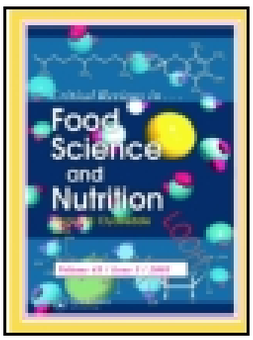

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REVIEW

The impact of the micronutrient iodine in health and diseases

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ABSTRACT

Adequate iodine nutrition is crucial for all mammals by playing his starring role as a component of thyroid hormones, which are key regulators of cellular processes for life such as differentiation, growth, function, and metabolism. Deficiency or excess of iodine in the diet are worldwide highly frequent conditions that are responsible of health problems like hypothyroidism, hypothyroxinemia, goiter, thyroiditis, hyperthyroidism, and autoimmune thyroid diseases among others. The incorporation of iodine in salt or other nutrients resolved the consequences of severe iodine deficiency like goiter, cretinism. However, this strategy in several countries led to other ailments like Hashimoto autoimmune thyroiditis, hyperthyroidism, and hypothyroidism. The goal of this review is to analyze and discuss the different aspects of iodine nutrition for human health comprising its biological role through thyroid hormones, pathogen control, and the regulation of the intestinal microbiota.

KEYWORDS

Bactericide; intestinal microbiota; iodine; nutrition; thyroid diseases; thyroid hormones

1. Introduction

Iodine is a trace element on earth that mammals will incorporate in the chemical form of iodide (I^-) (Zbigniew 2017). In this review we will use the term "iodine" for referring to the chemical name of the element (Zbigniew 2017). Adequate iodine nutrition is fundamental for all mammals. In fact, five grams of iodine will be enough to fulfill the needs of a human being for 70 years (Cavalieri 1997). Iodine is incorporated from the diet by the intestinal epithelial cells to the blood (Nicola et al. 2009). Then, iodine is transported from blood into thyroid gland, where the 80% of total iodine in the body is stored and used for the synthesis of thyroid hormones 3,3′,5-triiodothyronine (T_3) and thyroxine (T_4) (Ahad and Ganie 2010; Mansourian 2011). Thyroid hormones are essential for the metabolism of all cells and for the proper fetal development. Besides being iodine a structural and functional component of the thyroid hormones, it also plays an important role as bactericide due to its oxidative properties (McDonnell and Russell 1999). This role is performed in the gastrointestinal tract, where iodine is secreted by epithelial cells of the stomach to the gastric acid and from the salivary glands to the saliva (Josefsson and Ekblad 2009). This review discusses the aspects of the iodine nutrition status worldwide, highlighting its roles for human health and microbiota.

1.1. Iodine sources and human iodine nutrition status

1.2. Sources of iodine for the human diet

For humans an adequate iodine nutrition status has been difficult to achieve due to the low availability of this element in the common food. The amount of iodine in natural foods is highly variable and mainly depends on the soil were plants and animals grow (Fuge and Johnson 1986; Teas et al. 2004). The oceans are the main source of iodine (45–60μg/L, at the surface) (Korzh 1984). For the contrary, the soil has small quantities of iodine and it is considered to be the second most important reservoir for mammals. Soils from coastal areas are more abundant in iodine than soils from the mountains (0.24 μg of iodine/g of soil), given it evaporates from the sea and precipitate in the surrounded areas (Whitehead 1984). Seaweeds have a great capacity to capture and store iodine from the sea and they are the richest iodine foods on earth (Teas et al. 2004). Even though, lettuce and spinach have low iodine content compared to seaweeds, they are considered to be a valuable source of iodine for human nutrition (see Table 1) (Weng et al. 2003; Zhu et al. 2003; Dai et al. 2004; Teas et al. 2004; Pearce et al. 2004; Zealand, Food Standards Australia New 2015; Leung and Braverman 2014; Johnson 2003). The spinach is capable to concentrate iodine proportionally to the available

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Table 1. Iodide sources.

Source	I^- content
Edible seaweeds	22–8165 μg/g (Teas et al. 2004)
Bread	0.09–23.31 μg/g (Pearce et al. 2004)
Milk	88–168 μg/250 mL (Pearce et al. 2004)
Eggs	22 μg/g (Zealand, Food Standards Australia New 2015)
Fish	0.73 μg/g (Leung and Braverman 2014)
Leafy plants	89 μg/Kg (Johnson 2003)

iodine in the soil, thus making this ailment a promising candidate for iodine biofortification (Adams et al. 2006; Bath et al. 2017). Moreover, the comsuption of goitrogens will reduce the uptake of iodine by the thyroid gland and consequently will decrease the synthesis of thyroid hormones (Eastman and Li 2017). Examples of goitrogens are thioglycosides and cyanolglycosides found in broccoli, maize, and sweet potatoes; and thiocyanates and perchlorate found in cigars, tap-water, and vegetables (Gaitan 1990). Chronic ingestion of plants rich in goitrogens is considered a possible cause of goiter particularly in those regions with higher goiter rates (Bourdoux et al. 1978). Interestingly, Braverman showed with in a long term study that intermittent exposure to goitrogens did not altered thyroid hormone synthesis (Braverman et al. 2005). To overcome the poor iodine ingestion several strategies have been developed worldwide among these are fortification programs aiming to incorporate iodine in common food like milk, bread, water, and salt (Jong 2007; Sarah Davis et al. 2012; Aburto et al. 2014; Olivieri et al. 2017). According to the World Health Organization (WHO) the most successful strategy is the universal salt iodization (USI) program (WHO 2008). In this program, salt is used as a vehicle for iodine administration given that it is consumed fairly by most of the population through the year. The technologies required for this process are of easy implementation, do not affect the iodine organoleptic properties and the iodization process have reasonable costs (WHO 2004). However, after several years of implementation of USI programs in countries that previously suffered of mild or severe iodine deficiency were showing an increment of overt autoimmune hypothyroidism, subclinical hypothyroidism and thyroiditis (Palaniappan et al. 2017; Katagiri et al. 2017; Sun, Shan, and Teng 2014; Marwaha et al. 2012). Health authorities, medical doctors and scientists are reacting, discussing and rethinking new and more appropriate strategies to deal with iodine deficiency and iodine excess. It seems crucial to monitor continually the consumption of iodine in the population by age and gender. This parameter is necessary for taking the right health decisions to avoid the appearance of thyroid diseases due to iodine deficiency or excess.

1.3. Iodine nutrition status

Adequate iodine intake is crucial for proper thyroid function, being low iodine intake responsible for the highly frequent iodine deficiency disorders (IDD) (Zimmermann, Jooste, and Pandav 2008). Today and worldwide, more than the 90% of the human population have access to sufficient iodine from natural sources or from fortified food. However, iodine deficiency is still present in some remote populations that lack access to natural sources of iodine or to iodine fortified foods. The WHO/UNICEF/ICCIDD recommended a daily intake of 150 μg/day of iodine for an adult to avoid IDD. However, this recommendation varies depending of age and physiological status (see Table 2) to supply themselves, fetus and the newborn for thyroid hormones synthesis (Murcia 2018; Opazo and Haensgen, et al. 2017). Among the risk groups for iodine consumption are pregnant and lactating women, they require 50% and 100% more iodine than an adult, respectively (see Table 2) (Maalouf et al. 2015; Dzhatdoeva et al. 2005; Valeix et al. 2009; Manousou et al. 2017; Olivieri et al. 2017; Medicine, Institute of Iodine 2001; "Iodine: Fact Sheet by the Office of Dietary Supplements (ODS)" 2011; Institute of Medicine (US) Panel on Micronutrients 2001). The fact that iodine is a scarce element on earth it is important to determine whether an individual is under proper iodine nutrition, especially pregnant and lactating women. Today, the median urinary iodine concentration (UIC) is a parameter used worldwide to monitor iodine nutrition status in a population (Pearce et al. 2016). The UIC value corresponds to the median urinary excretion of iodine obtained after 24 hours of urine recollection or a spot urine sample taken in the morning (Pearce et al. 2016). The UIC values are really used as a parameter for the population of iodine nutrition status. For an individual the UIC accounts for the daily intake of iodine, but not for individual nutrition status due to its high intra- and inter- individual variation (Pearce et al. 2016; Rohner et al. 2014). Regarding to that, a consensus published by WHO indicated that UIC values of a population lower than 100 μg/L corresponds to insufficiency iodine intake and therefore this population it instead is at high risk of suffering IDD (see Table 2) (WHO 2008). Based on the UIC values there are 22 developing countries at risk of suffering severe iodine deficiency (Figure 1) (IGN 2017). Iodine nutrition status of a population could vary inside of a country or region or person to person (Laurberg et al. 2010). It has been reported that countries like Finland, Italy and Russia have regions with iodine deficiency (IGN 2017). Even though, iodine supplementation programs had helped to reduce significantly areas with severe iodine deficiency, there are regions that still not achieve sufficient levels to fulfill the requirements

Table 2. Recommended median daily intake and tolerable upper intake level (UIL) of iodide by age or population group (Maalouf et al. 2015; Dzhatdoeva et al. 2005; Valeix et al. 2009; Manousou et al. 2017; Olivieri et al. 2017; Medicine and Institute of Iodine 2001; "Iodine: Fact Sheet by the Office of Dietary Supplements (ODS)" 2011; Institute of Medicine (US) Panel on Micronutrients 2001).

	I^- intake (μg/day)	UIL (μg/day)
Children 0–6 months	110	Not possible to establish
Children 7–12 months	130	
Children 1–8 years	90	200–300
Children 9–13 years	120	600
Children ≥14 years and adults	150	900
Pregnant	220	900–1100
Lactating	290	900–1100

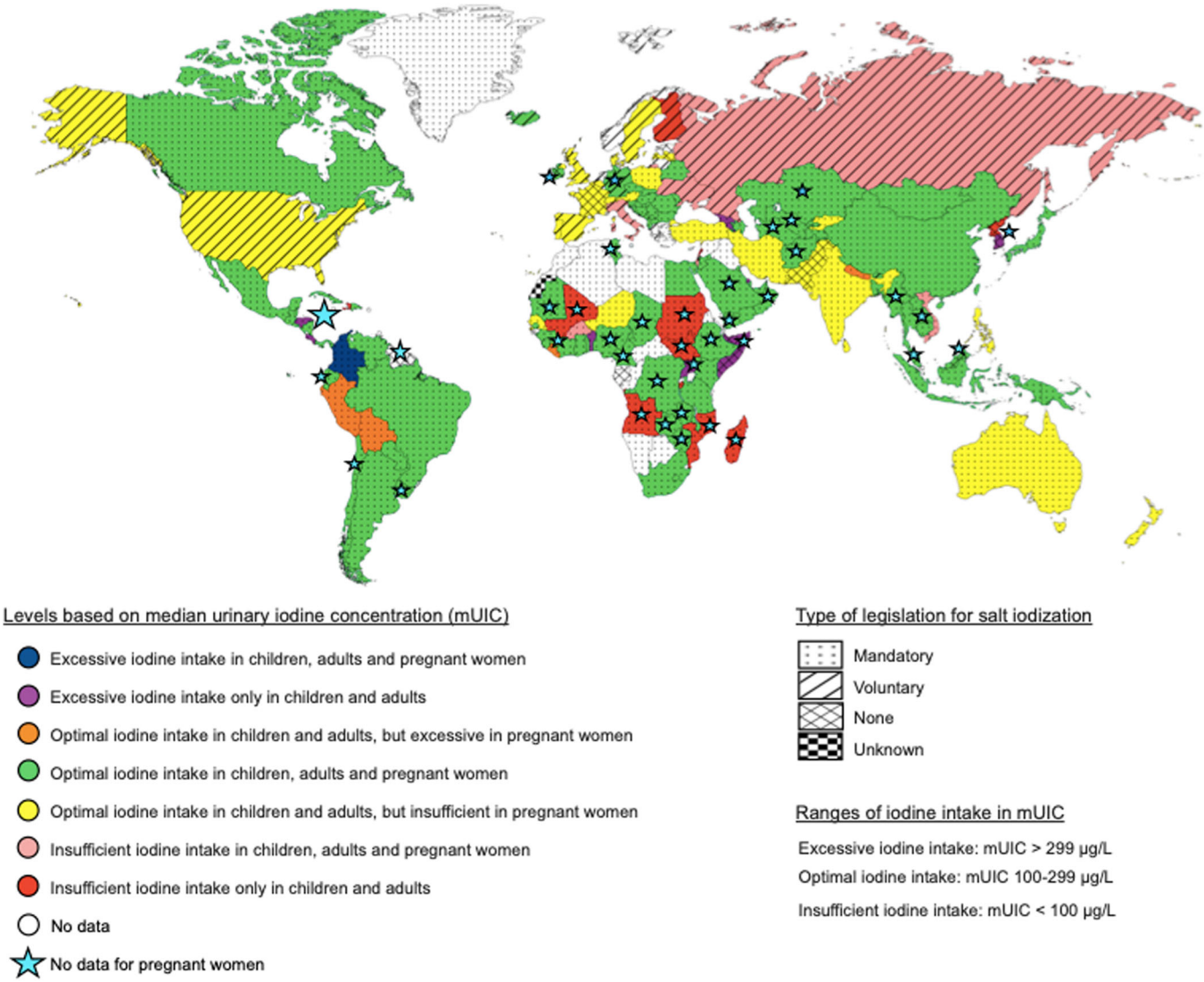

Figure 1. Global status of iodine intake and the legislation of salt iodization. The colors of the world map indicate the levels of iodine intake per person for each country. This was measured by the urinary iodine concentration (UIC). These data were obtained from children, teenagers and adults during the period between 1993 and 2011. Both national and subnational data from recent period was prioritized. The different fillings indicate per country the type of legislation of salt iodization that it has been or not implemented according to the Iodine Global Network (2016).

of iodine for pregnant women (Figure 1) (FAO and WHO 2001). In fact, there are countries, like United States, France Spain, England, Norway, Australia, Turkish, Romania, Poland, that today have an adequate iodine nutrition status for adults and school-age children, however insufficient for pregnant women (Maalouf et al. 2015; Dzhatdoeva et al. 2005; Valeix et al. 2009; Manousou et al. 2017; Olivieri et al. 2017) (IGN 2017). Thus, it is important to count with a biomarker to determine properly iodine nutrition status individually. The determination of TSH, T_3 and T_4 are insensitive indicators for nutritional iodine status. Specially, these hormones they cannot be used to detect mild or moderate iodine deficiency (Pearce et al. 2016). The determination of thyroglobulin (Tg) in blood is a promising biomarker for nutritional iodine status particularly in populations with mild iodine deficiency, however there is a lack of evidence supporting its use in populations other than children (Pearce et al. 2016).

2. Iodine for human health

2.1. Iodine incorporation into the thyroid hormones

Iodine forms part of the structure of thyroid hormones, which are essential for cell metabolism, differentiation, and for fetus development (Mullur, Liu, and Brent 2014). I^- disposition is a key factor that affects thyroid physiology and thyroid hormone synthesis (Chung 2014). All mammals capture iodine from the diet in the form of an anion like iodate (IO_3^-) or iodide (I^-) which are combined with sodium or potassium to form salt (Patrick 2008). Dietary I^- first is taken up from food and water through the Na^+/I^- symporter (NIS) that localizes at the intestinal epithelial cells of intestine (Nicola et al. 2009). I^- is transported by NIS from the blood to tissues like the thyroid gland and lactating mammary gland for thyroid hormone synthesis (Portulano, Paroder-Belenitsky, and Carrasco 2014). It is important to recall that iodine plays its main physiological role by being

part of thyroid hormones. Thyroid hormone synthesis occurs at the thyroid gland and the first and limiting step for the synthesis of thyroid hormones is the I^- uptake mediated by NIS (Ravera et al. 2017). NIS transports I^- against its electrochemical gradient by using the energy released by the co-transport of Na^+, in favor of its electrochemical gradient (Portulano, Paroder-Belenitsky, and Carrasco 2014). Once in the cytosol, I^- diffuses to the apical side of the cell, where it is transported to the colloid by Pendrin and other transporters (Bizhanova and Kopp 2009; Zbigniew 2017). In the colloid, Tg, the most abundant protein of the thyroid gland, provides the polypeptide backbone for the organification of I^- at specific tyrosine residues. This reaction is mediated by thyroid peroxidase (TPO) and dual oxidase 2 (DUOX2) (Di Jeso and Arvan 2016). Tg will then be endocytosed by thyroid follicular cells and these endosomes will fuse with lysosomes, allowing the proteases to digest Tg in T_3 and T_4. These endosomes will fuse to the plasma membrane for the exocytosis of T_3 and T_4 into the blood (Becker 2002; Ahad and Ganie 2010). It has been described that the enzyme iodotyrosine dehalogenase (DEHAL1) is also present in apical side of the thyroid cell and can deiodinated Tg and release of iodotyrosines that contributes as an intracellular source of iodide allowing iodide recycling (Carvalho and Dupuy 2017) All these steps of thyroid hormone synthesis are positively regulated by thyroid stimulating hormone (TSH). Only 30% of the thyroid hormones secreted by the thyroid gland corresponds to T_3 and 70% correspond to T_4 (Bianco et al. 2002) and once in the blood 99.7% of T_3 and 99.95% of T_4 are found bound to proteins like thyroxin-binding globulin (TBG), transthyretin (TTR) and human serum albumin (HAS) (Janssen and Janssen 2017). In fact, this high percentage of thyroid hormones bound to proteins constitute a big reservoir of thyroid hormones for the organs (Janssen and Janssen 2017). It has been reported that both T_3 and T_4 to enter into the cell require carriers like the organic anion transporting polypeptides OATP1A2, OATP4A1, OATP1C1, the L type amino acid transporter LAT1 and LAT2 and monocarboxylate transporter MCT8 and MCT10 (Visser et al. 2011). T_3 is the principal physiological active thyroid hormone (Bianco et al. 2002). To understand the physiological aspects of thyroid hormones homeostasis is necessary to emphasize that the active T_3 in most cells is produced in those cells mainly by the conversion of T_4 into T_3 and not by T_3 secreted from the thyroid gland (Rousset et al. 2015). Therefore, the requirement of T_3 for each organ or tissue is controlled, managed and supplied through the deiodination of T_4 into T_3 for each tissue (Mondal et al. 2016). This process is carried out by deiodinases 1 (D1) and/or deiodinases 2 (D2) (Bianco et al. 2002). Each tissue regulates the expression of these enzymes (Bianco and da Conceição 2018) and their enzymatic activities depend on selenium which will be bound to D1 and D2 (Köhrle 2005). T_3 will perform its biological role by binding to nuclear receptors that are transcription factors that will increase or repress the expression of genes (Cheng, Leonard, and Davis 2010). Thyroid hormones also function by non-genomic mechanisms please refer to more specific reviews (Davis, Goglia, and Leonard 2016).

3. Compensation and diseases caused by unappropriated iodine nutrition

3.1. Mechanisms of compensation under iodine deficiency or excess

Insufficiency or excess of I^- affects the physiological process of thyroid hormones synthesis and several compensatory mechanisms will run to maintain the synthesis of thyroid hormones (Leung and Braverman 2014). Under I^- deficiency the thyroid gland compensates I^- insufficiency by increasing the production of T_3 and decreasing T_4 (Chung 2014; Karmarkar et al. 1969). Authors discuss that the mechanisms behind, are related with turning on the production to monoiodotyrosines (MIT) than diiodotyrosines (DIT). Another mechanism is the increasing expression and activity of deiodinase 2 (D2) at the extrathyroid tissues having as a consequence a higher conversion of T_4 into T_3 (Wang et al. 2009). Interestingly, the opposite occurs at the hypothalamus and hypophysis where the expression and activity of D2 decrease (Mullur, Liu, and Brent 2014). Then the conversion of T_4 into T_3 decreases in these tissues and as consequence the less content of T_3 will stimulate the synthesis of TSH and thyrotropin releasing hormone (TRH). TSH will stimulate the enlargement of the thyroid gland aiming to increase I^- uptake and thyroid hormone synthesis (Mullur, Liu, and Brent 2014). The excess of iodide in the diet for a short period (3 to 4 days) induces a compensatory mechanism that aims to reduce the uptake of iodide by the thyroid gland and the synthesis of thyroid hormones (Leung and Braverman 2012). This mechanism is named the Wolff-Chaikoff effect. However, if the ingestion of iodide remains higher for more than five days the thyroid gland escapes of the Wolff-Chaikoff effect and begins to capture the excess of I^- and the patient increases its risk to develop thyroiditis (Luo et al. 2014).

3.2. Endocrine disruptors that affect iodine incorporation into thyroid hormones

Endocrine disruptors agents can alter the gland function at different levels (Schug et al. 2013). This is the case for endocrine disrupting chemicals (EDC) that affect iodine uptake in the thyroid gland (Diamanti-Kandarakis et al. 2009; Diamanti-Kandarakis et al. 2009). Perchlorate, a contaminant found in water and food (Murray et al. 2008), thiocyanate, a component found in plants, chlorate and nitrates are EDC because they compete with iodide by being transported by NIS inducing thyroid dysfunction (De Groef et al. 2006; Dohán et al. 2007). The same iodine uptake reduction has been observed when FTRL-5 cells where incubated with the soy isoflavone genistein (Schmutzler et al. 2007) that interferes with thyroid hormone synthesis by inhibiting TPO (Marini et al. 2012) and it has been also described that is able to inhibit iodine reutilization by the inhibition of

sulfotransferase enzymes (SULT1A1 and SULT1A13) which contributes to the processing of thyroid hormones for the reutilization of iodine (Ebmeier and Anderson 2004). Second, there are small non-coding RNAs (nc-RNA) which are able to control gene expression in a sequence specific way (Catalanotto, Cogoni, and Zardo 2016). The most studied are micro-RNAs (miRNAs) (Catalanotto, Cogoni, and Zardo 2016). Recent studies have identified several miRNAs that are able to modify the expression/function of NIS. Lakshmanan et al., demonstrated using an *in vitro* model that miR-339-5p is able to decrease NIS radioiodine uptake rate (RAUI) (Lakshmanan et al. 2015). Moreover, gene sequencing analyses showed that the products of miR-146, identified in papillary thyroid carcinoma cells, are also able to bind to the UTR region of the NIS gene impairing protein translation and in consequence reduce iodine uptake (Riesco-Eizaguirre et al. 2015). Another important factors that influence thyroid function are trace elements as iron, zinc, copper, calcium and selenium. Selenium is an interesting essential trace element with anti-inflammatory and antioxidant properties (Drutel, Archambeaud, and Caron 2013), able to interact with iodine to contribute to thyroid hormone production (Köhrle 2015). The intake of this micronutrient is highly variable around the world (Rayman 2012). Even though there are several sources such as vegetables, seafood, meat and nuts among others that contain selenium (Finley 2006). Selenium is incorporated as selenocysteine (Sec) to selenoproteins and it is highly concentrated in the thyroid gland where selenium dependent deiodinases are able to produce T_3 from T_4 (Schomburg and Köhrle 2008). In fact, selenium is incorporated to the iodothyronine deiodinase 1 (DIO1) decreasing the conversion of T_4 to T_3 as was observed by Kawai et al., in a study in a Japanese population with severe selenium deficiency where a decreased in the selenium intake is correlated with an increase in free T_4 serum levels meanwhile supplementation of selenium was able to increase free T_4 levels in these patients (Kawai et al. 2018).

3.3. Iodine deficiency disorders

As mentioned above, iodine is a key structural component of thyroid hormones. As it is well known iodine deficiency will cause diverse pathologies such as goiter (Gizak, Gorstein, and Andersson 2017), hypothyroidism (Niwattisaiwong, Burman, and Li-Ng 2017), and hypothyroxinemia (Dosiou and Medici 2017). Other consequences of iodine deficiency during pregnancy to the offspring are intellectual impairment like low intellectual coefficient, autism (Błażewicz et al. 2016), schizophrenia (Harper and Brown 2012), and mental retardation (Walker et al. 2007; Pharoah, Buttfield, and Hetzel 1971). Recently, iodine deficiency has been associated also to anxiety (Młyniec et al. 2015), depression (Młyniec et al. 2015), obesity (Verheesen and Schweitzer 2008) and fibromyalgia (Verheesen and Schweitzer 2008). In the following section of this review we will discuss relevant clinical data of several diseases and health impairment associated with iodine deficiency.

3.3.1. Goiter

Goiter affects a 15.8% of general population and it is characterized by an enlargement of the thyroid gland that occurs in response to high levels of TSH in the blood (Dauksiene et al. 2017). The high levels of TSH are product of low insufficient level of thyroid hormones that can be the result of iodine deficiency or inactivating mutations at Tg (Siffo et al. 2018) and TPO (Ris-Stalpers and Bikker 2010) genes. Goiter is higher in women than in men (Dauksiene et al. 2017) and it increases with age (Gizak, Gorstein, and Andersson 2017).

3.3.2. Hypothyroidism and hypothyroxinemia

Hypothyroidism and hypothyroxinemia are conditions classified among iodine deficiency disorders (IDD). Hypothyroidism, is clinically classified as overt hypothyroidism where patients have low thyroid hormones levels and high TSH levels and affects 1–2% of the population (Seo and Chung 2015). Second, subclinical hypothyroidism is characterized by the solely increase of TSH levels in the blood and it has a 3–15% prevalence worldwide (Peeters 2017). Considering both types, hypothyroidism affects between 4% to 10% of the population (Vanderpump 2011; Taylor et al. 2018). Iodine deficiency is the most important cause of hypothyroidism worldwide, however in those countries where there is sufficient iodine in the diet the main cause of hypothyroidism is autoimmune Hashimoto thyroiditis (Ragusa et al. 2019). Other factors that can provoke hypothyroidism are an impaired function of hypothalamus, pituitary and/or thyroid gland (Kapil 2007). Iodine deficiency it also exposed the appearance of hypothyroidism in those patients that are heterozygous for mutations in DUOX oxidase (Moreno and Visser 2007). The authors emphasize that patients with these mutations require a more elevated amount of iodine in the diet to avoid the development of hypothyroidism. Patients that suffer overt hypothyroidism frequently deal with overweight, coldness, constipation, dry skin among other symptoms. Some patients could also show several health consequences due to the low levels of T_3 down regulates cell metabolism and impair the expression of genes that are important for cell function. It has been reported that hypothyroid patients could develop depression (Larisch et al. 2004; Fardella et al. 2000; Gloger et al. 2001), infertility (La Vignera et al. 2017; Dunn and Turner 2016) and miscarriages during pregnancy (Weiss and Clapauch 2014). It has been observed in hypothyroid patients a systemic vascular resistance leading to an increase of diastolic blood pressure resulting in diastolic hypertension that is often sodium sensitive (Klein and Danzi 2016). It has been reported that patients that suffer of subclinical hypothyroidism also develop heart problems like congestive heart failure (Rodondi et al. 2005) or cardiomyopathy (Zoltowska et al. 2018). The hypothyroxinemia condition is an asymptomatic condition in adults and clinically characterized by the solely decrease of serum T_4 (below the 2.5th percentile), while the levels of T_3 and TSH remain normal. It has been proposed that hypothyroxinemia is a compensatory mechanism to overcome iodine deficiency, thus keeping normal the level of

active thyroid hormone T_3 in the blood (Alexander et al. 2017; Henrichs et al. 2013). Hypothyroxinemia reaches higher relevance at the first trimester of pregnancy given that the fetus depends of maternal T_4. According to the available data, the prevalence of hypothyroxinemia worldwide varies from region to region and it is believed that this condition could be more frequent than hypothyroidism. In those territories with iodine deficiency maternal hypothyroxinemia varies from 3.2% to 23.9%, respectively (López-Muñoz et al. 2019). Impressive is the information that declares that hypothyroxinemia in pregnant woman is also highly prevalent in countries with sufficient iodide nutrition, such as the United States and the Netherlands with 1.3% and 4.3%, respectively (Moleti, Trimarchi, and Vermiglio 2011) . Iodine deficiency during pregnancy could induce the occurrence of maternal hypothyroidism or maternal hypothyroxinemia (Negro et al. 2011). Several reports have shown that both conditions have irreversible consequences to the offspring given that the mother supplies the fetus with her thyroid hormones at least until gestational weeks 17–20 (Thompson et al. 2018). This is because the fetus thyroid gland and the axis hypothalamus, hypophysis and thyroid gland has not properly developed and mature to produce thyroid hormones (Opazo, Haensgen, et al. 2017). Thus, the fetus requires maternal thyroid hormones, especially T_4, because this thyroid hormone is the principal hormone that crosses the placental barrier (Patel et al. 2011). Maternal thyroid hormones are needed for the development of important structures of the fetus like central nervous system (CNS) (Stiles and Jernigan 2010), cells from the immune system (Foster et al. 1998) and gastrointestinal tract (Sirakov and Plateroti 2011) among other organs (Colony 1983). Severe iodine deficiency during pregnancy has been associated with cognitive impairment in the offspring being mental retardation and cretinism the most dramatic consequences (Redman et al. 2016; Dunn 1993). Several studies shown that mild and moderate iodine deficiency during pregnancy can impairs cognition in the offspring, being attention deficit hyperactivity disorder (ADHD), and low intellectual quotient the most frequent observations (Vermiglio 2004; Moleti et al. 2016; Zhou et al. 2015) However, there are controversial results whether maternal iodine supplementation during pregnancy can rescue the offspring from cognitive impairment (O'Donnell et al. 2002; Murcia 2018; Taylor et al. 2017; Moleti et al. 2008). There is an important issue to consider before concluding that iodine supplementation during pregnancy will not rescue cognitive damage in the offspring. That is iodine supplementation must start in women before or at the beginning of pregnancy given that the offspring CNS development begins earlier as the third week of pregnancy (Silbereis et al. 2016). It has been shown that the strongest association among gestational factors and cognitive damage in the offspring is the level of maternal T_4 during pregnancy converting gestational hypothyroxinemia in a harmful condition for the offspring (Levie et al. 2018; Chang and Shin 2014; Korzeniewski et al. 2013; Román 2007). Studies using animal models have also shown a deleterious consequences for CNS development (Lavado-Autric et al. 2003; Cuevas et al. 2005) and cognitive performance (Opazo et al. 2008). At molecular level, it has been described that maternal hypothyroxinemia alters the expression and localization of key proteins that participate in the long-term potentiation (LTP) process, which is essential for a proper cognitive capacity (Opazo et al. 2008; Cisternas et al. 2016). In the last 11 years have appeared studies in humans that gestational hypothyroxinemia increases the probability of the offspring to develop autism (Román et al. 2013; Hamza, Hewedi, and Sallam 2013; Levie et al. 2018; Chang and Shin 2014; Korzeniewski et al. 2013; Román 2007). The consequences of gestational hypothyroxinemia or gestational hypothyroidism seem to be beyond the CNS, in fact there are reports using animal models that indicated that the offspring is more susceptible to suffer inflammation (Albornoz et al. 2013; Haensgen et al. 2018). Albornoz et al. (2013) showed that adult offspring gestated under hypothyroid condition where more susceptible to develop the EAE, increased $CD4^+$ T cell infiltration and demyelination in the spinal cord of the offspring gestated under hypothyroidism (Albornoz et al. 2013). Moreover, gestational hypothyroxinemia in mice impairs the suppressive capacity of T regulatory lymphocytes after EAE (Haensgen et al. 2018). Another study, using a murine model, reported that maternal hypothyroxinemia increases the inflammatory response of astrocytes to an inflammatory stimulus (Opazo, Gonzalez, et al. 2017). Still gestational hypothyroxinemia is not considered clinically a dreadful condition for diagnose and treatment, this decision is based on the evidences that showed that T_4 therapy did not revert the harmful effects in the offspring (Alexander et al. 2017).

3.4. Consequences of iodine excess intake

Previously in this review it was mention that in most cases the thyroid gland is able to compensate acute periods of iodide excess intake. However, in certain individuals iodine excess for chronic periods or after a period of iodine deficiency could increase the susceptibility to suffer thyroid disorders like hyperthyroidism, hypothyroidism, goiter, and autoimmune diseases (Farebrother, Zimmermann, and Andersson 2019).

3.4.1. Autoimmune thyroiditis

Iodine excess intake has been associated with the development of autoimmune thyroiditis (Leung and Braverman 2014; Katagiri et al. 2017). There are some hypotheses regarding how excess of iodine in the diet can induce autoimmune thyroid diseases. It has been proposed that excess of iodine will increase the iodine organification in thyrocytes leading to oxidative cell damage, recognition of thyrocytes molecules as dangerous for the immune system, and the recruitment of lymphocytes to the thyroid gland (Luo et al. 2014). It also has been proposed that the iodine excess could alter the conformation of Tg and when it is processed by antigen presenting cells (APC), will produce antigens that

will be recognized as hazardous for the immune system (Luo et al. 2014).

Also, cells from the immune system, mainly T cells, infiltrate the thyroid gland and induce cell death by secreting antibodies against thyroid proteins, such as TPO or Tg (Antonelli et al. 2015). Furthermore, recruitment of T helper 1 (Th1) lymphocytes leads to the secretion of inflammatory cytokines, such as TNF-α and IFN-γ, which activate the synthesis of chemokines by the thyrocytes, which stimulates Th1 lymphocytes activation and perpetuates the immune response (Antonelli et al. 2014). Thus, patients that have been diagnosed with autoimmune thyroiditis its thyroid gland will not able to produce and secrete thyroid hormones due to cell thyrocytes death caused by inflammation. In fact, most of these patients are diagnose first as hypothyroid patients and they will be treated with thyroxine for life (Brenta et al. 2013).

3.4.2. Grave's disease

Graves's disease is an autoimmune disease characterized by antibodies against TSH receptor (Antonelli et al. 2015). These antibodies have the capacity to stimulate the thyroid gland for the overproduction of thyroid hormones and development of hyperthyroidism (Antonelli et al. 2015). This disease may be promoted by an increased iodine intake. However, this is not the only factor involved in the development of Grave's disease. For instance, genetic disposition seems to be the principal risk factor, although it may develop earlier when is high the iodine intake. Furthermore, in Graves' disease the thyroid gland will uptake more iodine and the patient will develop hyperthyroidism (Laurberg et al. 2010).

4. The effects of iodine in microorganisms

Although few studies have been performed on the role of iodine and thyroid hormones and microorganisms, in this chapter we have summarized the information available so far. Considering the growing numbers of studies supporting the role of microbiota in health and disease, it is possible that the amount of ingested iodine in the diet and the levels of thyroid hormones could have an important impact in the intestinal microbiota. Iodine has not been described as an essential trace element for microorganisms, but it has been described some strains that able to accumulate radioactive iodine (Amachi et al. 2005; Li et al. 2011). Thus, in the following sections we will discuss the effects of iodine in pathogen control and the effects of iodine intake for the intestinal microbiota.

4.1. Iodine for pathogen control

Iodine is the principal specie responsible for antimicrobial efficacy, being one of the main anti-pathogenic agents used today to kill bacteria, viruses and fungi. Iodophors or "iodine releasing agents" had been developed due to iodine itself is very unstable in aqueous solution it stablishes a complex equilibrium between iodine species and iodine. The principal iodophor is the povidone solution. The povidone acts as an active iodine reservoir, releasing iodine to attack microorganisms (McDonnell and Russell 1999). The antimicrobial mechanism of iodine in bacteria seems to be related to the interference with the electron chain transport, preventing respiration and ATP production in aerobic bacteria (Maris 1995). There are evidences that support that iodine also disrupts the cell wall of microorganisms and then attacks nuclear and cytoplasmic structures inside them (McDonnell and Russell 1999). A seminal work performed by Seymour Klebanoff showed that myeloperoxidase, an enzyme found in granules of polymophonuclear plus hydrogen peroxide and iodine induces iodination of bacteria that accounts for its antimicrobial activity (Klebanoff 1967). The authors proposed that an active intermediate compound is formed in the presence of myeloperoxidase, hydrogen peroxide and iodine, which can be precipitated trichloroacetic acid (TCA) and showed bactericidal effects, showed bactericidal effects has a short half-life because this activity is observed only when bacteria are incubated within this compounds and not after the reaction has occurred (Klebanoff 1967). The authors also shown that for higher bactericidal activity the three compounds must be present (Klebanoff 1967). Another study by Simmons and Karnovsky (1973) have shown that iodination also increases the ability of phagocytes from different animals to uptake *Mycobacterim tuberculosis* (Simmons and Karnovsky 1973). Moreover, the intermediate antimicrobial compounds that show the bactericidal ability could be also generated when myeloperoxidase and hydrogen peroxide are incubated with thyroid hormones T_3 and T_4 (Klebanoff 1967). Also, it was demonstrated that human leukocyte myeloperoxidase, in the presence of hydrogen peroxide, degrades thyroid hormones and in turn promote iodination of microorganisms (Klebanoff and Green 1973). These early studies support the notion that iodination used by biological systems is key tool for the immune system to control bacterial burden. Further, these studies suggest that proper iodine nutrition and the presence of adequate levels of thyroid hormones might be relevant for fighting bacterial infections.

Iodine can also kill viruses due to its ability to destroy inner structural components, such as nucleoproteins and genetic material (Sriwilaijaroen et al. 2009). A recent study has also shown that the presence of povidone-iodine inhibits the entry of human and avian influenza virus into MDCK cells (Sriwilaijaroen et al. 2009), as well as the release of viral particles from infected cells. In this study, the mechanisms of viral infection and replication inhibition proposed was inhibition of virus binding to the sialo-glycoconjugate receptor and inactivation of the sialidase activity of influenza, both human and avian (Sriwilaijaroen et al. 2009). The primordial factor that determines the antimicrobial action of iodine is its working concentration. In fact, there is an optimal working concentration that determines its effectivity against each pathogen, without causing cytotoxicity in mammalian cells (Shirai et al. 2000; Sriwilaijaroen et al. 2009). Further, there are several studies suggesting that the

antimicrobial effect of iodine is a promising tool for infectious diseases that currently lack adequate treatment. This is the case for keratoconjunctivitis, an infection produced by adenovirus that lacks effective antiviral therapy. A clinical study showed that the combination of 1.0% povidone-iodine with 0.1% dexamethasone promoted an important decrease in viral titers, as compared to the other treatments tested, and eliminated the virus after seven days (Kovalyuk et al. 2017). Moreover, the antimicrobial effects of iodine against foodborne pathogens like *Listeria monocytogenes*, *Staphylococcus aureus* and *Escherichia coli* had been studied using biofilms and compared to other disinfectants (Cabeca, Pizzolitto, and Pizzolitto 2012). The disinfectants were in contact with the pathogens for 10 minutes after that the viable cells are registered in the biofilm. Bacteria like L. *monocytogenes*, S. aureus, and E. coli growth in the biofilms, 6.3, 5.9, and 4.7 CFU/cm^2, while with 0.20% w/v iodine treatment these numbers decreased to 2.0, 2.4, and 0.8 CFU/cm^2, respectively. Iodine was the best antimicrobial against these three bacteria as compared to biguanide, quaternary ammonium and peracetic acid (Cabeca, Pizzolitto, and Pizzolitto 2012). Another study showed that povidone-iodine nanoparticles had 100% effectivity as antimicrobial against Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa grown in agar plates (Gao et al. 2017). Moreover, povidone-iodine combined with glue, ink and dye have also shown a total inhibition of *Escherichia coli* growth (Gao et al. 2017). The use of iodine in combination with fluorides, has been investigated as dental therapy, given that fluoride by itself is not enough to eliminate dental caries (Featherstone 2006). The effect of single and combined effect of sodium fluoride with iodine was tested against *Streptococcus* mutants, the main cause of the dental caries, showing that the combination of these two agents exerted a beneficial antimicrobial effect against this bacterium (Featherstone 2006). This study also indicated that healthcare professionals must use this combination at lower concentrations to avoid irritation of the mucous membranes (Caufield and Wannemuehler 1982).

4.2. Iodine for the regulation of normal microbiota

It is very relevant to evaluate the effect of iodine over normal microbiota, considering that iodine is a micronutrient and it has an antimicrobial effect. However, there are few studies in the literature that have evaluated the effect of iodine over the oral and the intestinal microbiota. It is possible that dietary iodine, even though in small quantities, could affect the intestinal flora. In support of this notion, a study evaluated the quality of milk and the quantity of microorganism in the milk of cows that were fed with marine brown algae *Ascophyllum nodosum* as an iodine supplement. The authors found that even though the milk of these cows has a high level of iodine, this level was below the maximum permitted. Interestingly, the consumption of *Ascophyllum nodosum* reduced the proportion of *Pseudomonas* genus in the milk from 73.19% to 32.87% and increased the proportion of *Lactococcus* from 22.14% to 66.37%. A remarkably fact was that the lifespan of the milk increased due to the reduction of the genus *Pseudomonas* (Chaves Lopez et al. 2016). Another study by Shen et al. (2019) evaluated the effect of iodine supplementation (18 µg/K/day) in normal and obese rodents (Shen et al. 2019). The authors found that after 8 weeks of treatment normal mice showed an increase abundance of beneficial intestinal bacteria, while obese mice showed a oppose phenotype. It has been also evaluated whether vulvar disinfection of mother during vaginal delivery affects the composition of the oral microbiota in newborns (Li et al. 2019). This study describes that both cesarian-delivered and conventional disinfected-delivery groups have a reduced abundance of the genus *Lactobacillus* and increased abundance of Proteobacteria and Bacteroidetes. Based on these studies, it is possible to suggest that the consumption or use of iodine could affect the human microbiota composition, which could be beneficial or detrimental depending on other health conditions of the host. We should take into account the importance of the quantity of ingested iodine, thinking that there are regions in the world were the consumption of iodine surpass 500 µg per day. These areas are considered to be in risk of thyroid diseases due to diets with iodine excess (WHO 2004) and unexplored effect in the intestinal microbiota can also be expected.

4.3. Effects of thyroid diseases on intestinal microbiota

Other studies have evaluated the effect of thyroid diseases in the intestinal microbiota. A study found that Bifidobacterium and *Lactobacillus* were decreased in hyperthyroid patients and that *Enterococcus* was increased (L. Zhou et al. 2014). Furthermore, it has been described that the intestinal microbiota of patients with Hashimoto's thyroiditis has important differences, as compared to healthy subjects (Ishaq et al. 2017). This study reported that some genera, such as Prevotella and *Dialister*, showed decreased abundance in Hashimoto's patients. In contrast, *Escherichia*, *Shigella* and *Parasutterella* were increased. These results confirmed dysbiosis in Hashimoto's Thyroiditis patients, which could be closely related with iodine intake (Ishaq et al. 2017).

Another recent study stablished a correlation between intestinal microbiota of Hashimoto's patients and clinical parameters. This study shows that Hashimoto's patients have greater gut microbiota diversity than healthy controls (Zhao et al. 2018). This result may be due to bacterial overgrowth in the gastrointestinal tract of patients. Furthermore, the authors described a positive correlation between eighteen microbiota genera and TPO and Tg antibodies (Zhao et al. 2018).

It has been also suggested that intestinal microbiota may play a role in the absorption of I^-. Vought et al. (1972) made a first approach by treating rats with kanamycin and then measuring I^- absorption. Results showed that radioiodine uptake was significantly lower in treated rats than untreated rats, at 3 hours and after 42 and 72 days of treatment (Vought et al. 1972). Also, it has been described that

Escherichia coli binds T_3 and uptake iodothyronines. These bacteria have been related to decarboxylation, deiodination and deamination of iodothyronines. Additionally, Virili and Centanni (2017) suggested that intestinal microbiota may modulate the absorption of oral T_4. Finally, lipopolysaccharide (LPS) from Gram-negative bacteria can stimulate TSH-induced iodine uptake by thyroid cells, by activation of NF-kB pathway and expression of Na^+/I^- symporter (NIS) (Nicola et al. 2010). Therefore, it is possible that commensal bacteria have a huge impact in the balance of thyroid hormones, and that I^- intake affect the composition and diversity of intestinal microbiota. Further studies are required to evaluate these hypotheses.

5. Concluding remarks

Iodine is an essential nutrient for human life and the reality that there is a great disparity in its consumption around the world. This causes that approximately 36.5% of the people suffer of IDD and paradoxically 10 countries have high iodine intake (FAO and WHO 2001). Moreover, there are countries that the general population had sufficient iodine ingestion, however pregnant women are suffering mild iodine deficiency. To resolve these problems the governments will have to do a real effort for improving iodine intake in their countries. These tasks will involve health professionals, epidemiologist and politicians aiming to develop health policies that will eradicate IDD or high iodine intake especially in pregnant women and neonates. Governments must establish adequate and strategic plans that will precisely regulate and monitor iodine intake. Given that, the needs for iodine consumption are different depending of age, physiological status or region, the designed health plans have to fulfill these different necessities. Moreover, gestational hypothyroxinemia is still considered a condition and not a disease and for that it is not diagnosed or treated, even though there are strong evidences showing that impairs the cognitive capacities of the offspring. In animal models it has been shown that gestational hypothyroxinemia also affects the offspring immune response, specially increasing the intensity of autoimmune diseases like multiple sclerosis (Haensgen et al. 2018). In addition, there are several ailments like autoimmune diseases, autism, gastrointestinal alterations and dysbiosis that are linked to IDD. Thus, the consequences of IDD are wide and for this reason are important not only to be aware of them but also to take actions in their prevention. Iodine nutritional status needs to be evaluated constantly in human population, because iodine is essential for humans and it is a common health issue problem around the world. Now, there is not one a simple way to resolve this problem, given that iodine nutritional status varies between regions of the word or in the same country. Thus, it is important for each country to be aware of the status of iodine nutrition in order to develop the proper strategies to eliminate IDD or to avoid thyroid disfunction due to iodine excess intake. Future research should focus in the development of biomarkers that allow the appropriate determination of iodine status in individuals.

Conflicts of interest

The authors declare no conflict of interest.

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