mammary gland, ovaries, gastric mucosa, adrenal gland, heart, thymus, lung, gallbladder, kidney, and colon.[10-12]

Iodine deficiency is the most common cause of thyroid disorder, and deficiency in adults can result in hypothyroidism, impaired mental function, goiter, increased susceptibility of the thyroid gland to nuclear radiation and in development of cancer.[1,2,10,11] Low levels of iodine increase the risk of thyroid cancer and is postulated to be a precursor for breast, ovarian, endometrial and prostate cancer development.[4] In a study conducted in Switzerland, researchers reported a decrease in thyroid cancers from 2 to 3 per 100,000 in 1950 to 1 to 2 per 100,000 in 1988, following increases in iodine intake during this period.[15]

According to the National Health and Nutrition Examination Surveys (NHANES), median national urinary iodine excretion has been declining over the past decades in the United States.[16,17] The Total Diet Study of the U.S. Food and Drug Administration reported similar decreases in iodine consumption during similar periods.[18]

Early clinical symptoms of iodine deficiency include low circulating thyroid hormone, high thyroid stimulating hormone (TSH), and subsequently goiter (thyroid enlargement due to hyperplasia).[4,5] Because the ovaries need a large amount of iodine to function properly, anovulation, cyst and infertility can occur in women when iodine deficiency is present.[19,20] In North America, neonates are screened at birth for hypothyroidism since hypothyroidism secondary to iodine deficiency during the entire pregnancy is associated with mental retardation and cretinism.[4]

ASSESSING IODINE AND OTHER HALOGEN LEVELS IN THE BODY

There are several laboratory tests available for assessing iodine levels in the body including the iodine spot test, iodine loading test, bromide spot test, bromide loading test, fluoride spot test, fluoride loading test and sodium/iodide symporter (NIS) test. Tests for bromide and fluoride are important as these are iodide antagonists in the body and prevent the effective absorption of iodide via the NIS system. Fluoride can be found in public water systems, in toothpaste and in some medications. Bromide can be found in wheat flour, some medications and some citrus flavored drinks.

The iodine, bromide, and fluoride spot tests are performed on the first urine samples of the morning and measure the amount of these compounds ingested in the diet over the previous 24 hours. The loading tests involve consuming a 50 mg tablet of iodine and then assessing the amount of iodine, bromide or fluoride excreted via the kidneys. Assessments are made using urine since approximately 90% of iodine is excreted by the kidneys (the remainder is excreted in bile, feces and sweat).[4,21]

Results of iodine loading tests have shown good correlation to the clinical response of patients supplemented with iodine.[20,22]

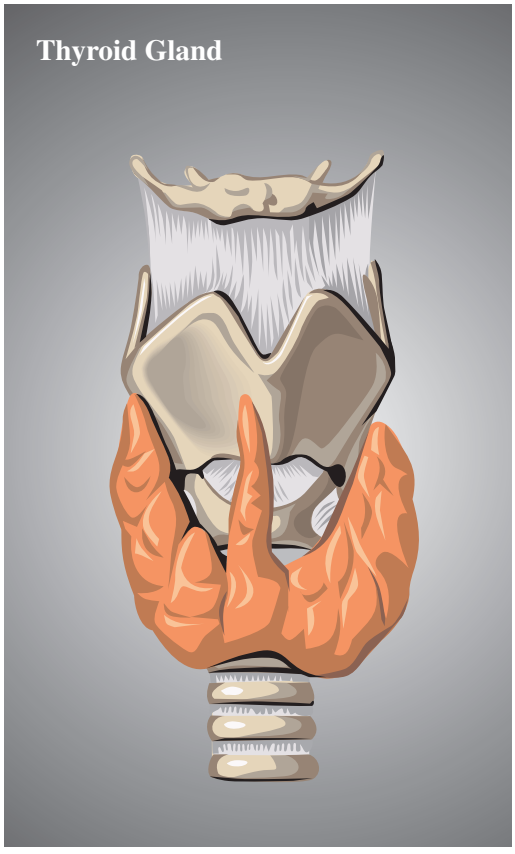
The sodium iodide symporter (NIS) transfers iodide from the blood into the thyroid gland in order to synthesize thyroid hormones. When the body experiences iodine deficiency, iodide is concentrated in the thyroid gland via uptake from the blood circulation through the sodium iodide symporter.[23,24] The NIS test shows if the body has a sodium iodide symporter (NIS) defect and gives an idea of the degree of defectiveness in symporter function.

IODINE DEFICIENCY AND THYROID HORMONE LEVELS

According to the World Health Organization, urinary spot iodine levels of 149-100 ug/L is considered mild deficiency, 99-50 ug/L is considered moderate deficiency and <49u/L is considered severe deficiency.[25,26] Iodine deficiency requires iodine supplementation. Prior to supplementation, thyroid hormone levels should be checked to establish baseline levels.[27] If a thyroid goiter or thyroid nodule is diagnosed, a thyroid ultrasound should be done to establish a baseline size of the goiter or the nodule. A fine needle aspiration (FNA) may be necessary as a diagnostic tool if the goiter is growing rapidly or if the thyroid gland is larger on one side than the other. The three main thyroid hormones are: TSH (thyroid stimulating hormone), the hormone from the brain which stimulates the thyroid to produce thyroid hormone; serum total thyroid T4 (thyroxine), the main hormone produced by the thyroid (contains four iodine molecules but is biologically inactive at the cellular level); and thyroid free T3 (triiodothyronine), which is thyroid T4 minus one iodine molecule (is the biologically active thyroid hormone that interacts with the DNA of cells and is involved in protein synthesis and enzymatic processes).

If thyroid hormone testing reveals an abnormal TSH level, further investigation is required to determine the cause of this abnormal value. An elevation in TSH (with low serum total T4 and/or low T3 values) may indicate low iodine levels and/or Hashimoto's thyroiditis (also known as autoimmune thyroiditis/hypothyroidism, the current preferred term for this condition). In order to diagnose autoimmune thyroiditis/hypothyroidism, thyroid peroxidase (TPO) antibodies and/or antithyroglobulin antibodies should be assessed. If one or both antibodies are elevated, autoimmune thyroiditis/hypothyroidism is the typical diagnosis. If testing shows TPO antibodies and antithyroglobulin antibodies to be absent or low normal, then the hypothyroidism with elevated TSH may be due to iodine insufficiency, which is a more typical diagnosis.

Low TSH levels with high serum thyroid T4 and/or high free T3 values can also be seen. Low TSH levels are typically associated with either Graves' disease (also known as autoimmune thyroiditis/hyperthyroidism, the medically preferred term for this condition) or a hot thyroid nodule. If testing for TPO antibodies and antithyroglobulin antibodies shows that one or both antibodies are high, autoimmune thyroiditis/hyperthyroidism is the typical diagnosis. One can also see TSH receptor antibod-



ies in autoimmune thyroiditis/hyperthyroidism. If test results for TPO antibodies and antithyroglobulin antibodies are normal (negative) and the TSH level is low (less than or equal to 0.5) with the thyroid T4 level above 12, it is possible that the thyroid contains a hot thyroid nodule. In such cases, consultation with an endocrinologist is warranted. A hot thyroid nodule is a piece of thyroid tissue that is absorbing a large portion of the iodine available to the thyroid either from iodized salt or from iodine supplementation and is, thus, producing a large amount of thyroid T4. An overactive thyroid nodule that is not treated can be fatal. The main symptom of this condition is a fast heart rate (greater than 100bpm) upon awakening. Heart rate should be checked each morning for the first month,[26] assuming …, the typical test used to detect a hot thyroid nodule is the radioactive iodine I-123 uptake and scan. Prior to conducting this test, the patient should discontinue thyroid hormone and all iodine supplementation for at least three weeks. A positive radioactive iodine I-123 uptake and scan necessitates the destruction of the hot spots. An endocrinologist should direct the treatment of this condition.

IODINE SUPPLEMENTATION

Taking iodine supplements is effective for treating iodine deficiency disorders including endemic goiter; thyroid conditions such as thyroid storm and hyperthyroidism (for these conditions, iodine supplementation should be administered and monitored by a endocrinologist); and for preventing uptake of radioactive iodine by the thyroid if taken immediately following radiation exposure.[4,21-23] Typically, for a person taking 12.5 – 100 mg of iodine per day, it is recommended, that serum TSH, T4 and free T3 is monitored every three to six months.[20] More recently, FNA or ultrasound guided FNA has been indicated as a front-line diagnostic tool.[26,29,30] The typical recommendation for iodine supplementation is 12.5 - 50 mg per day.[24] However, sufficiency is dependent upon many different factors including but not limited to the amount of iodine that is ingested (food plus supplementation) and levels of iodine antagonists (*i.e.* fluoride and bromide). Liquid iodine preparations applied to the skin have a very poor absorption rate, with only about 7% of the iodine being absorbed and approximately 93% of the iodine evaporating.[31] The ability to attain iodine sufficiency can also be affected by the ability of the body to organify the iodine and by the effectiveness of the sodium iodide symporter. Iodine treatment activates a caspase-independent and mitochondrial-mediated apoptotic pathway and is known to be cytotoxic to breast cancers.[32] It may be beneficial for cancer patients to take approximately 100 mg of iodine/iodide along with Vitamin B_2 and Vitamin B_3.[20]

The thyroid is not the only tissue in the body that requires iodine to function properly. Iodine saturation is required for the best of health for many other body tissues. Iodine supplementation of 12.5 – 50 mg per day should facilitate iodine sufficiency in the vast majority of patients [24]. In order to obtain iodine sufficiency, prolonged iodine supplementation may be necessary for some patients. When supplementing obese patients, the time required for the body to reach iodine sufficiency will be greater due to the presence of a large amount of body fat.[8,20] Patients who are obese will in general require more than the usual 12.5 – 50 mg per day, due to the absorption of iodine by the fat tissue (35% of total body iodine sits in the fat tissue).[9,20]

MONITORING THE THYROID AND THYROID HORMONES

A lack of iodine in the thyroid can cause thyroid enlargement (goiter) and can induce problems such as with hyperplasia.[33] Hyperplasia is regulated by intracellular iodine content. In contrast, TSH induces hypertrophy. A lack of iodine in the thyroid can also be responsible for nodules and for cancer. Iodine supplementation has been found to help reduce goiter and thyroid nodules.[20,34]

A thyroid ultrasound is recommended if a thyroid goiter or nodule is detected prior to initiating iodine supplementation. Small nodules, measuring less than 1 cm by 1 cm may be watched and a repeat thyroid ultrasound done at six months and at one year after the start of iodine supplementation. If a thyroid nodule continues to grow in the presence

of taking iodine, this suggests the possibility of a thyroid cancer, and an endocrinologist or an otolaryngologist should be consulted immediately for a biopsy of this nodule.

Repeat thyroid testing of TSH, serum total thyroid T4 and free T3 is mandated one month after the start of iodine therapy. If the TSH has gone up from the baseline and the serum total T4 has gone down, a defect in the organification process should be considered. An organification defect prevents the iodine that a person ingests from being oxidized by the body (*i.e.* the iodine does not bind to the thyroglobulin protein inside the thyroid), and thus, thyroid T4 production goes down.

Typically, for those patients taking thyroid hormone, the thyroid hormone dosage can be reduced after a period of time on iodine supplementation. However, the vast majority of people will still need to continue taking thyroid medication along with the iodine supplementation. In the presence of iodine, the body may become more sensitive to thyroid hormone. If symptoms of hyperthyroidism (such as nervousness, insomnia, irritability, sweaty hands, etc.) develop, the general recommendation is to cut the thyroid dosage in half for a few weeks or a few months. If, after this time, symptoms of hyperthyroidism return (with continued supplementation of iodine), the thyroid hormone dosage should be reduced once more. For the first year of iodine supplementation, thyroid testing (TSH, serum total T4, and free T3) every three months is encouraged.[20] This will ensure that the thyroid dosage is appropriate as the body adjusts to the presence of thyroid hormone plus iodine. After the first year of iodine supplementation, annual thyroid testing (TSH, serum total T4, and free T3) is indicated.[20]

Cases have also been reported where the body becomes more sensitive to other supplemented hormones (such as testosterone, progesterone, insulin, cortisone) that are being taken by the patient.[20] If increased sensitivity occurs and symptoms develop, the dosage of these hormones may also need to be reduced. In the case of estrogen supplementation, the estrogen dosage may need to be increased since iodine reduces the body's ability to produce estrogen.[33] All patients using some form of hormone replacement are encouraged to have regular testing done to insure proper hormone levels are maintained.

SAFETY & TOLERABILITY

Daily dietary intake of iodine is high in some regions of the world such as Japan as compared to the United States.[5] In Japan, estimated dietary intake of iodine ranging from 5.3 - 13.8 mg/day has not caused adverse effects.[2] Clinical trials have suggested that side effects of iodine supplementation such as abdominal pain, nausea, rhinorrhea, headache and diarrhea can be minimized by increasing dosage slowly.[35,36] Current evidence demonstrates that the benefits of correcting iodine deficiency outweigh the risks that may be associated with iodine supplementation.[37] If a fast heart rate should develop while taking supplemental iodine, consider a hot thyroid nodule and check T4 and T3 levels as well as RBC magnesium levels.[39] Low levels of magnesium are also associatedwith a fast heart rate. Some medical practitioners have considered iodine as a source of autoimmune thyroiditis.[40,41] The current medical literature suggests that this condition is due to activation of the inflammatory gene nuclear factor–kappa beta (nf-kappa beta or nf-kb). It is rare to see a person develop thyroiditis secondary to iodine.[41] Medical supervision and monitoring of thyroid levels during periods of iodine supplementation, especially in cases of prolonged use or high dose, is necessary to ensure patient safety.

CONCLUSION

With the decline in iodine intake through dietary sources in recent years, supplementation may be warranted since iodine deficiency can result in serious medical conditions. However, it is also important to recognize that many thyroid conditions are not solved by just giving iodine. Healthcare providers need to be familiar with the standard of care for treatment of different conditions of the thyroid. As there are some risks and adverse effects associated with iodine supplementation, healthcare practitioners should advise patients on the benefits and risks associated with iodine and should monitor patients using appropriate testing when recommending iodine supplementation.

DISCLOSURE OF INTERESTS

Dr. Flechas has nothing to disclose.

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