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Mini Review

A High Dietary Iodine Intake Associated with Thyroid Diseases and PTC

George Zhu*

The Institute of Oncology, Tehran University of Medical Sciences, Tehran, Iran

***Corresponding Author:** George Zhu, The Institute of Oncology, Tehran University of Medical Sciences, Tehran, Iran.

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Iodine is a trace element that is essential for the synthesis of thyroid hormone [1]. Both chronic iodine deficiency and iodine excess have been associated with hypertrophy and hyperplasia of thyroid follicular cells [2]. Using experimental mice, an extensive study of benign and malignant thyroid tumors were induced with radioiodine [3-7]. External (I131 or ionizing) radiation exposure to the head and neck region in children is well known causes of thyroid cancer [8,9]. Another environmental etiology for thyroid cancer is dietary iodine content [10,11]. Increased PTC occurs with a high frequently in region with a high dietary iodine intake such as Iceland and Pacific Bay Area [12,13].

Iodine-induced goiter, hyperthyroidism (IIH) and thyrotoxicosis (ITT) and the prevalence of papillary carcinoma (PTC).

According to WHO in 1994 [14] and the Korea Centers for disease control and prevention (KCDC) in 2012 [15] food products such as processed, agricultural, meats, and marine products were monitored for measuring dietary iodine. The recommended iodine daily allowance of 70 - 150 ug [16]. An excess of iodine through dietary intake, drugs or other iodine-containing compounds can lead to goiter [17,18], hyperthyroidism [19-26], hashimoto's thyroiditis [27] and thyrotoxicosis [28-35] through increasing thyroid hormone synthesis in the presence of underlying thyroid disease, particularly multinodular goiters containing previously existing area of autonomous function. There are hundreds of reports which focused on this area. In 1958, introduction of potassium iodide (KI) in order to the prevention of goiter in French, many students developed iodine goiter with oral high dosage of 1% KI or 10 mg KI daily. In the past decades there have been at least 46 reported cases of goiter in man associated with iodine (KI, NaI, Lugol solution and antiarrhythmic agent amiodarone). From epidemiology, in China, there were 16% rate incidence of iodine goiter for tangle salt diet (iodine content 1089.2 ug/kg); and 28.36% (total 4344 analysis) rate incidence of iodine goiter in higher iodine drinkers from deep well water (iodine content 661.2 ug/L) compared to 8.37% (4158) of goiter in low iodine water drinker (iodine content 27.2 ug/L) [36]. Moreover, it has been successfully induced higher iodine goiter with increased levels of serum T3 and T4 in mice (Yin, 2002). Potassium iodide (KI) at 10^{-4}--10^{-7} mol/L concentration stimulate the proliferation of thyroid cancer BPH 10^{-3} cells, increased levels of serum T3 and T4, increased cyclin D1 mRNA and protein (Nie, 2005; Li, 2013). In rats serum thyroxine (TT4, FT4, rT3) was higher in higher iodine than the result in lower iodine (Nie, 2005).

Iodine-induced hyperthyroidism (IIH) has been frequently described when iodine is introduced into an iodine-deficient area [19], patients residing in iodine-sufficient areas [26] and iodinated preparation for water purification [22]. Excessive iodine intake might also be due to a long-term topical exposure (iodine solution dressing or topical iodine application) or by intravenous administration of iodine-containing substances [21,27]. In a classical study, four euthyroid patients with a single autonomous nodule from the slightly iodine-deficient Brussels region received a supplement of 500 ug iodine per day. This caused a slow but constant increase of thyroid hormone. After four weeks, the patients became hyperthyroid [28]. Therefore, individuals with multinodular goiters living in iodine-replete regions can also develop hyperthyroidism, confirming that nodular goiters are particularly prone to developing IIT [29]. Iodine-induced IIT was recognized as early as 1821 by Coindet [30], who reported that goitrous individuals treated with iodine developed hyperthyroidism. Comparative survey of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland, it occurs that high incidence of multinodular

toxic goitre in the elderly population in a low iodine intake area whereas high incidence of Grave's disease in young in a high iodine intake area [37]. In northern Tasmania in UK, in 1964 and in 1971 respectively, the incidence of thyrotoxicosis rose substantially because of the addition of iodate to bread to prevent goitre or iodine residues in milk [32]. In Vigo, Spain, dietary of iodine supplementation in iodine sufficient areas may induce the increase of thyrotoxicosis (TT) (7.68/100,000), as opposed to 3.1/100,000 in area without iodized salt [38]. IIT has been reported after initiating iodine supplementation, also with use of iodinated drugs, radiographic contrast agents and food dietary iodine [29-39] (Table 1). Table 1 present iodine-containing compounds related to IIT.

Radiological contrast agents: Diatrizoate, Iopanoic acid, Ipodate, Iothalamate, Metrizamide, Iopromide, Iopamidol, Iotrolan
Topical iodine preparation: Iodine tincture, povidone iodine (Betadine), Iodoform gauze
Solution: Saturated potassium iodide, Lugol solution, iodinated glycerol (organidin), echothiopate iodide, hydriodic acid syrup
Drugs: Amiodarone, vitamins containing iodine, potassium iodide, Isopropamide iodide
Food components: Kelp, kombu and other marine algae, iodine compounds in bread, Hamburger thyroiditis

Table 1: *Iodine-containing compounds potentially associated with IIT.*

Amiodarone is the most common source of iodine in the United States. Amiodarone-induced thyrotoxicosis (AIT) type I results from iodine increase in thyroxine synthesis (200 mg of amiodarone containing 75 mg of iodine). Patients developing AIT type I usually have a pre-existing nodular goiter. AIT type II is caused by cytotoxic effects of medication that results in the release of preformed thyroxine [29]. AIT occurs late after amiodarone withdrawal [40].

Thyroid neoplasia can result from many different causes. These include low iodine diets, radioactive iodine and natural goitrogens. Dietary iodine intake act as a potential relevance risk factor of thyroid cancer [41-46]. Elevated incidence and mortality rate of thyroid cancer have been found in areas where iodine intake is high (Howaii, Iceland) [42,43]. In South India, among 300 patients with goiter and 100 euthyroid health non-goitrous volunteers, iodine-induced hyperthyroidism or IIT (34%) and thyroid cancer (15%) have been observed after continued supplement of edible salt fortified with excess iodine [47]. In China, using comparative analysis of 4679 post-operative patients with universal salt iodization (USI) during 1994 - 2008 and 3325 post-operative patients without USI during 1979 - 1993, the incidence ratio of thyroid carcinoma after USI was 5.6% (308/4679) compared to 2.9% (95/3325) in patients without USI, 32.7% (1530) of thyroid adenoma after USI compared to 20% (665) before USI, and 4.5% (212) of toxic goiter after USI compared to 2.7% (95) before USI [48]. Moreover, according to 1101 thyroid malignant tumors confirmed by pathological specimens, constitutional ratio of PTC (70.17%) increased obviously after USI compared with the results (55.84%) before USI whereas the proportion of FTC (11.05%) decreased accordingly after USI compared with the results (24.58%) before USI [49]. The same results was also reported based on 429 analyses [50]. The prevalence of PTC (80 - 90%) in thyroid carcinoma increased significant after USI. Therefore, in the presence of sufficient iodine intake, more than 80% of thyroid cancer consisted of papillary carcinoma (PTC), whereas in area with iodine-deficiency, in contrast, have a higher incidence of FTC (Figure 1, Giusti, 2010 [46]). Compared with matched controls, urinary excretion of iodine excess was detected in 302 cases of thyroid benign tumors (519 ug/L) and 240 thyroid cancers (524 ug/L) (Liu, 2008). Higher urine iodine was associated with PTC (urine iodine: 355.3 +- 289.6 ug/L in 53 PTC, Zhou, 2014).

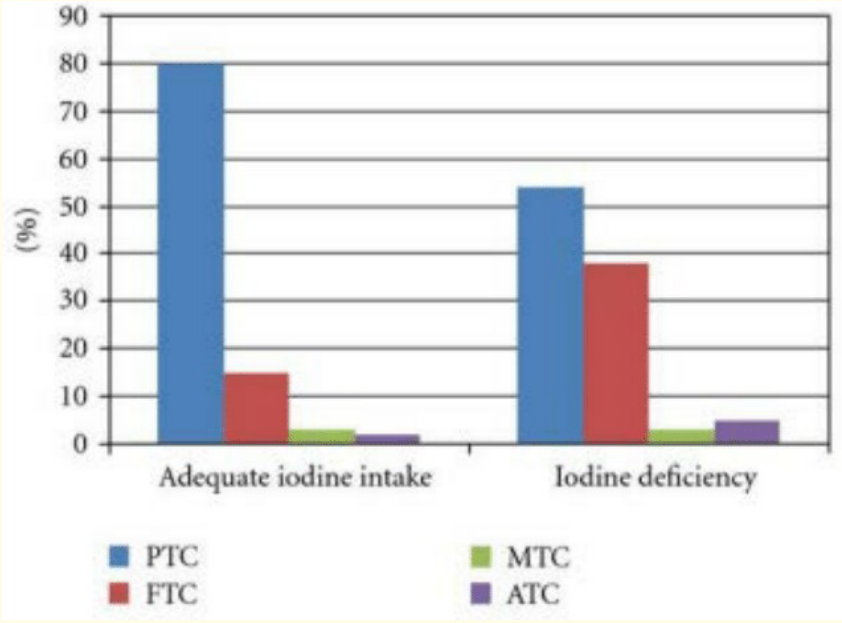

Figure 1: *Contribution of iodine in the food to the thyroid tumorigenesis (Data from Giusti F., et al. [45]).*

Kelp are large seaweeds, belonging to the brown algae and classified in the order *Laminariales*, and are an important food source in many Asian cultures [51]. The average iodine content of kelp of 1,500 to 2,000 ug/g was measured [52,53]. Herbal medicine, including kelp and kelp-containing dietary supplements, are also used by an increasing numbers of patients [54]. Suzuki [55] was the first to report a case of endemic seashore goiter following marine algae, the incidence of endemic coast goiter among students was 6.8 - 8.9%. At present there have been reported at least 6 patients with iodine-induced hyperthyroidism and 2 iodine-induced thyrotoxicosis after ingestion of kelp [51,56-61]. Another 12 thyrotoxicosis caused by weight-reducing herbal medicine [54]. In 2001, Zhu [62] reported a case of thyroid neoplasm following marine algae in a breast cancer. From epidemiologic studies in Korean population, high intake of iodine from marine products may increase thyroid cancer risk, particularly in women [11]. Accumulated data, seaweed accounts for about 80% of Japanese people's iodine intake, seaweed consumption was clearly associated with an increased risk of papillary carcinoma (PTC) in postmenopausal women [63].

In case-control studies, cruciferous plants were found an association with increased thyroid cancer risk. In epidemiology, in Sweden, the risk of thyroid cancer associated with a high cruciferous vegetable intake was higher among female who had ever lived in an endemic goiter area [64]. In Poland, frequent cruciferous vegetable consumption was associated with a 1.5-fold increase in the risk of thyroid carcinoma [65]. However, a study from New Caledonia among Melanesian women who consume large quantities of cruciferous vegetables, and low iodine intake (< 96.0 ug/day) showed a positive association [66]. The study from Kuwait, high intake of cabbage showed an increased risk with a borderline significance [67]. Thus, in this area, more accumulated results are needed to be testable.

Overall, the findings indicated clearly carcinogenesis of I131 or/and radiogenic transformation on thyroid glands in the rats and man. Dietary iodine intake is another care of environmental relevance factor in thyroid diseases and papillary carcinoma.

Oncogenic thyroid hormone receptor mutants

It has been demonstrated that thyroid status had a modulating effect on neoplasia. Like iodine-induced hyperthyroidism and IIT, using thyroxine L-T4 which 65% of T4 weight is iodine, Ciosek [68] induced experimental model of rat hyperthyroidism. Administration of thyroid hormone to thymectomized rodents is a prerequisite for the induction of hepatomas by chemicals, indicating a role in the initiating action of carcinogen [69]. This thyroid hormone (T3) signaling through thyroid hormone receptor (THRa1) regulates hepatoma cell growth [70]. In literature, there have been more 10 cases of earlier reports on the thyroid carcinomas and concurrent hyperthyroidism (Grave's disease), and also concurrent toxic nodular goiters [71-73]. The other 11 cases were further reported [74,75]. Among 10 hyperthyroidism, of whom 6 with Grave's disease complicated with thyroid cancer, 2 hyperthyroidism with thyroiditis and thyroid cancer [74]. Another case was reported in a 43-old-man with initial hyperthyroidism, and two years later transformation of thyroid adenoma complicated with hyperthyroidism (nodule: 6 x 4 x 3 cm), suggesting an initiating role of thyroxine on neoplasm and a wide variety of metabolic effects, for instance, increased lipogenesis and hair growth [75]. In addition, the transformation of culture cells by radiation is *in vitro* facilitated by thyroid hormone [76].

In vivo, mice expressing THR alpha 1 specifically in the intestinal epithelium in wild-type THR alpha1 presented mucosal architecture and increased cell proliferation and develops adenoma at low rate [77]. This phenotype is due to cooperation between the activated THRa1 and WNT pathways [77]. Mutation of thyroid hormone receptor-beta (THRbeta) in mice promotes the development of mammary hyperplasia via aberrant activation of STAT5 [78]. THRbeta mutants can also induce spontaneous development of follicular thyroid carcinoma (FTC) similar to human cancer in a knocking mouse model harbouring a mutated THRbeta (Thrb, denoted PV) [79-81], and thyroid hormone play a critical role in promoting thyroid carcinogenesis of Thrb (PV/PV) mice via PI3K-AKT-beta-Catenin signaling pathway [82]. Moreover, southern analysis revealed a rearrangement of oncogenic THRA1/BTR fusion in the BT474 breast cancer cell line [83]. This rearrangement represented a deletion of THRA1 allele that was coamplified with ERBB2 in breast cancer.

In clinics, almost 63% of 16 papillary thyroid carcinoma (PTC) were found to have mutations in THRa1, and a remarkable 94% in THRbeta1, in contrast 22% and 11% of thyroid adenomas harboring mutations in these isoforms respectively, and no mutations were found in normal thyroid controls, which implicate the differential effects of normal and oncogenic thyroid hormone receptor [84] signaling in PTC and normal health controls [85]. The findings suggest a possible oncogenic action for thyroid hormone receptor mutation in the tumorigenesis of human thyroid carcinoma [86]. Other infact, the 25 - 40% of PTCs are associated with activating oncogenic RET receptor gene rearrangements [87-89]. More others, CLIC1 was identified as a novel dominant pro-oncogenic receptor from proteomic profiling of pleomorphic human sarcoma [90]. Thus, an extensive study of thyroid hormone receptor (THR) mutations, TSH/TSHR in thyroid disease and thyroid cancer, and also its target therapy [91,92], is further perspective.

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