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Iodine-induced thyroid dysfunction

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Abstract

Purpose of review—To summarize the mechanisms of iodine-induced hypothyroidism and hyperthyroidism, identify the risk factors for thyroid dysfunction following an iodine load, and summarize the major sources of excess iodine exposure.

Recent findings—Excess iodine is generally well tolerated, but individuals with underlying thyroid disease or other risk factors may be susceptible to iodine-induced thyroid dysfunction following acute or chronic exposure. Sources of increased iodine exposure include the global public health efforts of iodine supplementation, the escalating use of iodinated contrast radiologic studies, amiodarone administration in vulnerable patients, excess seaweed consumption, and various miscellaneous sources.

Summary—Iodine-induced thyroid dysfunction may be subclinical or overt. Recognition of the association between iodine excess and iodine-induced hypothyroidism or hyperthyroidism is important in the differential diagnosis of patients who present without a known cause of thyroid dysfunction.

Keywords

hyperthyroidism; hypothyroidism; iodine; thyroid

INTRODUCTION

Iodine is required for the synthesis of the thyroid hormones. Guidelines by the US Institute of Medicine recommend a daily iodine intake of 150 µg and a tolerable upper level (the approximate threshold below which significant adverse effects are unlikely to occur in a healthy population) of 1100 µg in adults (Table 1) [1–3]. Excess iodine ingestion or exposure above this limit, which can occur via iodinated contrast agents in radiologic studies, iodine-rich medications, and the diet, is generally well tolerated. However, in certain susceptible individuals, the iodine load induces thyroid dysfunction.

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Conflicts of interest

There are no conflicts of interest.

IODINE EXCESS

In a series of elegant experiments during the 1940s, Wolff and Chaikoff [4] reported that in rats given large amounts of iodide intraperitoneally, there was a transient inhibition of thyroid hormone synthesis lasting approximately 24 h (acute Wolff–Chaikoff effect) resulting from increased intrathyroidal iodine stores [5]. Although the mechanism for the acute Wolff–Chaikoff effect remains incompletely understood, it has been hypothesized to be due to the generation of intrathyroidal iodolactones, iodoaldehydes, or iodolipids, which inhibit thyroid peroxidase activity [6,7]. Reduced intrathyroidal deiodinase activity induced by high concentrations of iodine may also contribute to decreased thyroid hormone synthesis [8].

With continued administration of iodide, normal thyroid hormone synthesis resumes (escape from or adaptation to the acute Wolff–Chaikoff effect) [4,9]. The mechanism responsible for the escape from the acute Wolff–Chaikoff effect was postulated in 1963, that following the temporary inhibition of thyroid hormone synthesis, there is an abrupt decrease in the active transport of iodine into the thyroid, thereby relieving the thyroid of excess intrathyroidal iodine levels [10]. Following the cloning of the sodium iodide symporter (NIS), which actively transports iodine into the thyroid, in 1996 by Dai *et al.* [11], the effect of excess iodine on thyroid function in the rat was revisited. In 1999, it was reported that in the normal rat thyroid, there was a marked decrease in NIS expression by 24 h following excess iodine administration [12]. This was accompanied by the disappearance of the inhibition of thyroid hormone synthesis and the resumption of normal thyroid function. Thus, it is likely that escape from the acute Wolff–Chaikoff effect is associated with decreases in NIS synthesis, resulting in a decrease in intrathyroidal iodine concentrations, and the resumption of normal thyroid hormone synthesis.

There are limited data which suggest that exposure to large concentrations of iodine may also decrease thyroid hormone release. In a study of 32 euthyroid patients given 250–1500 µg iodine daily for 14 days, small decreases in serum T4 and T3 levels, and a small compensatory rise in serum TSH to maintain normal thyroid function (all values within the normal range, thus suggesting an iodine effect on thyroid hormone release), in the group of patients given 1500 µg iodine daily [13]. This effect was unlikely due to the acute Wolff–Chaikoff effect, which is typically much more transient. Similar findings were reported in other studies of 12 euthyroid volunteers who performed daily vaginal douching with polyvinylpyrrolidone-iodine daily for 14 days [14] and of 20 euthyroid volunteers given 50–250 mg iodine daily for 13 days [15].

IODINE-INDUCED THYROID DYSFUNCTION

Failure to escape from the acute Wolff–Chaikoff effect may result in iodine-induced hypothyroidism, which may be transient or permanent, in susceptible individuals with predisposing risk factors (see below list).

1. Individuals with underlying thyroid disease

- a. euthyroid Graves' disease previously treated by radioactive iodine, thyroidectomy, or antithyroid drugs,
 - b. Hashimoto's thyroiditis,
 - c. euthyroid with a history of subacute thyroiditis,
 - d. euthyroid with a history of postpartum thyroiditis,
 - e. euthyroid with a history of type 2 amiodarone induced thyrotoxicosis,
 - f. euthyroid post hemithyroidectomy, and
 - g. euthyroid after interferon- α therapy.
2. The fetus *in utero* (secondary to transplacental passage of iodide).
 3. Individuals given other potential goitrogens (e.g. lithium).

It has been postulated that hypothyroidism may arise from iodine-induced inhibition of thyroid hormone synthesis and/or development of autoimmune thyroiditis [3].

In contrast, impaired autoregulation in other individuals may be associated with an increased risk of iodine-induced hyperthyroidism following an iodine load. The occurrence of thyrotoxicosis arising from excess iodine exposure is termed the J $\ddot{o}$ d–Basedow phenomenon, named after the word for iodine in German (J $\ddot{o}$ d) and the German physician, Karl Adolf van Basedow. Risk factors for this disorder include a history of nontoxic diffuse or nodular goiters, which occur most commonly in areas of iodine deficiency [16], although iodine-induced thyrotoxicosis among euthyroid patients with nodular goiter in iodine sufficient areas has also been described [17]. Withdrawal of the excess iodine source is usually associated with restoration of normal thyroid function.

IODINE SUPPLEMENTATION IN ENDEMIC AREAS

Iodine supplementation has been the primary mechanism of reducing the risks of iodine deficiency on a global scale over the course of the 20th century. Prophylaxis has historically been implemented through various public health approaches. These routes have included the oral administration or intramuscular injection of iodized oil, the iodination of the water supply, the irrigation of crops with iodinated water, the addition of iodine to animal fodder, the use of iodophors in the dairy industry, and the fortification of salt with iodine [3]. The World Health Organization recommends salt iodization at 20–40 mg iodine/kg [18], but universal salt iodization and other mechanisms of employing the food industry in iodine supplementation programs continue to vary by country [19]. Salt iodization in the USA began in the 1920s as a result of research led by David Marine and colleagues. Salt iodization in Canada and the USA is achieved with potassium iodide at 100 ppm (77 μ g iodine/g salt), concentrations that are higher than those of most other global programs (10–40 ppm) [20,21].

Increased incidences of both hypothyroidism and hyperthyroidism have been observed after the introduction of iodized salt in various countries. In particular, individuals living in regions of endemic iodine deficiency, in which goitrous disease is more common, may be at

risk for iodine-induced hyperthyroidism following salt iodization. Cerqueira *et al.* [22] reported a 46% increase in the incidence of antithyroid medication use during the first 4 years of salt fortification (1998–2001) in a previously moderately iodine-deficient region in Denmark. There was similarly an increased incidence of thyrotoxicosis among long-term iodized salt users in Bangladesh [23]. Conversely, fortification of salt increases the median urinary iodine concentration and decreases the overall prevalences of hypothyroidism and hyperthyroidism in a population, as was demonstrated in a retrospective Iranian study [24].

IODINATED CONTRAST MEDIA

The use of diagnostic radiologic studies, particularly computed tomography (CT) and coronary angiography, has been steadily rising in recent decades. As such, iodinated contrast agents have become an increasingly common source of supraphysiologic iodine exposure. A typical iodinated contrast study confers approximately 13 500 µg of free iodine and 15–60 g of bound iodine (as much as several hundred thousand times above the recommended daily intake) [1,2,25[■]]. Iodine-induced hypothyroidism and iodine-induced hyperthyroidism have been observed following iodinated contrast media use [26], particularly among the elderly [27].

In two small studies, subclinical hypothyroidism developed in four of 22 German patients [28] and in three of 56 US patients [29] 1 week following either coronary angiography or iodinated CT. Another Japanese report of 214 women (mean ± SD age 34.5 ± 4.6 years) described that those with pre-existing subclinical hypothyroidism were more likely to develop overt hypothyroidism than those who were euthyroid following hysterosalpingography (35 and 2%, respectively) [30].

Iodinated contrast use can also predispose individuals to iodine-induced hyperthyroidism, particularly in those with underlying nodular thyroid disease. A German study demonstrated that serum TSH concentrations remained decreased 42 days (although still within the normal range) following iodine exposure from endoscopic retrograde cholangiopancreatography (ERCP) among 70 patients [31]. Another case report described a 62-year-old Japanese woman who developed iodine-induced thyroid storm 5 h after an iodinated CT scan [32]. In a large recent case–control study spanning 20 years in the USA, a region that is considered generally iodine-sufficient, iodinated contrast media use was associated with increased incidences of hyperthyroidism and overt hypothyroidism (both occurring at a median of approximately 9 months following iodine exposure) [25[■]]. Pretreatment with short-term methimazole (which blocks thyroid hormone synthesis) or perchlorate (which blocks iodine uptake by the sodium-iodide symporter) has been proposed to decrease the risks of iodine-induced hyperthyroidism, particularly in Europe, but their use is not standard of care [33,34].

AMIODARONE

Amiodarone is a class III antiarrhythmic medication that is 37% iodine by weight and has a half-life of approximately 100 days. As usual doses range from 100 to 600 mg daily, individuals may receive 3–21 mg iodine daily as a result of amiodarone treatment [35].

Amiodarone-induced thyroid dysfunction is a particular concern in individuals with underlying thyroid disease [17] and is estimated to induce thyroid dysfunction in 15–20% of users [36]. Amiodarone-induced hypothyroidism appears to be more common in iodine-sufficient areas of the world, whereas amiodarone-induced hyperthyroidism is seen more frequently in iodine-deficient regions [37].

Individuals with Hashimoto's thyroiditis are at increased risk for amiodarone-induced hypothyroidism [38]. Some have proposed that serum TSH and thyroid antibodies be measured in all patients prior to amiodarone therapy [39]. Amiodarone has been shown to decrease NIS mRNA expression, which is reversible upon amiodarone withdrawal [40], secondary to escape from the acute Wolff–Chaikoff effect.

Amiodarone-induced thyrotoxicosis (AIT) has been categorized into type 1 and type 2 AIT [39]. Type 1 AIT is a form of iodine-induced thyrotoxicosis that is more prevalent among individuals with pre-existing thyroid disease living in regions of low iodine intake and occurs secondary to the Jöð-Basedow phenomenon. It is treated with a combination of antithyroid medications, beta-blockade, and if available, perchlorate, to decrease the entrance of iodine into the thyroid. Type 2 AIT is a destructive thyroiditis in which thyrotoxicosis results from thyroid hormone release from the gland. It usually occurs in patients with no history of thyroid disease; the prevalence of type 2 AIT in iodine-deficient regions is estimated to be 5–10% and occurs in a male-to-female ratio of 3:1 [16]. Treatment is primarily corticosteroids and symptomatic relief. The ability to distinguish between the two types of AIT is often challenging, and a mixed presentation may occur in some individuals [41].

SEAWEED CONSUMPTION

Dietary seaweed ingestion in large amounts represents a potential source of excess iodine exposure in many parts of the world. In particular, seaweed intake is common in Asia [42,43], where it is a frequent component of the daily diet and among women during the postpartum period, who consume seaweed soup to promote breastmilk supply [44,45]. In a US study, 36 euthyroid individuals were administered low-dose and high-dose kelp capsules daily for 4 weeks [46]. Although there were significant increases in serum TSH compared with baseline levels (from 1.5 to 2.1 mIU/l for the low-dose group and 1.8 to 2.5 mIU/l for the high-dose group), free thyroxine concentrations and basal metabolic rates remained unchanged. Subsequent data have demonstrated that the iodine content of seaweed can vary widely. In a survey of 12 species of seaweed harvested from the USA, Canada, Tasmania, and Namibia, iodine concentrations ranged from 16 to 8165 µg/g [47]. Others have reported the association between kelp ingestion and mild-to-moderate increases in serum TSH concentrations. Among euthyroid Japanese adults consuming 15 or 30 g of Kombu daily, serum TSH increased from 1.54 and 2.15 to 4.31 and 3.09 mIU/L, respectively, by the end of the 7–10-day study [48]. Similarly, Key [49] reported that geometric serum TSH was 47% higher among 48 British kelp-consuming vegan men compared with 53 omnivores.

The risk of iodine-induced hyperthyroidism is also increased among individuals who consume large amounts of seaweed regularly, particularly in those residing in areas of iodine

deficiency or in those with nodular goiters. One report described the diagnosis of thyroid storm in a 39-year-old German woman with underlying thyromegaly following 4 weeks of drinking a kelp-containing tea [50]. In Australia, thyrotoxicosis was reported in eight adults associated with drinking soy milk manufactured with Kombu seaweed [51].

MISCELLANEOUS SOURCES OF EXCESS IODINE EXPOSURE

Excess iodine ingestion or exposure secondary to other sources are also associated with an increased risk of thyroid dysfunction. Iodine is present in various expectorants, vitamins and supplements, food preservatives, prescribed medications, parenteral preparations, and topical antiseptics [17]. We recently reported a patient with iodine-induced thyrotoxicosis, which developed in a paraplegic woman secondary to several years of topical povidone-iodine application used with her urinary self-catheterization several times daily [52[■]]. American Pearce Corp workers in Niger were found to have small increases in serum TSH (mean 4.9 mIU/l) associated with a faulty iodine-based water filtration system during the 1990s, which normalized following withdrawal of the chronic iodine excess (mean TSH 1.8 mIU/l) [53]. Significant mild increases in serum TSH, with values remaining within the normal range, have been reported following the use of iodinated mouthwash [54] and iodinated vaginal douches [12]. Reversible elevations in serum TSH have also been observed among US astronauts drinking iodinated water [55] and individuals ingesting water purified by iodinated tablets [56].

CONCLUSION

Iodine is a micronutrient essential for the production of thyroid hormones. In the USA, usual daily intake is 150 µg iodine for nonpregnant, non-lactating adults, and iodine exposure or ingestion above this threshold is generally well tolerated. However, particularly among individuals with pre-existing thyroid disease or other risk factors, iodine-induced hypothyroidism or hyperthyroidism can result from acute or chronic excess iodine exposure. Thyroid dysfunction may be either subclinical or overt, and the source of iodine excess may not be easily recognizable.

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- of outstanding interest Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 433).

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KEY POINTS

- Iodine intake is recommended to be 150 µg per day in nonpregnant, nonlactating adults.
- The tolerable upper limit for iodine is 1100 µg per day, but excess ingestion or exposure above this threshold is generally well tolerated.
- Certain individuals, particularly those with pre-existing thyroid disease, are at risk for iodine-induced hypothyroidism or hyperthyroidism following an iodine load.
- Sources of iodine excess are varied and are important in the understanding of mild or overt thyroid dysfunction associated with iodine excess.

Table 1Tolerable upper limits of iodine (μg per day)

Age group	European Commission/Scientific Committee on Food [2]	US Institute of Medicine [1]
1–3 years old	200	200
4–6 years old	250	300
7–10 years old	300	300
11–14 years old	450	300
15–17 years old	500	900
Adults	600	1100
Pregnancy	600	1100

Adapted with permission from [3].