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Iodinated contrast media-induced hyperthyroidism

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ABSTRACT

Currently, iodinated contrast media (ICM) is widely used in radiology, therefore numerous patients are exposed to contrast administration during diagnostic and interventional procedures. ICM contains an amount of iodine well above the recommended dietary allowance, which can lead to thyroid dysfunction. Indeed, individuals that are highly susceptible to increased iodine intake are often patients with pre-existing thyroid disease. ICM-induced hyperthyroidism (IIH) is usually transient, however, it may present as clinically significant thyrotoxicosis. Although IIH has been investigated in multiple studies, there is still a lack of consensus regarding prophylactic therapy of IIH and no specific guidelines. This review aimed to summarise previous literature concerning the influence of ICM exposure on thyroid status and prophylactic therapy of IIH.

Introduction

Adequate iodine intake is essential for thyroid hormone synthesis, with insufficient, as well as excessive iodine intake leading to thyroid dysfunction. Individuals that are at risk of iodine-induced thyroid dysfunction are often patients with pre-existing thyroid disease, such as Graves' disease and multinodular goitre [1]. Iodine-induced hyperthyroidism, known as the Jod-Basedow phenomenon, may lead to severe health consequences and is especially important when considering elderly patients with comorbidities. The use of iodinated contrast media (ICM) during diagnostic and interventional procedures has increased considerably over the past years. ICM contains an amount of iodine which may result in thyroid dysfunction, such as hypo- and hyperthyroidism, both subclinical and overt [2]. ICM-induced hyperthyroidism (IIH) is usually transient, however, it may present as clinically significant thyrotoxicosis. Although IIH has been investigated, the prevalence has not been well established based on these studies and varies between 0% and 10%. Prophylactic therapy of IIH is still a matter of debate and the guidelines concerning this subject are not transparent. Until now, thiamazole and/or sodium perchlorate have been suggested for use as a prophylactic therapy of IIH [3]. This reviewed aimed to summarise the literature concerning the influence of ICM exposure on thyroid status and prophylactic therapy of IIH.

Thyroid function

Thyroid hormones, tetraiodothyronine (T4) and triiodothyronine (T3) are crucial for humans to maintain homeostasis, by regulating biochemical reactions, such as protein synthesis, enzymatic activity and are important for cell metabolism and immune response. They are also responsible for the correct development of the central nervous system, the musculoskeletal system and the lungs in the foetus and infants [4].

The production of thyroid hormones is dependent on the physiological function of the hypothalamus-pituitary-thyroid (HPT) axis and adequate release of thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH). TRH is synthesised in the periventricular nucleus of the hypothalamus, then released to the anterior pituitary gland, where it stimulates the biosynthesis and secretion of TSH in thyrotrope cells. TSH stimulates the production of T4 and T3 in the thyroid gland by binding to the thyroid-releasing hormone receptor (TSH-R) on the thyroid follicular cells. Thyroid hormone levels in the circulation determine the secretion of TRH and TSH by negative feedback [5].

The thyroid gland is composed of follicles, which consist of colloid surrounded by follicular cells. Thyroglobulin (TG) is a glycoprotein precursor of thyroid hormones, containing tyrosine residues within its structure. TG is produced by the endoplasmic reticulum of follicular cells of the thyroid and stored in the colloid [6]. Thyroid hormone synthesis is dependent on iodine metabolism, with iodide transported from the circulation into the thyroid cells by Na+/I- symporter located in thyroid epithelial cells and further iodide oxidised to iodine by the enzyme thyroid peroxidase. Oxidation leads to simultaneous iodination of tyrosyl residues in TG and formation of 3-monoiodotyrosine (MIT) and 3,5-diiodotyrosine (DIT). Afterwards, thyroid peroxidase catalyses coupling of MIT with DIT or two DITs, producing T3 and T4, respectively. Iodinated TG is then stored in the thyroid follicles. When thyroid hormone levels in the circulation decrease, internalisation of TG by follicular cells and digestion by lysosomal enzymes occurs, followed by secretion of free T4 and free T3 [7,8]. T4 and T3 then attach to thyroid hormone-binding proteins synthesised in the liver, including thyroxine-binding globulin (TBG), transthyretin (TTR), and albumin. Within the target cells, T4 is deiodinated to T3, which presents the greatest activity.

Iodine

The recommended dietary allowance (RDA) for iodine intake suggested by the World Health Organization is 90 µg for preschool children, 120 µg for schoolchildren, 150 µg for adolescents (above 12 years) and adults, and 250 µg for pregnant and lactating women [9]. Iodine is an element that occurs mostly as a salt and is present in many forms including inorganic iodine (I2), sodium and potassium salts, iodate, and iodide. It is widely present in food, added to salt as iodate and is also offered as a dietary supplement. Most iodine consumed by humans is reduced in the gastrointestinal tract to iodide and absorbed in the stomach and duodenum [10], then enters the circulation and is retrieved mostly by the thyroid gland and kidneys. It is concentrated in the thyroid in amounts adequate for hormone synthesis. An adult contains about 15–20 mg of iodine, 70–80% of which is stored in the thyroid, one-third in the form of thyroid hormone and two-thirds as precursors [11]. The iodine stored in thyroglobulin is removed from the tyrosine by a specific deiodinase and recycled within the thyroid. The iodine of T4 is returned to the serum after deiodination of T4 and may be included again in the cycle of iodine or excreted in the urine. The remaining iodine is excreted with median concentrations of 100–199 µg/L in children and adults, 150–249 µg/L in pregnant women and >100 µg/L in lactating women [9].

According to the WHO global scorecard of iodine nutrition in 2019, among countries with available data on iodine status, 135 presented with adequate, 25 insufficient and 14 with excessive iodine intake [12]. Iodine prophylaxis in Poland includes obligatory iodisation of household salt and neonate formula and additional supplementation for pregnant and breastfeeding women with 150–200 µg of iodine. In 1994, the Polish Council for Control of Iodine Deficiency Disorders (PCCIDD) defined iodine deficiency in Poland as moderate and slight in the coastal area. In 1997, the iodisation of table salt was re-introduced and Poland is currently within the European countries with optimal supplementation of iodine [13].

An iodine-deficient population is defined by a median urinary iodine concentration (UIC) below 100 µg/l for nonpregnant woman and children [14]. During iodine deficiency, TSH secretion rises when iodine intake decreases below 100 µg per day. Very low iodine intake may result in reduced thyroid hormone production, causing hypothyroidism, sometimes accompanied by goitre. Chronic iodine deficiency is associated with an increased risk of the follicular thyroid cancer [15]. Iodine deficiency is a dangerous state during pregnancy, as it can lead to miscarriage, stillbirth, neurodevelopmental deficits and growth abnormalities in the foetus [10]. Proper iodine intake prevents cretinism in the foetus, a disorder characterised by physical and neurological abnormalities such as intellectual disability, deaf-mutism and motor spasticity.

The tolerable upper intake level for iodine (UL) is the highest level of iodine consumption that is unlikely to cause adverse effects in most individuals. The value of UL has not been established and varies between 600 and 1100 µg/day. Gardner et al. and Paul et al. conducted studies that involved the supplemental intake of 500 and 1500 µg iodine per day, in addition to the usual iodine intake in the diet (200–300 µg/day). They showed that for those who were supplemented with 1500 µg of iodine per day, TSH concentrations increased significantly with a decrease in serum T4 concentration. It was also observed that the supplementation of 500 µg iodine daily caused no significant changes in the basal serum TSH or T4 levels [16,17]. Based on these results, the lowest-observed-adverse-effect-level (LOAEL) of iodine intake was assumed to be 1700 µg/day. The Institute of Medicine set UL at 1100 µg/day for adults by dividing the LOAEL by an uncertainty factor (UF), also known as the margin-of-safety, which was determined by the Institute of Medicine to be 1.5 [4]. The European Commission Scientific Committee on Food selected higher UF of 3 and set UL at 600 µg/day [18]. The Expert Group on Vitamins and Minerals and the Council for Responsible Nutrition established a guidance level for supplemental iodine intake of 500 µg/day [19,20]. The American Thyroid Association (ATA) caution against the ingestion of iodine and kelp supplements with the amount of iodine above 500 µg/day [21].

Amounts greater than UL may lead to thyroid dysfunction, such as thyroiditis, goitre, hypothyroidism and hyperthyroidism, both subclinical and overt, and sensitivity reactions [4]. In the state of excess iodine, Wolff-Chaikoff effect occurs, resulting in the discontinuation of the production and release of thyroid hormones. This effect is mostly transient, however, failing to escape from the acute Wolff-Chaikoff effect may lead to iodine-induced hypothyroidism. Another effect caused by excess iodine intake is the Jod-Basedow phenomenon (iodine-induced hyperthyroidism), which occurs mostly in individuals with dysregulation of the thyroid follicular cell [22]. The most susceptible to the adverse effects of excess iodine are patients with autonomously functioning nodular goitre living in moderate to mild iodine-deficient areas, patients with Graves' disease, also in remission after treatment, Hashimoto's disease, history of partial thyroidectomy [21,23,24]. Iodine-induced hyperthyroidism has also been reported in a situation of excess iodine in euthyroid patients with nodular goitre in iodine sufficient areas [25].

ICM-induced thyroid dysfunction

ICM typically contains 13500 µg of free iodine and 15–60 g of bound iodine [2], a quantity greatly exceeding UL. Contrast media is widely used in radiology to increase the contrast between the tissues in the images. Iodine-based contrast agents are commonly used during computed tomography (CT) and interventional procedures. However, they are known to cause various adverse effects, leading to acute reactions such as allergy-like or hypersensitivity reactions or chemotoxic responses. Late adverse reactions include post-contrast acute kidney injury and thyroid dysfunction [26]. ICM can be classified as high, low and iso-osmolar, with high osmolar ICM ranging from 1400 to 2500 mOsm/kg, low osmolar from 290 to 702 mOsm/kg, and iso-osmolar of 290 mOsm/kg. ICM with an osmolality closer to serum osmolality (285–295 mOsm/kg) has a lower incidence of side effects but contain more particles in solution per iodine atom (iodine ratio). Nevertheless, both high and low osmolar ICM contain an amount of iodine well above the RDA. Low and iso-osmolar ICM are more frequently used because of the lower risk of renal adverse effects in patients with chronic kid-

ney disease [27,28]. The required amount of ICM varies between 50 and 100 mL for CT scan and up to 200 mL for invasive procedures [29], and iodine levels continue to be elevated for up to 1–2 months after ICM injection [30]. ICM routinely used in practice are presented in **Table 1**.

ICM exposure is associated with an increased risk of developing thyroid dysfunction. Indeed, IIH has been confirmed in susceptible individuals as well as in patients with intact thyroid [31]. In a group of patients without pre-existing thyroid disease, Rhee et al. observed a 2–3 times increased probability of developing hyperthyroidism after coronary angiography compared to the control group [2]. The incidence of IIH is greater in iodine-deficient areas (up to 1.7%) and low in iodine sufficient areas [32]. Although IIH has been confirmed by multiple studies, the prevalence of IIH remains unclear [30,33-40], with the prevalence of subclinical IIH varying from 0% to 9% and overt IIH ranges between 0% and 10% (**Table 2**). The effect of ICM on thyroid status is believed to be transient and monitoring of thyroid function before and after ICM administration is not generally recommended [41]. However, published data shows that exposure to ICM can lead to severe thyrotoxicosis resulting in thyroid storm, cardiogenic shock and cardiopulmonary arrest [42,43]. Some authors recommend that patients who present risk factors for IIH should be examined for thyroid dysfunction after ICM [21].

ICM administration may also lead to the development of ICM-induced hypothyroidism, which is usually transient. In 2 to 3 weeks after iodide withdrawal, thyroid hormone synthesis usually returns to normal but some patients may develop permanent hypothyroidism [44], hence, the monitoring of patients diagnosed with ICM-induced hypothyroidism is necessary.

Prophylactic therapy

Prophylactic therapy of IIH has not been sufficiently investigated in prospective studies, with only a few studies on small groups of patients performed. Thiamazole and/or sodium perchlorate are generally considered as prophylactic therapy of IIH, but specific guidelines are needed to establish the regimen of prophylaxis. Thiama-

Table 1. Osmolality, iodine ratio and iodine content in iodinated contrast agents

Name	Type	Osmolality [mOsm/kg H_2O]	Iodine ratio	Iodine content [mg/ml]
metrizoate 370 (Isopaque)	ionic monomer	2100	0.5	370
diatrizoate (Renografin)	ionic monomer	1570	0.5	300
iopromide 370 (Ultravist)	nonionic monomer	774	3.0	370
iohexol 300 (Omnipaque)	nonionic monomer	672	3.0	300
iomeprol 350 (Iomeron)	nonionic monomer	618	3.0	350
iohexol 240 (Omnipaque)	nonionic monomer	518	3.0	240
iodixanol 320 (Visipaque)	nonionic dimer	290	6.0	320

Iodine ratio: ratio of iodine atoms to particles in solution; Serum osmolality: 285–295 mOsm/kg

Table 2. Summary of the studies that investigated ICM-induced hyperthyroidism

Study	Study group (n)	Follow-up (weeks)	Subclinical Hyperthyroidism n (%)	Overt Hyperthyroidism n (%)
Jarvis et al. [37]	102	8	2 (2.0)	0
Conn et al. [40]	73	8	4 (5.4)	2 (2.7)
Bonelli et al. [39]	810	52	74 (9.1)	7 (0.8)
Hintze et al. [38]	788	12	27 (4.9)	3 (0.4)
Ozkan et al. [34]	101	8	7 (6.9)	0
Lee et al. [30]	49	4	4 (8.1)	1 (2.0)
Skórkowska-Telichowska et al. [33]	59	26	3 (5.0)	6 (10.1)
Koroscil et al. [35]	56	1	0	0
Kaneshige et al. [36]	22	26	0	0

Abbreviations: ICM: iodinated contrast media

zole blocks the production of thyroid hormones by inhibiting thyroid peroxidase in the thyroid gland, thus inhibiting the iodination of tyrosine residues in TG [45]. Sodium perchlorate prevents iodide from entering the thyroid by an effect on the Na+/I- symporter, therefore stopping the synthesis of T3 and T4 [46]. Nolte et al. [47] observed that prophylactic treatment with monotherapy with 20 mg/day thiamazole or 900 mg/day sodium perchlorate has a protective effect against iodine excess in patients with euthyroid autonomy. Nevertheless, despite therapy with thiamazole or sodium perchlorate, two cases of mild hyperthyroidism have been reported. Another study investigated a group of 60 euthyroid patients, of which 27 individuals received prophylactic treatment with 60 mg methimazole and 1 g perchlorate administrated one day before and on the day of ICM exposure. Three cases of mild hyperthyroidism were observed in the control group. One case of hyperthyroidism was reported in the group with prophylaxis, however, this patient had another ICM injection without premedication 2 weeks after the first ICM injection [48]. Fricke et al. studied a group of 19 patients undergoing coronary angiography with technetium thyroid uptake greater than 1%. Patients were administered with the prophylactic treatment of 900 mg of perchlorate for two weeks in monotherapy or combined with 20 to 60 mg thiamazole for 1–2 weeks. Two cases of mild thyrotoxicosis were reported [49].

ATA does not recommend routine prophylaxis with antithyroid drugs before ICM but suggests considering prophylaxis in patients at risk of developing IIH [23]. The European Society of Urogenital Radiology (ESUR) introduced a sample combination regimen for prophylaxis with 30 mg once daily thiamazole and 300 mg three times a day sodium perchlorate, from the day before ICM and for the next 14 and 8–14 days, respectively. Both ATA and ESUR advise against the use of ICM in patients with hyperthyroidism [3].

Summary

In conclusion, IIH is an underestimated clinical condition, which, if not treated, may lead to severe health consequences, especially in the elderly and patients with cardiovascular disorders. The prevalence of IIH remains unclear. Until now, the prophylactic treatment of IIH with thiamazole and/or perchlorate in various regimens has been proposed, although the effectiveness of these drugs is uncertain. Further prospective, randomised studies on representative groups of patients concerning the prophylactic therapy of IIH are crucial for the proper prevention of this thyroid dysfunction.

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