

# Iodine: Deficiency and Therapeutic Considerations

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## Abstract

Iodine deficiency is generally recognized as the most commonly preventable cause of mental retardation and the most common cause of endocrinopathy (goiter and primary hypothyroidism). Iodine deficiency becomes particularly critical in pregnancy due to the consequences for neurological damage during fetal development as well as during lactation. The safety of therapeutic doses of iodine above the established safe upper limit of 1 mg is evident in the lack of toxicity in the Japanese population that consumes 25 times the median intake of iodine consumption in the United States. Japan's population suffers no demonstrable increased incidence of autoimmune thyroiditis or hypothyroidism. Studies using 3.0- to 6.0-mg doses to effectively treat fibrocystic breast disease may reveal an important role for iodine in maintaining normal breast tissue architecture and function. Iodine may also have important antioxidant functions in breast tissue and other tissues that concentrate iodine via the sodium iodide symporter. (*Altern Med Rev* 2008;13(2):116-127)

## Introduction

The oceans are the worldwide repository of iodine; very little of the earth's iodine is actually found in soil. Iodine in the soil is deposited as a result of volatilization from ocean water caused by ultraviolet radiation. As a result, coastal soils are significantly higher in iodine than soils further inland. So-called goiter belts can occur in areas of elevated soil iodine because iodine is bound strongly to soil and vegetable crops are poor iodine sources.<sup>1</sup>

## Deficiency Worldwide

Iodine deficiency is considered to be the most common endocrinopathy and most preventable cause of mental retardation globally. In 1998, one-third of the world's population lived in iodine-deficient areas.<sup>2</sup>

Although the primary recognized manifestation of iodine deficiency is endemic goiter, it is only the most visible and well-documented sign of a deficiency. There are several manifestations of iodine deficiency now termed iodine deficiency disorders. The majority of these manifest in infants and children as a result of maternal iodine deficiency.<sup>3</sup> Hearing loss, learning deficits, brain damage, and myelination disorders can occur due to fetal or perinatal hypothyroidism. Infant mortality rates have decreased 65 percent in communities where iodine deficiencies have been eliminated.<sup>4</sup> Maternal iodine deficiency manifests as low thyroxine, elevated thyroid stimulating hormone (TSH), and subclinical thyroid enlargement (subclinical goiter). As pregnancy and lactation increase iodine loss, the risk for goiter continues, and even after lactation ceases it may manifest as multinodular goiter and hyperthyroidism. Iodine deficiency in women can lead to overt hypothyroidism and consequent anovulation, infertility, gestational hypertension, spontaneous first-trimester abortion, and stillbirth.<sup>4</sup>

Iodine deficiency is also associated with increased risk for thyroid carcinoma in animal models and humans.<sup>5-8</sup> In the Bryansk region of Russia, an area of

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## Review Article

known radioactive I-131 exposure following the Chernobyl disaster, the risk of all types of thyroid cancer was directly inversely associated with urinary iodine excretion levels.<sup>9</sup> Multiple studies assessing radioactive iodine uptake in iodine-deficient thyroid glands have affirmed that iodine deficiency allows for increased radioactive iodine uptake. Although the pathology may be different in extrathyroidal cancers, Stadel has postulated that given the geographical associations of iodine deficiency, prevalence of goiter, and incidence of reproductive cancers, there is a direct association with iodine deficiency and increased risk for prostate, endometrial, ovarian, and breast cancers.<sup>10</sup>

**Table 1. Sources of Iodine**

Soil	
NaIO <sub>3</sub>	Sodium iodine
NaIO <sub>4</sub>	Sodium periodate
Seaweed/Algal Phytoplankton	
KI	Potassium iodide
NaI	Sodium iodide
I <sub>2</sub>	Iodine
I <sup>-</sup>	Iodide
Seawater	
I <sup>-</sup>	Iodide

In mild deficiencies, euthyroid (normal thyroid hormone levels) states may occur but at the expense of thyroid enlargement, neck compression, and thyroid nodules with possible development of hyperthyroidism.<sup>11</sup> Mild hypothyroidism in pregnant women secondary to iodine deficiency is associated with lower IQ and cognitive deficits in their children.<sup>12,13</sup>

In an area of endemic goiter, iodine administration to infants was shown to normalize delayed immunity using skin testing with tetanus toxoid, suggesting a role of iodine sufficiency in normal delayed immunity.<sup>14</sup>

### Iodine Deficiency in Developed Countries

Although frank iodine deficiency is primarily found in the underdeveloped world (Africa, Southeast and Central Asia), countries in Europe, including Germany, France, Italy, and Belgium, are also considered iodine-deficient. Germany spends the equivalent of one billion dollars annually in both healthcare expenditures and lost work time as a result of iodine deficiency and resultant thyroid disease.<sup>15</sup>

Although North Americans are considered an iodine-sufficient population, that assumption is changing. The National Health and Nutrition Survey (NHANES) data monitoring urine iodine shows iodine intake has dropped by 50 percent from the period of 1971-1974 to 1988-1994, with median urine iodine levels dropping from 320 mcg/L to 145 mcg/L.<sup>16</sup> Although the next NHANES 2001-2002 survey showed an increase in median urine iodine levels to 165 mcg/L, an apparent leveling off of a precipitous drop, women of childbearing age did not fare as favorably. According to a Centers for Disease Control (CDC) evaluation of NHANES 2001-2002, approximately 36 percent of women of childbearing age in the United States may receive insufficient dietary iodine.<sup>17</sup> Iodine insufficiency was defined by urine iodine levels below 100 mcg/L and assessed from single samples, the cutoff for iodine insufficiency defined by the World Health Organization (WHO) and diagnostic of mild iodine deficiency. The WHO found that in populations with mean values below this level the prevalence of goiter increases significantly.<sup>18</sup> Fifteen percent of the same sample of women from NHANES 2001-2002 had urinary iodine levels less than 50 mcg/L, a level at which thyroid hormone secretion is considered inadequate and is considered by the WHO to be an indication of moderate-to-severe deficiency.

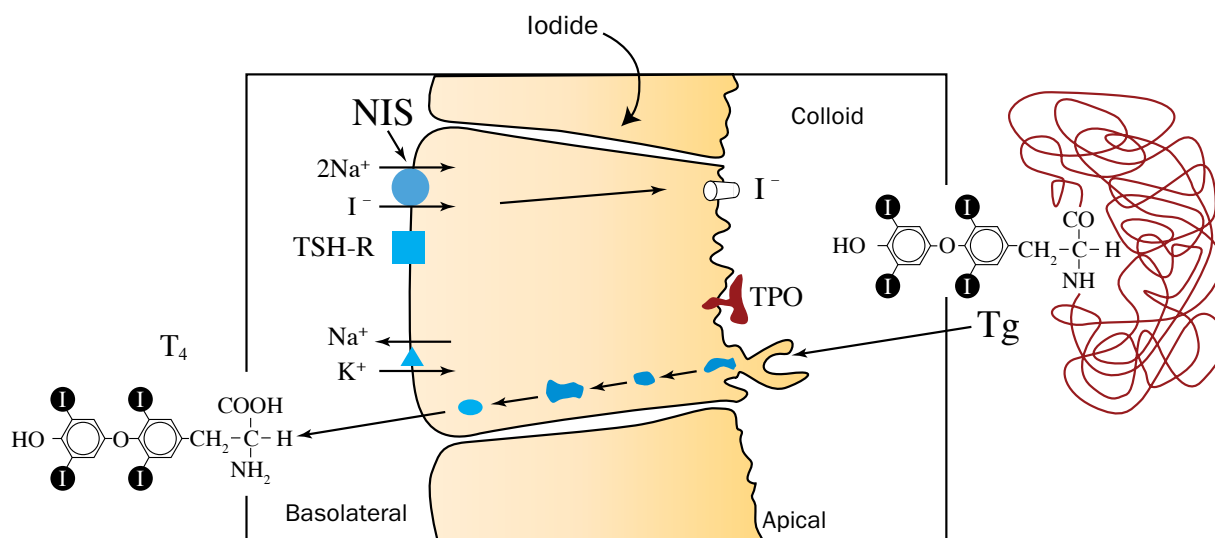
Public health officials voice concern over this data because of its implications for maternal/child health.<sup>19</sup> The thyroid gland and the hypothalamic/

pituitary/thyroid axis begins to function in the developing fetus at 11 weeks of gestation. The main role of fetal thyroid hormone secretion (T4 levels are demonstrable at 18-20 weeks of gestation) is development of the nervous system. A U.S. retrospective study assessing maternal hypothyroidism and subsequent IQ deficits in children ages 7-9 years found iodine deficiency may be causing fetal brain damage and other neurological defects, including lowered IQ, spasticity, ataxia, and deaf-mutism.<sup>20</sup> Evidence also indicates autoimmune thyroiditis occurring during pregnancy appears to be the result of iodine deficiency.<sup>21</sup> Iodine is also crucial during lactation to provide continuing neurological development of the infant.<sup>22</sup> Breast-milk iodine levels in a recent study of lactating mothers in Boston revealed 47 percent had levels insufficient to provide adequate iodine to meet infant requirements.<sup>23</sup>

## Dietary Levels of Iodine: The Japanese Phenomenon

Japanese populations have historically consumed significant amounts of dietary iodine from seaweed intake, possibly consuming a minimum of 7,000 mcg iodine daily from kombu alone.<sup>24</sup> Estimates of the average daily Japanese iodine consumption vary from 5,280 mcg to 13,800 mcg;<sup>25,26</sup> by comparison the average U.S. daily consumption is 167 mcg. The Japanese, therefore, consume dietary iodine approximately 5-14 times above the upper safety limit of 1 mg by U.S. standards. Mean urinary iodine levels in Japanese populations are approximately twice the levels found in the U.S. NHANES 2001-2002 data.<sup>27</sup> These higher levels, however, appear to have no suppressive effect on thyroid function as indicated by thyroid volume measurements, the accepted standard for assessing thyroid

Figure 1. Thyroid Hormone Synthesis



Adapted from: De la Vieja A, et al. *Physiol Rev* 2000;80:1083-1105.

Iodine, in the form of iodide, is absorbed in the thyroid follicle through the sodium/iodide symported protein (NIS) found in the basolateral membrane of the follicular cell. The activity of NIS is up-regulated by the binding of TSH to the TSH receptors on the follicular cells (TSH-R). This allows the absorption and concentration of iodine inside the cell to levels 20-40 times greater than that found in the blood. Iodide is then organified (oxidized) to iodine by thyroid peroxidase (TPO) and incorporated into the thyroglobulin molecule (Tg). Thyroid hormones (T<sub>3</sub> and T<sub>4</sub>) are then secreted into the bloodstream from the follicular cell.

## Review Article

enlargement. A study comparing urine iodine and thyroid volume in Japanese children showed 16 percent of those tested excreted over 1,000 mcg/L.<sup>24</sup> Elevated levels of urinary iodine did not predict increased thyroid gland volume, as might be expected from data in studies of Chinese populations associating excess levels of iodine with autoimmune thyroiditis and hypothyroidism.<sup>28</sup> Japanese women who consume a traditional high-seaweed diet also have a low incidence of benign and malignant breast disease.<sup>29</sup> Japanese women who

## The Role of Iodine in the Human Body

Iodine is found in nature in various forms: inorganic sodium and potassium salts (iodides and iodates), inorganic diatomic iodine (molecular iodine or  $I_2$ ), and organic monoatomic iodine (Table 1). Seaweeds, such as wakame, nori or mekabu (used in sushi, soups, salads, and in powdered form as a condiment) and widely consumed in Asian cultures, contain high quantities of iodine in several chemical forms, including iodine in the molecular form ( $I_2$ ) and iodine organified

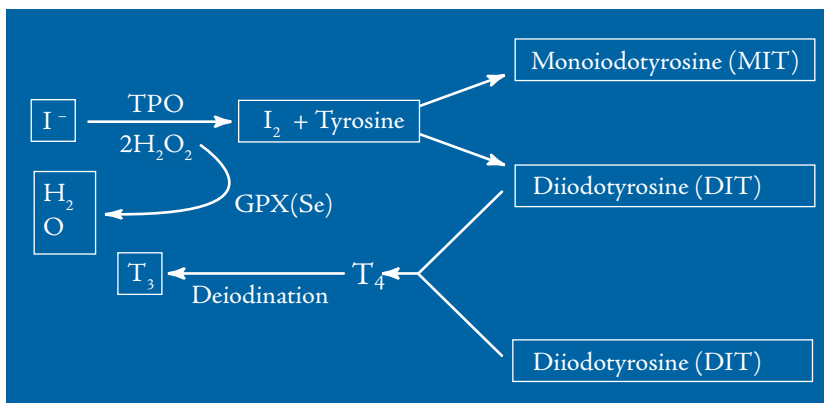
to proteins. These forms of iodine are absorbed through the intestinal tract via two different mechanisms. Molecular iodine ( $I_2$ ) is transported by facilitated diffusion. Iodides ( $I^-$ ) are absorbed via a transport protein in the gastric mucosa called the sodium-iodide symporter, a molecule found in a variety of tissues in the body that utilize and concentrate iodine – the thyroid, mammary tissue, salivary gland, and cervix.<sup>33</sup>

In order to produce concentrated iodine-based hormones, the thyroid tissue sodium-iodide symporter protein, a critical plasma membrane protein in the thyroid follicular cells, sequesters iodide from the extracellular fluid. The iodide molecule then moves across the apical membrane to the cell-colloid surface where it is oxidized by thyroid peroxidase (TPO). In this form it is bound to tyrosine residues in the thyroglobulin molecule and these mono- and diiodotyrosines become the precursors to commonly known thyroid hormones  $T_3$  and  $T_4$  (Figure 1). Iodine accounts for 65 percent of the molecular weight of  $T_4$  and 59 percent of the molecular

weight of  $T_3$ .<sup>11</sup>

In an adult with sufficient iodine intake, approximately 15-20 mg iodine is concentrated in the tissues of the thyroid gland. However, only 30 percent of the body's iodine is concentrated in the thyroid tissue and thyroid hormones. The remaining nonhormonal iodine is found in a variety of tissues, including mammary tissue, eye, gastric mucosa, cervix, and salivary glands. With the exception of mammary tissue, the function of

Figure 2. Antioxidant Functions of Iodine



Iodine ( $I_2$ ) is catalyzed by thyroid peroxidase using  $H_2O_2$ .  $H_2O_2$  used in this reaction decreases the amount of  $H_2O_2$  that would otherwise be available for damaging oxidation reactions. Selenium containing GPX removes  $H_2O_2$  from the tissues, also decreasing oxidative damage.

TPO - Thyperoxidase  
 GPX - Glutathione Peroxidase  
 $T_3$  - Triiodothyronine  
 $T_4$  - Tetraiodothyronine

Adapted from: Smyth PP. Role of iodine in antioxidant defence in thyroid and breast disease. *Biofactors* 2003;19:121-130.

consume a Western diet low in seaweed or who emigrate to the United States lose this protective advantage and gain the same risk for fibrocystic breast disease and breast cancer as their Western counterparts.<sup>30,31</sup> Japan also has a low incidence of iodine-deficiency goiter and autoimmune thyroiditis.<sup>32</sup> It has been hypothesized the amount of iodine in the Japanese diet has a protective effect for breast and thyroid disease.<sup>25</sup>

iodine in these tissues is largely unknown.<sup>11</sup> Mammary tissue's role in sequestering and concentrating iodine is related to fetal and neonatal development and is largely evolutionary, as detailed below. However, iodine's role in mammary and other tissues has also been shown to have an antioxidant function. Iodide can act as an electron donor in the presence of hydrogen peroxide, peroxidase, and some polyunsaturated fatty acids, decreasing damage by free oxygen radicals (Figure 2).<sup>34,35</sup> Iodine-deficient glands contain increased amounts of malondialdehyde, a product of lipid peroxidation that can occur as a result of inadequate iodine stores.<sup>36</sup> Concentrations of iodine as low as 15 micromolar (achievable in human serum) have the same antioxidant activity as ascorbic acid.<sup>37</sup> This antioxidant effect of iodine 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.<sup>37</sup>

Animal studies have shown iodine normalizes elevated adrenal corticosteroid hormone secretion related to the stress response<sup>38</sup> and reverses the effect of hypothyroidism on the ovaries, testicles, and thymus in thyroidectomized rats.<sup>39</sup> Iodine may also have a role in immune function; when placed in a medium containing  $10^{-6}$ M iodide, human leukocytes synthesize thyroxine.<sup>40</sup>

### Testing Iodine Levels

More than 90 percent of dietary iodine is excreted in the urine. Single random urine sampling is the standard accepted method of measuring body stores of iodine. The World Health Organization has determined 50-99 mcg/L indicates mild deficiency, 20-49 mcg/L indicates moderate deficiency, and less than 20 indicates severe deficiency.<sup>18</sup> Because random urine samples have been found to be adequate for population screening, there is little advantage in calculating urine iodine:creatinine ratios. For individual measurements, however, multiple spot urine iodine measurements or 24-hour urine iodine evaluations are more precise.<sup>41</sup>

## Medical Uses of Iodine

### Lugol's Solution

Lugol's solution (produced by French physician Jean Lugol in 1829) consists of five-percent iodine and 10-percent potassium iodide in solution. It was originally used to treat "scrofula" and 40 years later to treat anthrax infections. Lugol's solution became widely used in medicine in the early 1900s to treat a variety of disorders, including simple goiter and Graves disease,<sup>42</sup> and by 1932 had become commonplace in medical practice.<sup>43</sup> Even as late as 1995, pharmaceutical texts recommended the use of 0.1-0.3 mL Lugol's five-percent solution for the treatment of simple goiter,<sup>44</sup> the equivalent of 12.5-37.5 mg iodine. Lugol's solution fell out of favor for the treatment of iodine-deficiency diseases as the availability of thyroid extracts and iodized salt became more widely used. Multiple pharmaceutical medications used currently contain iodine.

### Iodine and Fibrocystic Breast Disease

The breast concentrates iodine to a greater degree than the thyroid gland;<sup>45</sup> human milk contains a concentration of iodine four times greater than thyroid tissue.<sup>45</sup> This evolutionary mechanism is necessary for neonatal thyroid function and consequent normal neural development.<sup>46</sup> Mammary tissue also produces two separate deiodinase enzymes: deiodinase type 1 and deiodinase type 2, which can convert  $T_4$  to  $T_3$ . Deiodinases control the amount of free iodine present in breast tissue – higher levels during puberty, pregnancy, and lactation, and lower levels in nonpregnant or postpartum phases (Figure 3).<sup>47</sup>

Biopsy-proven studies find fibrocystic breast disease (FBD) in nine percent of women. Autopsy studies, however, reveal only 10-20 percent of FBD cases appeared to have been biopsied, leading to a significantly larger prevalence.<sup>48</sup> Studies by Eskin et al found iodine deficiency in a rat model resulted in breast hyperplasia that responded to iodine repletion at a dose of 0.1 mg/kg body weight,<sup>49</sup> equivalent to a 5-mg dose in a 50-kg (110-pound) female. This group also determined that molecular iodine is the active form of iodine in breast tissue in animal models and it is less thyrotoxic than iodide because more of the molecular iodine is selectively concentrated in breast tissue than thyroid tissue. A significant amount of data shows the mammary gland is

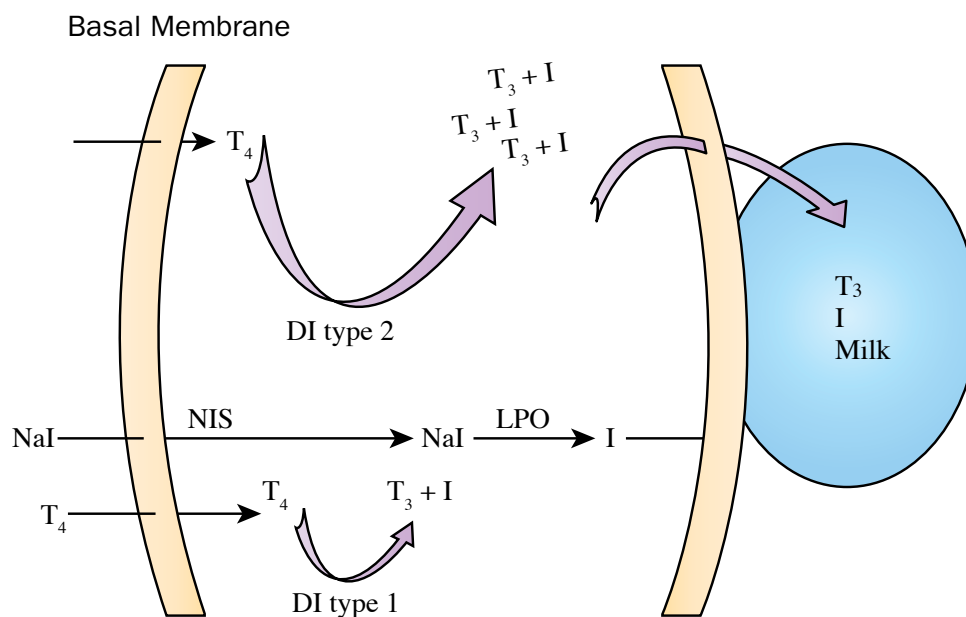
more efficient in capturing and concentrating molecular iodine than the thyroid gland.<sup>49</sup>

Ghent and Eskin continued their iodine-repletion studies in women with diagnosed FBD.<sup>50,51</sup> Through a series of three trials assessing different forms of iodine – first sodium iodide or protein-bound iodide, then molecular iodine – they examined efficacy and toxicity of weight-based iodine dosing, extrapolating from the animal model dose. Beginning with an uncontrolled study of 233 women with FBD, they compared sodium iodide to protein-bound iodide for a period of 2-5 years. 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. They concluded that the molecular form of iodine was more effective and had a significantly lower side-effect profile than iodide forms. Both subjective and physician-evaluated clinical improvements were noted in 65 percent of women on a weight-based dose of 3-6 mg molecular

iodine. This compared to a subjective improvement of 33 percent in the placebo group (Table 2). 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 study #3, 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.<sup>50</sup> 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.<sup>52</sup> Based on animal studies showing molecular iodine is less thyrotoxic than

**Figure 3. Deiodinase Control of Iodine in Breast Tissue**



Mammary gland produces either a majority of deiodinase type 1 (DI1) during pregnancy/lactation or a majority of deiodinase type 2 during nonpregnant or postpartum (postlactation) periods. Iodine is absorbed via the sodium iodine symporter (NIS) and oxidized by lactoperoxidase (LPO).



Table 2. Iodine Repletion Studies in Women with FBD

Type of Study	Study #1 Prospective Uncontrolled	Study #2 Prospective Control Crossover	Study #3 Prospective Control Double-blind
Duration	2 years/5 years	9.9 months post crossover	6 months
Number of Participants	233 on Lugol's for 2 years 588 on iodized casein for 5 years	1,365 for minimum of 8.9 months: total treatment time 4,813 woman-years	56
Medication & Dosage	31-62 mg I (n=233) Iodine caseinate 10 mg/day (n=588)	Molecular iodine 0.07-0.09 mg/kg body weight/day	Molecular iodine 0.07-0.09 mg/kg body weight/day
Evaluation	Subjective and clinical evaluation	Subjective and clinical evaluation	Pre & post mammography; TSH, T <sub>3</sub> , T <sub>4</sub>

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 month 3, occurred at the 6.0-mg dose. By month 6, 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 (Table 3). Due to the small number of women in the study, however, the p value did not reach significance.

### Iodine and Breast Cancer

In Japan, age-adjusted breast cancer incidence is 6.6 per 100,000. In comparison, the U.S. age-adjusted breast cancer incidence is 22 per 100,000 and the U.K. rate is 27 per 100,000.<sup>53</sup> Japan also has significantly lower rates of hypothyroidism, autoimmune thyroid disease, and hyperthyroid conditions, while the average daily dietary iodine intake may be as high as 25 times that of the United States.<sup>27</sup> The incidence of breast cancer in Japanese women who emigrate to the United States and adopt a Western diet equals that of non-Japanese women living in the United States.<sup>53</sup> The lower incidence of both FBD and breast cancer have been attributed to the increased dietary intake of iodine in the traditional Japanese diet.<sup>25</sup>

Data on the link between breast cancer and thyroid disease is unclear, with some studies clearly showing an increased incidence of hypothyroidism and autoimmunity in breast cancer patients, while other studies

Table 3. Dose-dependent Efficacy of an Iodine Compound for FBD

	Placebo	1.5 mg iodine	3.0 mg iodine	6.0 mg iodine	p
All randomized subjects with pain, tenderness, and nodularity at baseline	0/15 (0%)	0/10 (0%)	7/28 (25.0%)	5/27 (18.5%)	0.047
All randomized subjects with moderate or severe pain, tenderness, and nodularity at baseline	0/12 (0%)	0/9 (0%)	5/22 (27.3%)	5/27 (18.5%)	0.106

Adapted from: Kessler JH. The effect of supraphysiologic levels of iodine on patients with cyclic mastalgia. *Breast Journal* 2004;10:328-336.

show no significant association.<sup>54-57</sup> Smyth found a significantly greater mean thyroid volume in female breast cancer patients compared to controls.<sup>58</sup>

The studies on iodine and breast cancer in both humans and animal models point to a closer 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.<sup>49</sup> A clinical study of breast cancer patients found breast tissue levels of iodine were significantly lower in the breast tissue of women with diagnosed breast cancer than in breast tissue of women with either normal breasts or benign fibroadenoma.<sup>58</sup>

Animal and human studies show that in iodine-deficient states the breast parenchyma in rodents and women show atypia, dysplasia, and even neoplasia.<sup>59</sup> Eskin et al demonstrated 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.<sup>60</sup> Clinically, Eskin also demonstrated that women with hyperplastic breast tissue have significantly higher radioactive iodine uptake than women with normal breast tissue. The author hypothesized this was a result of inadequate breast tissue iodine levels.<sup>61</sup>

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 of 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).<sup>62</sup> 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 Eskin's 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.<sup>49</sup>

Another study of chemically-induced mammary cancer in rats found molecular iodine is more effective at inhibiting mammary cancer than iodide or thyroxine.<sup>63</sup> 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.<sup>37</sup> In both studies, no toxic effects of iodine on thyroid function or other side effects



at effective dosages were noted. Both authors recommend the initiation of human breast cancer trials with iodine.<sup>62,63</sup>

### Thyroid Toxicants: Perchlorate

Perchlorate is an inorganic anion that occurs naturally in soil and is also made synthetically. The ammonium salt of perchlorate is manufactured primarily for use as a rocket propellant, in explosives manufacturing, and as a pharmaceutical. Perchlorate is also naturally occurring in fertilizers that contain nitrate-rich mineral deposits.<sup>64</sup>

Recent studies have found significant perchlorate contamination in groundwater throughout the western United States as a result of ammonium perchlorate disposal. Perchlorate (at levels over 4 ppb) has been found to contaminate the drinking water of 11 million people in the United States, and high levels of perchlorate have also been found in the food supply. Human milk has been found to contain five times the perchlorate levels (10.1 mcg/L) of cow milk (2 mcg/L).<sup>65</sup> Perchlorate contamination has also been documented in grain, fruit, vegetables, dietary supplements, and forage crops for livestock.<sup>65-68</sup>

Perchlorate is a known competitive inhibitor of the sodium-iodide symporter in humans and can inhibit iodide uptake, leading to the suppression of  $T_3$  and  $T_4$ . Potassium perchlorate is currently used as a pharmaceutical to treat thyrotoxicosis and hypothyroidism induced by amiodarone.<sup>69</sup>

Due to recent evidence that perchlorate contamination of food and water is a widespread phenomenon, attempts have been made to evaluate the effect of perchlorate contamination on thyroid function in the general population. An evaluation of the recent NHANES 2001-2002 survey examined the relationship of urinary perchlorate levels, urinary iodine levels, serum TSH, and serum  $T_4$  levels in adult men and women,<sup>70</sup> resulting in three surprising findings. First, 36 percent of women in the NHANES subset had low urine iodine levels (<100 mcg/L), equivalent to 2.2 million women nationwide, considering that the NHANES subset is representative of the population in general. The second finding was that perchlorate contamination, as low as 5 ppb, is associated with elevations of TSH and decreased serum  $T_4$  in all 1,111 women regardless

of iodine status. Third, in women with low urine iodine levels under 100 mcg/L (suggesting iodine insufficiency), perchlorate at levels as low as 5 ppb was associated with a 16-percent decrease in  $T_4$  levels and elevation of TSH levels, consistent with inhibition of iodide uptake. In the group at highest risk of thyroid deficits, women with urine iodine levels under 100 mcg/L, exposure to 5 ppb perchlorate could theoretically cause subclinical hypothyroidism in 10 percent of that population.<sup>70</sup>

Subclinical hypothyroidism is currently defined as an elevated TSH with  $T_3$  and  $T_4$  levels within normal reference ranges.<sup>71</sup> The concern with this population of women of childbearing age who have low urine iodine levels is that undetected, subclinical hypothyroidism can lead to fetal neurological damage.<sup>70</sup>

### Iodine Toxicity

The U.S. recommended daily intake (RDI) for dietary iodine is 150 mcg for adults, 220 mcg for pregnancy, and 270 mcg during lactation.<sup>72</sup> The safe upper limit has been set at 1,000 mcg (1 mg) as a result of studies assessing TSH levels with supplementation. Iodine supplementation over this limit has been shown to potentially contribute to an underlying thyroid pathology in those with Hashimoto's thyroiditis, Graves' disease, or exacerbation of nodularities in euthyroid individuals if intake exceeds 20 mg iodine or iodide.<sup>73-75</sup>

Population studies have shown excessive iodine intake may increase the prevalence of autoimmune thyroiditis in animals and humans, increasing the risk of overt hypothyroidism.<sup>28</sup> Studies following individuals with elevated anti-thyroid antibody titers have shown that progression of hypothyroidism is correlated with increasing iodine intake.<sup>28</sup> 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.<sup>76</sup> 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.<sup>28</sup>

In addition to pre-existing thyroid pathologies exacerbated with iodine supplementation, excessive ingestion of iodine in medication (amiodarone) or water



## Review Article

contamination may contribute to goiter, hypothyroidism, elevated TSH levels, and ocular damage.<sup>77</sup> However, in studies referenced above by Eskin and Ghent,<sup>50</sup> which excluded patients with pre-existing autoimmune thyroid pathologies and used 3-6 mg molecular iodine for up to five years, no associated thyroid abnormalities were observed.<sup>50,52</sup>

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.<sup>78</sup> One French study found an inverse relationship between selenium status and thyroid volume.<sup>79</sup> 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 iodine supplementation in selenium-deficient individuals.<sup>80</sup>

### Conclusion

Iodine is an essential mineral for normal thyroid function, mammary gland development, and fetal and infant neurological growth. Iodine deficiency is epidemic in developing countries and parts of Europe. Recent evidence shows iodine deficiency is also strikingly common among adult women in the United States. The resulting risk for neurological impairment in fetal and infant brain development and potential for mammary dysplasia warrants closer evaluation of the general female population for iodine sufficiency. Also of concern is widespread contamination of food and water supplies with the known thyroid toxicant perchlorate, which blocks iodine uptake in the thyroid gland and mammary gland via competitive inhibition of the sodium iodide symporter protein. Perchlorate may also increase the risk for subclinical hypothyroidism in a subgroup of women with low urine iodine levels.

The safety and efficacy of molecular iodine as a therapeutic tool in the treatment of fibrocystic breast disease has been well documented. Animal studies using iodine as a therapeutic intervention in breast cancer have created an opportunity to investigate this therapy in human breast cancer trials. Iodine replacement in situations of diagnosed iodine deficiency must consider pre-existing thyroid disease and the possibility of co-existing selenium deficiency.

### References

1. Fuge R. Iodine deficiency: an ancient problem in a modern world. *Ambio* 2007;36:70-72.
2. Dunn JT. Seven deadly sins in confronting endemic iodine deficiency, and how to avoid them. *J Clin Endocrinol Metab* 1996;81:1332-1335.
3. Dunn JT, Delange F. Damaged reproduction: the most important consequence of iodine deficiency. *J Clin Endocrinol Metab* 2001;86:2360-2363.
4. DeLong GR, Leslie PW, Wang SH, et al. Effect on infant mortality of iodination of irrigation water in a severely iodine-deficient area of China. *Lancet* 1997;350:771-773.
5. Schaller RT Jr, Stevenson JK. Development of carcinoma of the thyroid in iodine-deficient mice. *Cancer* 1966;19:1063-1080.
6. Mellemegaard A, From G, Jorgensen T, et al. Cancer risk in individuals with benign thyroid disorders. *Thyroid* 1998;8:751-754.
7. Burgess JR, Dwyer T, McArdle K, et al. The changing incidence and spectrum of thyroid carcinoma in Tasmania (1978-1998) during a transition from iodine sufficiency to iodine deficiency. *J Clin Endocrinol Metab* 2000;85:1513-1517.
8. Franceschi S, Preston-Martin S, Dal Maso L, et al. A pooled analysis of case-control studies of thyroid cancer. IV. Benign thyroid diseases. *Cancer Causes Control* 1999;10:583-595.
9. Shakhtarin VV, Tsyb AF, Stepanenko VF, et al. Iodine deficiency, radiation dose, and the risk of thyroid cancer among children and adolescents in the Bryansk region of Russia following the Chernobyl power station accident. *Int J Epidemiol* 2003;32:584-591.
10. Stadel BV. Dietary iodine and risk of breast, endometrial, and ovarian cancer. *Lancet* 1976;1:890-891.
11. Dunn JT. What's happening to our iodine? *J Clin Endocrinol Metab* 1998;83:3398-3400.
12. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neurophysiological development of the child. *N Engl J Med* 1999;341:549-555.
13. Klein RZ, Sargent JD, Larsen PR, et al. Relation of severity of maternal hypothyroidism to cognitive development of offspring. *J Med Screen* 2001;8:18-20.
14. Marani L, Venturi S. Iodine and delayed immunity. *Minerva Med* 1986;77:805-809. [Article in Italian]
15. Gutekunst R. Iodine deficiency costs Germany over one billion dollars per year. *IDD Newsletter* 1993;9:29-31.

16. Hollowell JG, Staehling NW, Hannon WH, et al. Iodine nutrition in the United States. Trends and public health implications: iodine excretion data from National Health and Nutrition Examination Surveys I and III (1971-1974 and 1988-1994). *J Clin Endocrinol Metab* 1998;83:3401-3408.
17. Caldwell KL, Jones R, Hollowell JG. Urinary iodine concentration: United States National Health and Nutrition Examination Survey 2001-2002. *Thyroid* 2005;15:692-699.
18. WHO, UNICEF, and ICCIDD. *Assessment of the Iodine Deficiency Disorders and Monitoring their Elimination*. WHO/NHD/01.1. Geneva, Switzerland: World Health Organization; 2001:1-107.
19. Utiger RD. Maternal hypothyroidism and fetal development. *N Engl J Med* 1999;341:601-602.
20. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neurophysiological development of the child. *N Engl J Med* 1999;341:549-555.
21. Glinoe D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocr Rev* 1997;18:404-433.
22. Bazrafshan HR, Mohammadian S, Ordoorkhani A, et al. An assessment of urinary and breast milk iodine concentrations in lactating mothers from Gorgan, Iran, 2003. *Thyroid* 2005;15:1165-1168.
23. Pearce EN, Leung AM, Blount BC, et al. Breast milk iodine and perchlorate concentrations in lactating Boston-area women. *J Clin Endocrinol Metab* 2007;92:1673-1677.
24. Fuse Y, Saito N, Tsuchiya T, et al. Smaller thyroid gland volume with high urinary iodine excretion in Japanese schoolchildren: normative reference values in an iodine-sufficient area and comparison with the WHO/ICCIDD reference. *Thyroid* 2007;17:145-155.
25. Cann SA, van Netten JP, van Netten C. Hypothesis: iodine, selenium and the development of breast cancer. *Cancer Causes Controls* 2000;11:121-127.
26. Nagataki S, Shizume K, Nakao K. Thyroid function in chronic excess iodide ingestion: comparison of thyroidal absolute iodine uptake and degradation of thyroxine in euthyroid Japanese subjects. *J Clin Endocrinol Metab* 1967;27:638-647.
27. Konno N, Taguchi H, Miura K, et al. Serum thyrotropin concentration in apparently healthy adults, in relation to urinary iodide concentration. *Clin Chem* 1993;39:174-175.
28. Teng W, Shan Z, Teng X, et al. Effect of iodine intake on thyroid diseases in China. *N Engl J Med* 2006;354:2783-2793.
29. Pisani P, Parkin DM, Bray F, Ferlay J. Estimates of the worldwide mortality from 25 cancers in 1990. *Int J Cancer* 1999;83:18-29.
30. LeMarchand L, Kolonel LN, Nomura AM. Breast cancer survival among Hawaii, Japanese, and Caucasian women. Ten-year rates and survival by place of birth. *Am J Epidemiol* 1985;122:571-578.
31. Minami Y, Takano A, Okuno Y, et al. Trends in the incidence of female breast and cervical cancers in Miyagi Prefecture, Japan, 1959-1987. *Jpn J Cancer Res* 1996;87:10-17.
32. Konno N, Yuri K, Miura K, et al. Clinical evaluation of the iodide/creatinine ratio of casual urine samples as an index of daily iodide excretion in a population study. *Endocr J* 1993;40:163-169.
33. Spitzweg C, Harrington KJ, Pinke LA, et al. Clinical review 132: the sodium iodide symporter and its potential role in cancer therapy. *J Clin Endocrinol Metab* 2001;86:3327-3335.
34. Venturi S. Is there a role for iodine in breast diseases? *Breast* 2001;10:379-382.
35. Cocchi M, Venturi S. Iodide, antioxidant function and omega-6 and omega-3 fatty acids: a new hypothesis of biochemical cooperation? *Prog Nutr* 2000;2:15-19.
36. Many MC, Papadopolos C, Martin I, et al. Iodine induced cell damage in mouse hyperplastic thyroid is associated with lipid peroxidation. In: Gordon A, Gross J, Hennemann G, eds. *Progress in Thyroid Research*. New York, NY: Routledge; 1991:213-215.
37. Smyth PA. Role of iodine in antioxidant defence in thyroid and breast disease. *Biofactors* 2003;19:121-130.
38. Nolan LA, Windle RJ, Wood SA, et al. Chronic iodine deprivation attenuates stress-induced and diurnal variation in corticosterone secretion in female Wistar rats. *J Neuroendocrinol* 2000;12:1149-1159.
39. Thrall KD, Bull RJ. Differences in the distribution of iodine and iodide in the Sprague-Dawley rat. *Fundam Appl Toxicol* 1990;15:75-81.
40. Stolc V. Stimulation of iodoproteins and thyroxine formation in human leukocytes by phagocytosis. *Biochem Biophys Res Commun* 1971;45:159-166.
41. Andersen S, Pedersen KM, Pedersen IB, Laurberg P. Variations in urinary iodine excretion and thyroid function. A 1-year study in healthy men. *Eur J Endocrinol* 2001;144:461-465.
42. Thompson WW, Brailey AG, Thompson B, et al. Range of effective iodine dosage in exophthalmic goiter III. *Arch Int Med* 1930;45:430.
43. Crohn BNE. Absorption of compound solution of iodine from the gastrointestinal tract. *Arch Intern Med* 1932;49:950-956.
44. Gennaro AS. *Remington: The Science and Practice of Pharmacy*. 19th ed. Easton, PA: Mack Pub Co.; 1995:1267.
45. Bretthauer EW. Milk transfer comparisons of different chemical forms of radioiodine. *Health Phys* 1972;22:257-260.
46. Topper YJ, Freeman CS. Multiple hormone interactions in the developmental biology of the mammary gland. *Physiol Rev* 1980;60:1049-1106.

## Review Article

47. Aceves C, Rodon C, Ramirez-CI, et al. Mammary 5'deiodinase (5'D) during the breeding cycle of the rat: indirect evidence that 5'D type I is specific to the alveolar epithelium. *Endocrine* 1995;3:95-99.
48. Goehring C, Morabia A. Epidemiology of benign breast disease, with special attention to histologic types. *Epidemiol Rev* 1997;19:310-327.
49. Eskin BA, Grotkowski CE, Connolly CP, Ghent WR. Different tissue responses for iodine and iodide in rat thyroid and mammary glands. *Biol Trace Elem Res* 1995;49:9-19.
50. Ghent WR, Eskin BA, Low DA, Hill LP. Iodine replacement in fibrocystic disease of the breast. *Can J Surg* 1993;36:453-460.
51. Aceves C, Anguiano B, Delgado G. Is iodine a gatekeeper of the integrity of the mammary gland? *J Mammary Gland Biol Neoplasia* 2005;10:189-196.
52. Kessler JH. The effect of suprphysiologic levels of iodine on patients with cyclic mastalgia. *Breast J* 2004;10:328-336.
53. Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1997. *CA Cancer J Clin* 1997;47:5-27.
54. Ziegler RG, Hoover RN, Pike MC, et al. Migration patterns and breast cancer risk in Asian-American women. *J Natl Cancer Inst* 1993;85:1819-1827.
55. Smyth PP. The thyroid and breast cancer: a significant association? *Ann Med* 1997;29:189-191.
56. Goldman MB. Thyroid diseases and breast cancer. *Epidemiol Rev* 1990;12:16-28.
57. Turken O, NarIn Y, DemIrbas S, et al. Breast cancer in association with thyroid disorders. *Breast Cancer Res* 2003;5:R110-R113.
58. Smyth PP. Thyroid disease and breast cancer. *J Endocrinol Invest* 1993;16:396-401.
59. Kilbane MT, Ajjan RA, Weetman AP, et al. Tissue iodine content and serum-mediated 125I uptake-blocking activity in breast cancer. *J Clin Endocrinol Metab* 2000;85:1245-1250.
60. Eskin BA. Iodine and mammary cancer. *Adv Exp Med Biol* 1977;91:293-304.
61. Eskin BA, Parker JA, Bassett JG, George DL. Human breast uptake of radioactive iodine. *Obstet Gynecol* 1974;44:398-402.
62. Funahashi H, Imai T, Tanaka Y, et al. Suppressive effect of iodine on DMBA-induced breast tumor growth in the rat. *J Surg Oncol* 1996;61:209-213.
63. Garcia-Solis P, Alfaro Y, Anguiano B, et al. Inhibition of N-methyl-N-nitrosourea-induced mammary carcinogenesis by molecular iodine (I<sub>2</sub>) but not by iodide (I<sup>-</sup>) treatment. Evidence that I<sub>2</sub> prevents cancer promotion. *Mol Cell Endocrinol* 2005;236:49-57.
64. Greer MA, Goodman G, Pleus RC, Greer SE. Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans. *Environ Health Perspect* 2002;110:927-937.
65. Baier-Anderson C, Blount BC, Lakind JS, et al. Estimates of exposures to perchlorate from consumption of human milk, dairy milk and water, and comparison to current reference dose. *J Toxicol Environ Health A* 2006;69:319-330.
66. Sanchez CA, Krieger RI, Khandaker N, et al. Accumulation and perchlorate exposure potential of lettuce produced in the Lower Colorado River region. *J Agric Food Chem* 2005;53:5479-5486.
67. Sanchez CA, Krieger RI, Khandaker NR, et al. Potential perchlorate exposure from Citrus sp. irrigated with contaminated water. *Anal Chim Acta* 2006;567:33-38.
68. Snyder SA, Pleus RC, Vanderford BJ, Holady JC. Perchlorate and chlorate in dietary supplements and flavor enhancing ingredients. *Anal Chim Acta* 2006;567:26-32.
69. Wolff J. Perchlorate and the thyroid gland. *Pharmacol Rev* 1998;50:89-105.
70. Blount BC, Pirkle JL, Osterloh JD, et al. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. *Environ Health Perspect* 2006;114:1865-1871.
71. Cooper DS. Subclinical thyroid disease: consensus or conundrum? *Clin Endocrinol (Oxf)* 2004;60:410-412.
72. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 2004;291:228-238.
73. Dunn JT, Semigran MJ, Delange F. The prevention and management of iodine-induced hyperthyroidism and its cardiac features. *Thyroid* 1998;8:101-106.
74. Burgi H, Schaffner TH, Seiler JP. The toxicology of iodate: a review of the literature. *Thyroid* 2001;11:449-456.
75. Robison LM, Sylvester PW, Birkenfeld P, et al. Comparison of the effects of iodine and iodide on thyroid function in humans. *J Toxicol Environ Health A* 1998;55:93-106.
76. Markou K, Georgopoulos N, Kyriazopoulou V, Vagenakis AG. Iodine-induced hypothyroidism. *Thyroid* 2001;11:501-510.
77. Stanbury JB, Ermans AE, Bourdoux P, et al. Iodine-induced hyperthyroidism: occurrence and epidemiology. *Thyroid* 1998;8:83-100.
78. Giray B, Hincal F, Tezic T, et al. Status of selenium and antioxidant enzymes of goitrous children is lower than healthy controls and nongoitrous children with high iodine deficiency. *Biol Trace Elem Res* 2001;82:35-52.
79. Derumeaux H, Valeix P, Castetbon K, et al. Association of selenium with thyroid volume and echostructure in 35- to 60-year-old French adults. *Eur J Endocrinol* 2003;148:309-315.
80. Zimmermann MB, Kohrle J. The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. *Thyroid* 2002;12:867-878.