Iodine Deficiency and Its Proliferation in Cancer Increase

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Abstract

Iodine is an essential element in human physiology. It’s well known to play vital role in thyroid functions. However it has been updated to be the most important element with the highest percentage of demand by the human body. This is because iodine is the heaviest and richest in electrons among required elements in the animal diet. Inorganic iodides are necessary for all living vegetable and animal cells, but only the vertebrates have the thyroid gland and its iodinated hormones. In humans, the total amount of iodine is about 30-50 mg and less than 30% is present in thyroid gland and its hormones. About 60-80% of total iodine is non-hormonal as contained in its extrathyroidal tissues. Dietary iodine deficiency is associated with the development of mammary pathology and cancer. Mammary gland embryogenetically derived from primitive iodide-concentrating ectoderma, and alveolar and ductular cells of the breast specialize in uptake and secretion of iodine in milk in order to supply offsprings with this important trace-element. Breast and thyroid share an important iodide-concentrating ability and an efficient peroxidase activity, which transfers electrons from iodides to the oxygen of hydrogen peroxide, forming iodoproteins and iodolipids, and so protect the cells from peroxidative damage. Thyroid nodules are a common clinical problem, and differentiated thyroid cancer is becoming increasingly prevalent. The aim of these guidelines is to inform clinicians, patients, researchers, and health policy makers on published evidence relating to the diagnosis and management of thyroid nodules and differentiated thyroid cancer.

INTRODUCTION

The thyroid lies under the larynx and synthesizes two hormones, thyroxine and tri-iodothyronine. This gland takes up iodine from the blood and has the highest iodine level in the body. The iodine is incorporated into the thyroid hormones. Thyroxine has four iodine atoms and is called T4 while Tri-iodothyronine has three iodine atoms and is called T3. Both T3 and T4 function to increase the metabolic rate of several cells and tissues. The brain, testes, lungs, and spleen are not affected by thyroid hormones, however. T3 and T4 indirectly increase blood glucose levels as well as the insulin-promoted uptake of glucose by fat cells. Their release is modulated by Thyrotropin Releasing Hormone, TRH-RH from the hypothalamus. When temperature drops, a metabolic increase is triggered by Thyroid-Stimulating Hormone, TSH. Chronic stress seems to reduce TSH secretion which, in turn, decreases T3 and T4 output. Depressed T3 and T4 production is the trademark of hypothyroidism. If it occurs in young children, this decreased activity can cause physical and mental retardation. In adults, it creates sluggishness mentally and physically and is characterized further by weight gain, poor hair growth, and a swollen neck i.e. goiter. Excessive T3 and T4 cause sweating, nervousness, weight loss, and fatigue. The thyroid also secretes calcitonin, which serves to reduce blood calcium levels. Calcitonin's role is particularly significant in children whose bones are still forming. Ongoing epidemiological data has corroborated the association between goitrogenous regions and cancer incidence/mortality, particularly that of stomach cancer [1]. Epidemiological evidence also suggests that thyroid disorders, particularly goiter, may be associated with breast cancer incidence and/or mortality. Other cancers associated with goitrogenic state include prostate cancer, endometrial, ovarian, colorectal, and thyroid cancer [2]. It is not clear whether these associations are due to an underlying hypothyroid state, the presence of occult autoimmune processes, or iodine deficiency itself. Ultimately, the etiology of all cancers is multifactorial, with benefit assumed in the reduction of modifiable risk factors. There is substantial evidence that iodine deficiency is a modifiable risk factor in cancers of the stomach and breast and possibly many other organs. Total iodine content of the body is estimated at 25 mg to 50 mg, with 50%-70% of that found in extrathyroidal tissues [3]. Systemic absorption of iodine takes place in the small intestine, where it is absorbed and transported into the bloodstream primarily as iodide (1). Ultimately, excretion is via the kidneys with minor amounts excreted in feces. To enter
cells, iodide (I-) must be co-transported with 2 molecules of sodium to overcome the electrochemical gradient [4]. This sodium/iodide symporter (NIS) is well characterized on the basement membrane of thyroid follicular cells, where it allows for requisite iodide uptake. The means of iodide transport into enterocytes has only recently been attributed to the same symporter, NIS, that is expressed in the thyroid [5]. NIS found in enterocytes is controlled via a negative feedback system, such that high iodine intake reduces NIS production. Several extrathyroidal tissues also concentrate iodine via NIS found on their basement membranes. Most notably, the stomach mucosa, salivary glands, and the lactating mammary gland all have NIS that is identical to that found in the thyroid [6]. Other tissues with high concentrations of iodine include the choroid plexus, ciliary body of the eye, lacrimal gland, thymus, skin, placenta, ovary, uterus, prostate, and pancreas. The role of concentrating iodine in lactating mammary tissue is clearly to provide necessary iodine to the developing child. The role of iodine in most other tissues is believed to include antioxidant, anti-inflammatory, anti-proliferative, antibacterial, proapoptotic, and prodifferentiating effects [7].

Thyroid nodules are a common clinical problem. Epidemiologic studies have shown the prevalence of palpable thyroid nodules to be approximately 5% in women and 1% in men living in iodine-sufficient parts of the world. In contrast, high-resolution ultrasound (US) can detect thyroid nodules in 19%-68% of randomly selected individuals, with higher frequencies in women and the elderly [8]. The clinical importance of thyroid nodules rests with the need to exclude thyroid cancer, which occurs in 7%-15% of cases depending on age, sex, radiation exposure history, family history, and other factors [9, 10]. Differentiated thyroid cancer (DTC), which includes papillary and follicular cancer, comprises the vast majority (>90%) of all thyroid cancers. In the United States, approximately 63,000 new cases of thyroid cancer were predicted to be diagnosed in 2014 [11] compared with 37,200 in 2009 when the last ATA guidelines were published. Almost the entire change has been attributed to an increase in the incidence of papillary thyroid cancer (PTC). Moreover, 25% of the new thyroid cancers diagnosed in 1988-1989 were £1 cm compared with 39% of the new thyroid cancer diagnoses in 2008-2009 [12]. This tumor shift may be due to the increasing use of neck ultrasonography or other imaging and early diagnosis and treatment, trends that are changing the initial treatment and follow-up for many patients with thyroid cancer. A recent population-based study from Olmsted County reported the doubling of thyroid cancer incidence from 2000 to 2012 compared to the prior decade as entirely attributable to clinically occult cancers detected incidentally on imaging or pathology [12]. By 2019, one study predicts that PTC will become the third most common cancer in women at a cost of $19-21 billion in the United States [13].

METHODS

The present study is a review study that has used information banks and scientific internet search engines such as Google scholar using keywords like: obesity, cancer, thyroid, iodine and thyroid gland. All available articles on thyroid disorders from the sub-African continent, published until March, 2016, were included.

RESULTS

Iodine is a vitally important nutrient that is detected in every organ and tissue and many if not most are deficient in this nutrient. Along with being essential for healthy thyroid function and efficient metabolism, there is increasing evidence that low iodine is related to numerous diseases, including cancer. There are potentially serious risks to taking too much iodine, however, which is why we do not advise taking iodine supplements like Lugol’s or Iodoral. Your thyroid only transports iodine in its ionized form (i.e. iodide).

Your thyroid reduces iodide (I-) into iodine (I2) for use in formation of thyroglobulin. Your body doesn’t utilize iodide directly. It has to split the I2 into two I- ions, which is an oxidative reaction that causes oxidative stress. Taking too much iodine may also lead to subclinical hypothyroidism, which occurs when your thyroid produces too little thyroid hormone because hypothyroidism is often linked to iodine deficiency. We would recommend taking a large dose iodine supplement in the event of some type of nuclear fallout. In this case, if you are iodine deficient, taking a potassium iodide (a stable form of iodine) supplement can protect your thyroid by “flooding” your system with iodine so your thyroid has no need to take in the radioactive form.

Though thyroid health is often what people think of when they think of iodine, other tissues also absorb and use large amounts of iodine, including (Fig 1):

![Figure 1: Tissues Absorb Iodin](image)

Iodine deficiency or insufficiency, in any of these tissues will lead to dysfunction of that tissue. Hence the following symptoms could provide clues that you’re not getting enough iodine in your diet. For example, iodine deficiency in:

- Salivary glands, inability to produce saliva, producing dry mouth; Skin, dry skin, and lack of sweating. Three to four weeks of iodine supplementation will typically reverse this symptom, allowing your body to sweat normally again;
- Brain, reduced alertness and lowered IQ; Muscles, nodules, scar tissue, pain, fibrosis, fibromyalgia.

DISCUSSION

In a study of 111 women with cyclic mastalgia/mastodynia, women took either 6 mg/day, 3 mg/day, or 1.5 mg/day of a combination iodide/iodate (I/-/IO3-), or a placebo [14]. Sodium iodate (NaIO3) was used with the prediction of dissolution in the stomach to molecular iodine (I2). In that study, more than 50% of the women taking 6 mg/day had a reduction in mastalgia symptoms at 6 months. In keeping with iodine’s effects in benign breast conditions, in vitro and in vivo studies suggest that the therapeutic form of iodine in breast cancer is molecular iodine (I2). While NIS has been considered a necessary means for iodide uptake, human breast cancer cells (MCF-7) have been found to use facilitat-
ed diffusion of I\textsuperscript{-} as well [15]. This may explain why levels of iodine are higher in cancerous breast tissue than surrounding normal tissue [16]. As mentioned, I\textsuperscript{-} is capable of inducing apoptosis in human breast cancer cells through mitochondrial mediated pathways. A rodent model of mammary carcinogenesis molecular iodine, but not iodide, was able to prevent promotion of disease [17].

There are several lines of evidence to support the role of molecular iodine (I\textsuperscript{-}) as preventive of carcinogenic processes. In a chemical carcinogenesis model of mammary tumors, using Sprague-Dawley rats given methyl-nitrosourea, iodine (I\textsuperscript{-}) was given as a 0.05% of water source and the rats were allowed unrestricted access. The incidence of mammary tumors was 37.5% lower in the treated rats versus controls. Further, there was an increase in proapoptotic caspase 2 and PPAR gamma expression. They also demonstrated that the vasculature of tumors in the rats given iodine (I\textsuperscript{-}) as well as vascular endothelial growth factor expression was significantly less in the tumors developed by those consuming iodine. In rats that developed tumors, there was no difference in tumor number or volume [18].

Iodine may also be affecting the binding of estrogen receptors to the steroid-binding element. Using breast cancer cells (MCF-7 cells), Stoddard and colleagues demonstrated that Lugol’s solution (5% iodine/10% iodide) affected 43 genes involved cell cycle growth, proliferation, and differentiation [19]. Many of the 43 genes are those up regulated by estrogen, implying that the Lugol’s solution interfered with this action and had a net “anti-estrogenic” effect on gene expression. This is in keeping with a rodent study using DMBA-induced mammary cancers that found a supplement of 0.1% of a combination I\textsuperscript{-}/KI (0.05%/0.05%) lessened estrogen induced DNA adduct formation and increasing PPAR-gamma expression [20].

### Iodine and Breast Pathology

Recently, many researchers studied NIS in mammary gland. Tazebay et al. [21] reported that mammary NIS may be an essential breast cancer marker and that radiodiode should be studied as having a possible role in the diagnosis and treatment of breast cancer. Kilbane et al. [22] demonstrated NIS expression in benign fibroadenomata and breast carcinoma, but total tissue iodine levels in benign tumors were significantly higher than those in breast cancers taken from either the tumor or morphologically normal tissue taken from within the tumor-bearing breast. Kogai et al. [23] reported that the NIS stimulates iodide uptake in normal lactating breast, but is not known to be active in nonlactating breast or breast cancer. Retinoic acid induces sodium/iodide symporter gene expression and radiodiode uptake in breast cancer cells. So, stimulation of radiodiode uptake after systemic retinoid treatment could be useful for diagnosis and treatment of some differentiated breast cancers. Rillema et al. [24] have shown that iodide accumulates in milk at higher concentration than in maternal plasma and that PRL enhances iodide accumulation in cultured mammary tissues, via stimulation of NIS. Cho et al. [25] suggested that iodine uptake and NIS expression in mammary gland are modulated by hormones involved in active lactation. NIS is clustered on the basolateral membrane of alveolar cells. The iodine uptake of lactating mammary gland is partially inhibited by treatment with a selective oxytocin antagonist or bromocriptine, an inhibitor of PRL release.

### Iodine and Thyroid Hormone in the Therapy of Breast Diseases

Funahashi et al. reported recently that both Japanese edible Wakame seaweed and also a direct uptake of inorganic iodine [26] by tumor have experimentally a suppressive effect on DMBA-induced breast tumors growth in the rat. NIS expression is inversely related to undifferentiation, malignity and it is directly related to likelihood of therapeutic effectiveness of radioiodide therapy. Recent studies reported that genetic characterization and induction of the human NIS gene allows the development of novel gene therapy also for treatment of extrathyroidal and mammary malignancies. In fact, targeted expression of functional NIS in undifferentiated cancer cells would enable these cells to concentrate iodine and would therefore offer the possibility of radioiodide therapy. Boland et al. [27] propose to enlarge the therapeutic strategy to nonthyroid tumors by using an adenoviral vector to deliver the NIS gene into the tumor cells for a targeted radiotherapy.

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None declared.

### CONFLICTS OF INTEREST

There is no conflict of interests.

### REFERENCES


