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Prevention and Treatment of Iodine-Induced Thyrotoxicosis

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Abstract

Etiologies of thyrotoxicosis are diverse, one of them being caused by iodine-induced hyperthyroidism. The clinical signs of the disease are the classical signs of any form of hyperthyroidism, but the treatment of the different forms presents particular aspects. This chapter reviews the risk factors for thyrotoxicosis following an excess iodine load, pointing out the major sources of iodine: supplementation programs, dietary intake, nutritional supplements, iodine-containing contrast medium, and amiodarone. Prevention of iodine-induced thyrotoxicosis is critical in geriatric patients who often have thyroid nodular disease, underlying heart conditions, and therefore, hyperthyroidism may be more difficult to detect clinically. Treatment of iodine-induced thyrotoxicosis could be performed with thioamides or perchlorate prior to the administration of an iodine containing product (e.g., food, dietary supplements, and contrast media). On the other hand, amiodarone-induced thyrotoxicosis needs further attention and a close collaboration between cardiology and endocrinology to overcome complications, but individualization of the therapy should be undertaken. Based on the specific features of amiodarone-induced thyrotoxicosis thioamides, perchlorate, high-dose glucocorticoids, or radioiodine therapy may be considered for an optimal therapeutic intervention.

Keywords: iodine deficiency, iodine supplementation, dietary iodine, iodine containing contrast media, amiodarone, thyrotoxicosis, thioamides, perchlorate, glucocorticoids

1. Introduction

Thyroxine (T₄) and 3,5,3'-triiodothyronine (T₃) are the two thyroid hormones, each of them containing two iodine atoms on their inner (tyrosine) ring. The difference between them is that T₃ has only one iodine atom on its outer (phenyl) ring, whereas T₄ has two. Synthesis of reasonable quantities of thyroid hormones requires adequate iodine intake to allow sufficient thyroidal uptake. The World Health Organization (WHO) recommendation for daily intake of iodine is 90 µg for infants and children up to 5 years, 120 µg for children 6–12 years, 150 µg for children ≥12 years and adults, and 250 µg for pregnant and lactating women [1]. The worldwide variability of the dietary intake of iodine depends on the iodine content of the soil, water, and the dietary practice. After Iodine Global Network data [2], the iodine uptake in Romania in 2004 was considered adequate, the median urinary iodine content (MUIC, normal value ≥100 µg/L) being 102 µg/L in school-aged children, but in some geographic regions, such as mountainous villages of Mureş County, a mild iodine deficiency was detected [3]. The MUIC value (68 µg/L) in

pregnant women confirmed that iodine intake in this population of Romania is insufficient [2]. Administration of supplemental iodine to subjects with iodine deficiency goiter can result in iodine-induced hyperthyroidism in nonpregnant persons [4], but iodine supplementation in mild and moderate iodine-deficient pregnant women lowers thyroid hormone level [5].

2. Risk factors for thyrotoxicosis following an iodine load

2.1 Normal adaptation to iodine intake

Thyroid hormone secretion is regulated by two mechanisms: a central hypothalamic-pituitary and a local autoregulatory mechanism depending on the iodine content of the gland. The autoregulatory mechanism reduces the fluctuation of thyroid hormone secretion in the event of sudden changes in iodine supply. Iodine excess inhibits iodide accumulation, organogenesis, tyrosine binding, and thyroid hormone release. However, this inhibitory effect (Wolff-Chaikoff effect) lasts only 10–14 days, followed by the so-called escape phenomenon [6].

Iodine is a micronutrient that is present in foods (e.g., seaweed, seafood, dairy- and grain products, eggs), added to processed foods as iodized salt, and available as a dietary supplement, but the iodine concentration of water and foods is highly variable. Studies of iodine balance, based on the assumption that a healthy subject on an adequate diet maintains equilibrium between iodine intake and losses, have provided highly variable results, thus, cannot be used for setting daily reference values [7]. When iodine losses exceed intake (negative balance), deposits are progressively depleted resulting in biological signs and in clinical symptoms of deficiency. The physiological response to iodine deficiency is the preferential synthesis of T3 instead of T4. Long-term follow-up suggests that chronic iodine deficiency may lead to insufficient thyroid function (hypothyroidism) associated with a compensatory thyroid hypertrophy/hyperplasia with goiter (enlarged thyroid gland). Myxedema, observed with severe iodine deficiency, also results from hormone deficiency and is associated with reduced metabolic rate, weight gain, swollen face, edemas, hypothermia, and mental slowness. In euthyroid subjects, the plasma concentration of iodine (inorganic and organic iodine) ranged from 40 to 80 µg/L. Concentrations between 80 and 250 µg/L are associated with hyperthyroidism, whereas concentrations above 250 µg/L usually result from iodine overload with iodinated drugs [8, 9]. The thyroid gland, being highly flexible, is able to concentrate iodine up to 80-fold, and in most healthy adults, no clinical signs will appear at an iodine intake of up to 2 g/day [10]. However, if the adaptation to high iodine intake fails, various diseases occur. Chronic excessive iodine supply can also lead to goiter [11] and may accelerate the development of subclinical thyroid disorders to overt hypothyroidism or hyperthyroidism, increase the incidence of autoimmune thyroiditis, and increase the risk of thyroid cancer [10, 12, 13]. Recently, high iodine intake (exceeding 160 µg daily) was suggested as a risk factor for type 2 diabetes [14].

2.2 Iodine-induced thyrotoxicosis mechanisms

Iodine-induced hyperthyroidism (thyrotoxicosis) or Jod-Basedow effect is most frequently observed following iodine supplementation in individuals who had previously experienced severe iodine deficiency [15, 16]. A plausible explanation of this phenomenon can be the thyroid stimulating hormone (TSH) hyperstimulation of the thyroid gland, which may occur as an adaptive response to the iodine-deficient conditions and results in autonomous growth and function of thyrocyte

clusters. When iodine intake increases, these nodules may synthesize an excessive amount of thyroid hormones [10]. The mechanism consists of escape phenomenon when high doses of iodine are used for thyroid hormone synthesis, which can lead to severe thyrotoxicosis. The high iodine containing amiodarone and its metabolite N-desethylamiodarone (DEA) affects T cell function by increasing the number of both helper and cytotoxic T lymphocytes and induces destructive thyroiditis, resulting in transient thyrotoxicosis, as suggested by clinical, histological, and in vitro studies [17–19].

High levels of organic iodide (thyroid hormones) also reduce the accumulation of iodide ions in the thyroid gland inhibiting the TSH secretion.

The effects of iodine administration differ in patients with pre-existing thyroid pathology from those in healthy subjects and depend upon the underlying disease process.

3. Major sources of increased iodine exposure: iodine supplementation, dietary iodine, iodine-containing contrast media, amiodarone, and the clinical forms of amiodarone-induced thyrotoxicosis

3.1 Iodine supplementation

The assessment of iodine deficiency can be accomplished by assessing the prevalence and severity of goiter, by testing the excretion of iodine in urine, and by determining hormonal levels (e.g., TSH, FT4). When used alone, neither of these are sufficiently sensitive and specific to measure iodine deficiency of a population, but urinary iodine remains the index of choice in the monitoring of iodine supplementation programmes. The most successful method of intervention for iodine deficiency control is salt iodization, iodine being added to salt as potassium iodide (KI), potassium iodate (KIO₃), or sodium iodide (NaI). Due to the high prevalence of hypertension and cardiovascular diseases, many countries proposed to promote the reduction of salt intake to 5 g/day (<2 g of sodium), so complementary measures are needed in order to tackle iodine deficiency [20]. But iodine also binds to fatty acids, so iodine oil can also be given orally or intravenously to severely iodine-deficient patients in the short term. Nascent iodine is like the precursor form of iodine, which converts into thyroid hormones. The human body can recognize and assimilate this form more easily than potassium salt. Lugol's solution is a widely used commercial iodine source, which contains elemental iodine and potassium iodide also. If someone consumes high quantities of iodine-rich foods (e.g., marine food, kelp), the use of iodized salt or iodinated water may increase iodine levels above the safe upper level as recommended by WHO. Individuals, who consume large amounts of seaweed regularly, are also exposed to the risk of iodine-induced hyperthyroidism [21, 22]. Several reports are available describing diet-induced thyrotoxicosis in patients consuming seaweed-containing foods or beverages [23]. Risk factors for iodine-induced hyperthyroidism include nontoxic or diffuse nodular goiter, latent Graves' disease, and long-standing iodine deficiency [24].

3.2 Dietary supplements

Most dietary supplements, as well as food and water, contains iodine as salts: sodium iodide, sodium iodate, potassium iodide, and potassium iodate. Different solid dosage forms of potassium iodide are available, but around 20% is assimilated from inorganic forms of iodine into the body [25]. Iodine is also present in most multivitamin/mineral supplements. Some case reports described that previously

Nutritional supplement	Iodine content per serving (μg)	% RDA iodine per serving (%)
Natural Living Iodine Plus-2 [®]	12500	8333
Terry Naturally [®] (Europharma) Tri-Iodine [®]	25000, 12500, 6250, 3000	16667, 8333, 4167, 2000
Oradix StemDetox [™]	5000	3333
Survival shield X-2, Detoxadine [®] (nascent iodine)	1950	1300
Dr. Mercola Iodine	1500, 500	1000, 333
Life Extension [®] sea iodine	1000	667

Table 1.

Commercially available nutritional supplements with iodine content exceeding the daily intake recommended by WHO (RDA—recommended daily allowances).

euthyroid patients taking nutritional supplements developed iodine-induced hyperthyroidism [26–28]. The iodine content of dietary supplements shows high variability; some supplements may contain up to 160-fold of the recommended daily intake (**Table 1**). Short-term increase of basal and poststimulation TSH was described even in euthyroid patients administering dietary supplements with kelp [29, 30].

3.3 Iodine-containing contrast media

Iodinated contrast media (ICM) is given for computed tomography (CT), angiography, myelography, and arthrogram. The route of administration could be systemic as i.v, i.a., oral, rectal, and local. The pharmacokinetics of all currently available ICMs is similar. The half-life of ICM in normal renal function subjects is approximately 2 hours. Thus, approximately 20 hours are required for the total excretion of the administered ICM [31]. Referring to their iodine content and osmolarity, the contrast media are divided into ionic ICM with high osmolarity (1500–2000 mOsm/kg) or nonionic ICM with low and iso-osmolarity (600–1000 mOsm/kg). A list of iodinated contrast agents available in Romania and their molecular properties can be found in **Table 2**.

The safety profile of the systemic administered nonionic low- or iso-osmolar contrast currently in use is 5- to 10-fold better than the ionic high-osmolar agents [32, 33]. The ratio of iodine atoms to the number of contrast particles in low-osmolar solution is higher than compared with high osmolar ICM and hence have a greater concentration of iodine than the high osmolar [32]. In both low and high osmolar ICM, the iodine content is far greater than the recommended daily allowance. Patients generally are given 50 and 100 mL of contrast per CT scan; however, it is essential to know that not all CT scans require contrast media administration (see **Table 3**) [31, 33–35].

Higher doses of ICM may be required for invasive procedures such as cardiac catheterization. Typical doses for CT scans provide 2500–5000 μg of bioavailable free iodine and 15–37 g of total iodine [36]. Nonbioavailable iodine may be liberated to free iodide, particularly with increased half-times in the body (i.e., impaired kidney function) [35, 36]. After ICM administration, iodine deposits remain elevated for up to 4–8 weeks in patients with healthy thyroid. The urinary iodine excretion increased by 300–400% from baseline to peak levels after 1.1 week and normalized by 5.2 weeks following ICM administration [37].

After exposure to the iodine-containing contrast agent, the most rapid (hours to days) effect of pharmacologic doses of iodine is the Wolff-Chaikoff effect. The

Nonionic ICM	Iodine content, mg/mL	Osmolarity
Watersoluble, nephrotropic X-ray contrast media		
Iobitridol	300, 350	Low
Iodixanol	270, 320	Low
Iohexol	240, 300, 350	Low
Iomeprol	300, 350, 400	Low
Iopamidol	300, 370	Low
Iopromide	300, 370	Low
Ioversol	240, 300, 320, 350	Low
Non-watersoluble		
Ethiodized oil	480	

Table 2.
 The iodine content of nonionic iodinated contrast media (ICM) and their molecular properties.

CT type	Contrast indicated	Contrast not indicated
Head	Neoplasm, meningitis, encephalitis, focal neurologic deficits, skull base disorders, orbital and vision disorders, pituitary imaging, complicated sinonasal disease, seizures, cerebral angiography	Head trauma, acute stroke, intracranial hemorrhage
Cervical	Cervical mass or lymphadenopathy, suspected tumor or infection, abnormalities of cranial nerves X, XI, and XII, brachial plexopathy	Trauma unless arterial injury is a possibility or the mechanism of injury is penetrating
Cardiothoracic	Heart and thoracic vessels, trauma, staging primary thoracic neoplasms	Coronary calcium scoring, pulmonary parenchymal evaluation lymph node evaluation
Abdominopelvic	Virtually all other gastrointestinal, hepatopancreaticobiliary, genitourinary, gynecologic indications	Colonography, renal stone evaluation, extraparenchymal lymphoma
Musculoskeletal	Evaluation of soft tissue masses and suspected septic arthritis or infected prostheses	Extremities and spine
CT angiography	Evaluating the lumen of an artery, vein, or a pseudoaneurysm and to assess for end-organ ischemia outside the brain or lung to detect active bleeding	Monitoring a known aneurysm for growth or for detection of a hematoma

Table 3.
 Indications of contrast enhancement in CT imaging.

mechanism for this acute effect is partially explained by the generation of iodolactones, iodoaldehydes, and/or iodolipids, which inhibit thyroid peroxidase activity, necessary for thyroid hormone synthesis [37]. The decrease of thyroglobulin proteolysis resulting in reduced thyroid hormone secretion also may be contributing to the ICM-induced Wolff-Chaikoff effect. The diminished serum T4 and T3 concentrations temporarily increased the serum concentrations of TSH, in some cases above the normal range. The phenomenon is transient in euthyroid adult patients and does not typically determine permanent hypothyroidism [38].

ICM use could lead to thyroid dysfunction, namely to hypo- and hyperthyroidism. Iodine excess-induced hypothyroidism appears when the thyroid fails to escape from the acute Wolff-Chaikoff effect. It occurs in patients with a wide variety of underlying thyroid abnormalities, including Hashimoto's thyroiditis, previously treated Graves' disease, history of thyroid lobectomy, postpartum lymphocytic thyroiditis, interferon therapy, or type 2 amiodarone-induced thyrotoxicosis [12, 39, 40]. Not only the previous thyroid disorder but also the age of the patients is a contributing factor in hypothyroidism development. A systematic review evidenced that hospitalized neonates, especially premature infants exposed to iodinated contrast media, are at increased risk for development of hypothyroidism [41]. It could be hypothesized that hypothyroidism in this case to be partially secondary to an immature thyroid gland and an exaggerated Wolff-Chaikoff effect. Older age patients are also at high risk of developing hypothyroidism after ICM exposure, as reported in a study including the Asian population [42].

Patients with one exposure to ICM showed the highest risk of thyroid dysfunction compared with non-ICM exposure and a correlation was still found between the frequency of ICM exposure and the risk of hypothyroidism [42]. Conflicting data appear regarding to the time of onset of hypothyroidism after ICM administration: Rhee et al. [43] showed that the median time interval until the occurrence of hypothyroidism was 1 year, but Kornelius et al. [42] reported that hypothyroidism may develop 2.1 years after ICM exposure.

ICM-induced hyperthyroidism rarely occurs in individuals without prior thyroid dysfunction. Previously existent thyroid diseases, such as nodular goiter, Graves' disease, and long-standing iodine deficiency followed by thyroid autonomy, were reported to be associated with a higher risk of hyperthyroidism after ICM exposure [4, 13, 24, 36, 42]. The mechanism of ICM-induced hyperthyroidism involves impairment of the acute Wolff-Chaikoff effect due to rapid iodine excess and influx into the thyroid gland. Excess iodine intake will result in transient or permanent hyperthyroidism [13, 24, 42]. Kornelius et al. [42] found in their study a 22% increased risk of hyperthyroidism after ICM administration. Older patients (between 20 and 60 years) presented a more than twofold increased risk of hyperthyroidism compared with younger patients (less than 20 years old). The number of ICM exposures did not increase the risk of hyperthyroidism. It could be hypothesized that the "stunning effect" plays a certain role in hyperthyroidism, involving a diminished absorption of excess iodine in patients with repeated iodine exposure.

3.4 Amiodarone

3.4.1 Amiodarone pharmacology

Amiodarone is a class III antiarrhythmic agent, having short- and long-term actions on multiple molecular levels [44]. Its molecular structure resembles T₃. However, amiodarone can alter thyroid function (inducing both hypo- and hyperthyroidism), which is due to amiodarone's high iodine content and its direct toxic effect on the thyroid follicle cells. Amiodarone is a benzofuran derivative with great lipophilicity, which is extensively distributed in adipose tissue, cardiac and skeletal muscle, liver, lung, and the thyroid. During its liver metabolism, approximately 6 mg of inorganic iodine per 200 mg of amiodarone ingested is released into the systemic circulation [45]. The average iodine content in Romanian diet is approximately 50–75 µg/day [3, 46, 47]. Thus, 6 mg of iodine markedly increases the daily iodine load. Amiodarone elimination from the body occurs with a half-life of approximately 55–100 days. The long half-life of both amiodarone and his active

metabolite, DEA, contributes to his toxicity. For a therapeutic effect, a plasma concentration between 0.5 and 2.5 µg/mL is required; however, serum levels do not correlate well with efficacy or with adverse effects [45, 48–50].

3.4.2 Amiodarone and the thyroid

The effects of amiodarone on thyroid function can be divided into those effects that are due to iodine and those effects that are intrinsic properties of the drug.

3.4.2.1 Effects due to iodine

After chronic amiodarone administration, the thyroid dysfunctions may occur in 5–22% of the patients. Risk factors for the development of thyroid disease include not only treatment duration and cumulative amiodarone dose but also age, gender, pre-existing thyroid pathology, and associated nonthyroid conditions [51–53]. The normal autoregulation process of thyroid prevents normal individuals from becoming hyperthyroid after exposure to the high iodine content substances. When intrathyroidal iodine concentrations reach a critically high level, iodine transport and thyroid hormone synthesis are transiently inhibited until intrathyroidal iodine stores return to physiological levels (see the Wolff-Chaikoff effect). Patients with underlying thyroid pathology, however, have defects in autoregulation of iodine: for example, in autoimmune thyroid disease exists a “fail to escape” from the Wolff-Chaikoff effect. The result is the development of goiter and hypothyroidism in Hashimoto’s disease. Patients with areas of autonomous function within a nodular goiter do not autoregulate iodine and the addition of more substrate may result in excessive thyroid hormone synthesis and thyrotoxicosis (see Iod-Basedow) [13, 54, 55].

3.4.2.2 Intrinsic drug effects

Amiodarone inhibits peripheral deiodinase (outer ring 5'-monodeiodination of T₄), thus decreasing T₃ production and increasing T₄ level; reverse T₃ (rT₃) accumulates since it is not metabolized to T₂ [4, 56, 57]; amiodarone and, particularly, the metabolite DEA block T₃-receptor binding to nuclear receptors [58] and decrease the expression of some thyroid hormone-related genes [59]; amiodarone may have a direct cytotoxic effect on thyroid follicular structures, which results in a destructive thyroiditis [60]. Martino et al. described marked distortion of thyroid follicle architecture, necrosis, apoptosis, inclusion bodies, lipofuscinogenesis, markedly dilated endoplasmic reticulum, and macrophage infiltration after amiodarone [19]. The role of the pre-existing autoimmune process is widely debated, due to the conflicting results of the retrospective study data [17, 18, 55]. Even if amiodarone does not induce de novo autoimmune thyroid disease, by the direct cytotoxic effect, it may cause the release of pre-existing autoantibodies and thus worsen destructive thyroiditis. In a study [61], it was described that in women the prolonged amiodarone treatment (for over 2 years) increased the antithyroid peroxidase titer.

3.4.3 Risk of thyrotoxicosis after amiodarone administration

Predisposing factors for amiodarone-induced thyrotoxicosis include environmental factors such as dietary iodine (deficiency), as well as intrinsic factors such as pre-existing thyroid pathology. Depending on these factors, a great variability

exists regarding the incidence of amiodarone-induced thyroid dysfunction ranges (5–22%) [51, 52, 62, 63].

Dietary iodine intake affects an individual's risk of amiodarone-induced thyroid dysfunction: in iodine-deficient areas, amiodarone-induced thyrotoxicosis (AIT) appears to be more common than hypothyroidism [64], whereas in iodine-sufficient areas, amiodarone-induced hypothyroidism is more common than hyperthyroidism [19]. The incidence of reported AIT in different studies varies but remains within the range of 5–10% in most studies [51, 52, 63]. As was reported in a previous study from the UK, AIT appears more frequently in men than in women [65], but the time of onset of AIT is unpredictable. It can occur at almost any time throughout the course of amiodarone treatment and last for as long as 6–9 months after treatment withdrawal, almost certainly because of the drug's long half-life and associated iodine load [66]. One study illustrates the importance of the underlying thyroid status near the dietary iodine intake in relation to the risk of developing amiodarone-induced thyroid dysfunction. In Worcester, Massachusetts, an area with iodine sufficiency and a high prevalence of autoimmune thyroid disease, amiodarone was associated with a 2% rate of hyperthyroidism. In contrast, in Pisa, Italy, an area of borderline iodine intake and a high prevalence of nodular goiter, amiodarone was associated with 9.6% rate of hyperthyroidism [67].

The clinical effects of amiodarone on thyroid function in any individual are dependent upon the underlying status of that individual's thyroid gland. In euthyroid individuals receiving amiodarone, acute changes in thyroid function tests include [68, 69]:

- Serum total T4 and free T4 concentrations rise by 20–40% during the first month of therapy.
- Serum T3 concentrations decrease by up to 30% within the first few weeks of therapy.
- Serum rT3 concentrations increase by 20% soon after the initiation of therapy.
- Serum TSH concentration usually rises slightly after the initiation of treatment and may exceed the upper limit of normal.

After 3–6 months of therapy, a steady state is reached in most patients who were euthyroid at baseline:

- Serum TSH concentration normalizes.
- Serum total T4, free T4, and rT3 concentrations remain slightly elevated or in the upper normal range.
- Serum T3 concentrations remain in the low normal range.

Amiodarone may also cause destructive thyroiditis with transient thyrotoxicosis followed by hypothyroidism in patients without underlying thyroid disease [60].

Abnormal thyroid process: in patients with underlying multinodular goiter or latent Graves' disease, hyperthyroidism (increased synthesis of T4 and T3) may occur. The excess iodine from the amiodarone provides increased substrate, resulting in enhanced thyroid hormone production.

3.4.4 Clinical forms of amiodarone-induced hyperthyroidism

Three types of AIT can be distinguished. In type 1 AIT, thyroid hormone synthesis is increased, whereas in type 2 there is an excess release of T4 and T3 from the preformed thyroid hormones, due to destructive thyroiditis. Type 3 AIT is a mixed form, existing as an overlapping condition between type 1 and type 2 AIT. These types differ in their pathogenesis, clinical or paraclinical signs, and management [63].

The risk of either type increases with higher cumulative doses or reintroduction of amiodarone [53, 70].

The distribution of AIT by type (1 or 2) varies by geographical region. This is thought to be primarily due to differences in dietary iodine intake. In iodine-deficient regions, as some geographical zones were in Romania before universal salt iodization [3], AIT occurs in approximately 10–12% of patients with type 1 AIT usually predominating [64, 67]. However, the distribution of cases by type may be changing, as illustrated in a report of 215 consecutive patients with AIT seen at a single institution in Italy over 26 years [71]. In 1980 compared with 2006, 2 of 6 (40%) versus 12 of 14 (86%) of new AIT cases were type 2. Possible explanations for this observation include improved dietary iodine intake in the region and the avoidance of amiodarone use in case of previously diagnosed thyroid disease. Our unpublished data from a study conducted in a single institute (Endocrinology Clinic, Târgu Mureş, Romania) in two different periods, which included 5 years, similarly show a moderate increase of type 2 AIT after the introduction of universal salt iodization (governmental decision no. 586/5 June 2002; see **Table 4**).

Clinical signs of AIT are classical thyrotoxicosis symptoms such as unexplained weight loss, proximal myopathy, restlessness, heat intolerance, low-grade fever, or exacerbation of tachyarrhythmia, heart failure, or angina pectoris; however, the adrenergic manifestations of amiodarone-induced hyperthyroidism are often masked because of its distinct antiadrenergic properties and impairment of conversion of T4 to T3 [68, 72]. Patients with amiodarone-induced hyperthyroidism have a threefold higher rate of major adverse cardiovascular events (mostly ventricular arrhythmias) compared with euthyroid controls [73]. The presence of severe left ventricular dysfunction, especially in older patients with AIT, may be associated with increased mortality [74].

Differentiating the two types of AIT is critical since therapy differs. However, the distinction may be difficult using clinical criteria, partly because some patients may have a mixture of both mechanisms, presenting the type 3 (type 1 + type 2) AIT. Thyroid function tests (TSH, T4 and T3 plasma levels) do not help to distinguish type 1 AIT (hyperthyroidism) from type 2 AIT (transient thyrotoxicosis).

Type 1 AIT appears usually early after amiodarone introduction (3–20 months after exposure) [19, 66, 71]. It is characterized by hyperfunctional thyroid tissue with elevated blood flow on color Doppler [75, 76]. Furthermore, the enlarged or nodular thyroid tissue fixes either on 24-hour ¹²³I-scan or on 99 mTc-SestaMIBI radio isotope scan despite the daily ingestion of 6 mg or more bioavailable iodine [77, 78].

Study period	Type 1 AIT/total patients	Type 2 AIT/total patients	Type 3 AIT/total patients
1994–1998	4/7 (57%)	1/7 (14%)	2/7 (29%)
2001–2005	17/38 (45%)	9/38 (24%)	12/38 (31%)

Table 4. Distribution of AIT types in patients of the Endocrinology Clinic, Târgu Mureş, Romania, in two study periods (1994–1998 and 2001–2005).

	Type 1 AIT	Type 2 AIT
Pre-existing thyroid disease	Yes	No
Pathophysiology	Iodine overload	Destruction/inflammation
Ultrasound findings	Goiter/nodule(s)	Normal
Color flow Doppler	Increased or vascularity	Reduced or absent vascularity
Radio iodine uptake (I123-Scan)/ SestaMIBI-Scan	Normal or increased	Absent

Table 5. Characteristics of type 1 and type 2 amiodarone-induced thyrotoxicosis (AIT—amiodarone-induced thyrotoxicosis).

Type 2 AIT is a destructive thyroiditis which onset time is after 20–30 months of amiodarone introduction. It appears in patients with apparently normal thyroid morphology and is due to the massive release of thyroid hormones. The mechanism is similar to that of subacute thyroiditis, but the thyrotoxicosis is usually less severe and could spontaneously resolve in some cases [79]. The features of the two types of AIT are presented in **Table 5**.

However, interpretations of color flow Doppler sonogram in amiodarone-associated hyperthyroidism require an experienced sonographer, and other markers for differential diagnosis were also sought. In two studies, serum interleukin-6 concentrations were higher in patients with type 2 AIT [80, 81]. In a third study, interleukin-6 concentrations were not useful for distinguishing type 1 from type 2 AIT [76].

4. Prevention and treatment of iodine-induced thyrotoxicosis

Preventing therapy for iodine-induced hyperthyroidism is not generally recommended. However, older patients with known multinodular goiter and/or subclinical hyperthyroidism should be told of the risk for iodine-induced hyperthyroidism, and alternatives to contrast-enhanced CT scanning should be considered when appropriate (e.g., noncontrast CT, magnetic resonance imaging). Iodine-induced hyperthyroidism is particularly important in geriatric patients for several reasons: (1) the prevalence of thyroid nodular disease is higher in older patients than in younger patients, (2) the hyperthyroidism may be more difficult to detect clinically, (3) apathetic hyperthyroidism often being present, and (4) older adults more often have underlying heart disease [21]. In high-risk patients (older, history of multinodular goiter with autonomy), treatment with a thioamide or perchlorate prior to the administration of an iodine load may blunt or prevent the induction of hyperthyroidism [82, 83]. However, there are insufficient randomized trial data to support the use of thioamides or perchlorate. Routine measurement of thyroid function tests (TSH, and if low, free T4 and T3) in older patients after exposure to iodinated radiographic contrast agents is favored by some experts, particularly since the symptoms of hyperthyroidism in older adults may be atypical [84–86].

Iodine-induced hyperthyroidism (iodine content supplements and dietary nutrients, ICM, type 1 AIT) is usually self-limited (lasting 1–18 months) if the source of iodine is discontinued. The American Thyroid Association (ATA) [87] and European Thyroid Association (ETA) recommendations [40] as initial therapy for patients with iodine-induced hyperthyroidism are discontinuation of iodine (except for amiodarone, which could be continued in type 2 AIT), avoidance of further exposure, and administration of a beta-adrenergic antagonist drug (assuming there

are no contraindications to its use) to minimize the manifestations of the overactive thyroid. Thyroid tests (TSH, free T4, total T3) should be measured initially at 4- to 6-week interval and then less frequently (TSH and free T4 every 3 months) depending upon the results of prior testing. Beta blockers can be tapered and discontinued after thyroid tests return to normal.

Due to the lack of sufficient evidence, there is no consensus regarding the decision to continue or stop amiodarone in patients with type 1 AIT. The decision should be individualized taking into account the risks of patients and taken jointly by cardiologists and endocrinologist [40]. Amiodarone should be continued in critically ill patients with life-threatening cardiac disorders [88]. When deciding whether to discontinue amiodarone, the following should be considered: amiodarone may be necessary to control a life-threatening arrhythmia; since the half-life of elimination from the body is prolonged, there is no immediate benefit to stopping amiodarone; amiodarone appears to ameliorate hyperthyroidism by blocking T4 to T3 conversion, beta-adrenergic receptors, and possibly T3 receptors. Stopping amiodarone might actually exacerbate hyperthyroid symptoms and signs.

In case of amiodarone withdrawal, after the restoration of euthyroidism and normalization of urinary iodine excretion (generally 6–12 months), radioactive iodine (RAI) therapy can be performed. Recombinant human TSH (rhTSH) administration increases the sensibility of the thyroid gland to RAI therapy. If RAI administration is contraindicated, total thyroidectomy should be considered for definitive treatment of the underlying thyroid disease [40]. In the absence of the thyroid gland, amiodarone reintroduction, when necessary, could be safe. In the case of the thyroid gland is conserved, the recurrence rate of type 1 AIT after amiodarone reintroduction is 9% [89]. As ETA suggested, emergency thyroidectomy in severe cardiac patients may be required not only in type 1 but also in all types of AIT. Prior to thyroid surgery, plasmapheresis is able to remove the excess of thyroid hormones [40]. It was reported in a study, including seven patients with AIT, that iopanoic acid short-course administration prior surgery permitted a safe and uneventful thyroidectomy [90].

Thioamides (thiamazole, carbimazole, propylthiouracil) are effective in older patients with underlying heart disease having severe and prolonged (>1 month) hyperthyroid symptoms, except the emergency situations. All thioamides are blocking thyroid hormones synthesis, propylthiouracil having an additional inhibiting effect on T4–T3 transformation. ATA recommended, the starting dose of thiamazole, to be 10–20 mg once daily because of its long duration of action, allowing for once-daily dosing, more rapid efficacy, and lower incidence of side effects [87]. ETA recommended very high daily doses of the drug (40–60 mg/day of thiamazole) for a more extended time, considering that in type 1 AIT the iodine-enriched thyroid gland of patients is less responsive to thioamides [40]. Carbimazole, the prodrug of thiamazole, is an alternative choice of treatment, available in some European countries, but not in Romania. Due to the teratogenicity of thiamazole, propylthiouracil (not currently available in Romania) can be used in the first trimester of pregnancy [68]. To increase the sensitivity and response of the thyroid gland to thioamides, potassium or sodium perchlorate (not available in Romania) has been used. Perchlorate reduces thyroid iodine uptake by sodium/iodide symporter inhibiting action and discharge iodine from the thyroid, but toxic effects are limiting its use. To minimize the nephro- and medullotoxicity of the drug, doses not exceeding 4×250 mg/day and a shorter period than 4–6 weeks were used [40, 87, 91]. Thyroid function should be assessed after 4 weeks by measurement of serum TSH, free T4, and T3. The dose of thiamazole is then tapered with the goal of maintaining a euthyroid state. Thereafter, thyroid function tests (TSH, free T4) should be measured every 3 months. Many patients with underlying autonomous nodular thyroid disease are able to taper and discontinue thiamazole within 6–12 months. In

case of thioamide allergy, lithium is used to control the hyperthyroidism temporarily [91, 92], but it has a narrow therapeutic range, produces nephrotoxicity, and its efficacy is not well documented. Therefore, it is not recommended by ETA for the type 1 AIT treatment [40]. However, it was reported that lithium-associated rhTSH administration increases RAI sensibility of the thyroid follicles in AIT [93].

After resolution of the acute episode of iodine-induced hyperthyroidism, treatment of the underlying thyroid disease should be addressed. For patients with underlying Graves' disease, treatment options include continuing thiamazole, radioiodine ablation, or surgery. Patients with underlying autonomous adenoma or multinodular goiter who return to euthyroidism after discontinuation of iodine do not necessarily require definitive treatment. However, these patients are at risk for recurrent hyperthyroidism if given iodine again.

Type 2 AIT generally is self-limited and amiodarone is not necessary to discontinue. When the efficacy of non-thioamide type antithyroid drugs to restore euthyroid state was compared, the best results were obtained with 30 mg oral prednisone therapy. The rate of achievement of euthyroid state was 100% when glucocorticoids were used versus 71% obtained after perchlorate administration [94]. ETA recommendation, for this reason, is oral glucocorticoids as the first-line treatment for type 2 AIT. In patients in whom a mixed form of AIT is suspected, thioamides together with glucocorticoids should be given initially, or glucocorticoids should be added after a period of 4–6 weeks of inadequate response [40]. In addition, it must be noted that i.v. administration of glucocorticoids (hydrocortisone, dexamethasone) has crucial benefits (inhibiting T4 transformation to T3) in thyroid storm and preoperative management of any type of thyrotoxicosis [91]. It was reported that glucocorticoid therapy (oral prednisone) restored the normal thyroid function and shrink goiter, preventing surgery, in a patient diagnosed with iodine containing supplement-induced hyperthyroidism [95].

5. Conclusions

Iodine, as an essential microelement of the human body, plays a very important role in thyroid physiology. Adequate intake is necessary to keep thyroid hormone synthesis at normal rate. Dietary intake and urinary excretion should be equivalent, but a remarkable adaptive capacity of the thyroid gland can compensate for excess intake on short term. However, existing thyroid disease (subclinical or overt) or specific risk factors may impair the patient's response to high iodine exposure, which can result in hypothyroidism or hyperthyroidism. On the other hand, iodine excess may also be hardly recognizable because various sources (e.g. seafood, kelp, dairy products, iodized salt, iodized water, nutritional supplements, iodine containing contrast media, and drugs) can all contribute to iodine intake. Of these, iodine containing contrast media and drugs are administered only under controlled conditions but represent the most frequent cause of iodine-induced thyrotoxicosis. In general, preventive actions are not recommended, but screening for risk factors, such as elderly patients, persons with multinodular goiter, subclinical hyperthyroidism, or manifest hyperthyroidism should take place prior to iodine administration. Consequently, high-risk patients should benefit preventive treatment with thioamide or perchlorate. Amiodarone-induced thyrotoxicosis has remained a difficult task requiring a close collaboration between cardiology and endocrinology to overcome complications, but individualization of the therapy should be undertaken. Based on the specific features of thyrotoxicosis, thioamides, perchlorate, or high-dose glucocorticoids may be considered for an optimal therapeutic intervention. If contraindicated, radioiodine therapy may also be useful to treat amiodarone-induced thyrotoxicosis.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

AIT	amiodarone-induced thyrotoxicosis
ATA	American Thyroid Association
CT	computed tomography
DEA	N-desethylamiodarone
ETA	European Thyroid Association
ICM	iodinated contrast media
MUIC	median urinary iodine content
RAI	radioactive iodine
RDA	recommended daily allowances
rhTSH	recombinant human thyroid stimulating hormone
rT3	reverse 3,3',5'-triiodothyronine
T3	3,5,3'-triiodothyronine
T4	thyroxine
TSH	thyroid stimulating hormone
WHO	World Health Organization

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