Chapter 1
Iodine Deficiency and Thyroid Function

Antonella Olivieri, Simona De Angelis, Mariacarla Moleti, and Francesco Vermiglio

1.1 Introduction

Iodine deficiency has multiple adverse effects on growth and development in animals and humans. These are collectively termed the iodine deficiency disorders (IDD). These result from inadequate thyroid hormone production due to insufficient iodine intake and represent a global health threat to individuals and societies. Iodine deficiency during pregnancy and breast feeding adversely affects the development of the child. Adults living in iodine-deficient regions show a high risk of goiter, thyroid nodules, and hyperthyroidism. Subclinical hyperthyroidism is a common and frequently undiagnosed IDD and is associated with an increased risk of mortality and coronary heart disease [1–3]. In this chapter, the most important aspects concerning the effects of iodine deficiency exposure during all phases of life are discussed.

1.2 Iodine Absorption and Metabolism

Iodine is an essential dietary nutrient for humans and, as its water-soluble iodide ion (I^-), is a key component of the chemical structure of thyroid hormones, thyroxine (T4) and triiodothyronine (T3), comprising 65% and 59% of their respective weights. The availability of iodide depends on iodine intake. Overall, the natural

A. Olivieri (✉) · S. De Angelis
Department of Cardiovascular and Endocrine-Metabolic Diseases and Aging, Italian National Institute of Health, Rome, Italy
e-mail: antonella.olivieri@iss.it

M. Moleti · F. Vermiglio
Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

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iodine content of many foods is low, whereas foods from marine origin have a higher iodine content [4]. Nevertheless, sea salt has negligible amounts, because iodide in seawater is sublimated into the atmosphere as volatile organic iodine [5]. Iodine is ingested in several chemical forms. Iodide (I^-) is rapidly and nearly completely absorbed in the stomach and duodenum. Iodate (IO^-), widely used in salt iodization, is reduced in the gut and absorbed as iodide. In healthy adults, the absorption of iodide is greater than 90% [6].

Iodine is rapidly cleared from the circulation mainly by the thyroid gland and kidney. The urine contains the fraction of the serum iodine pool that is not concentrated by the thyroid gland. Typically, urine contains more than 90% of all ingested iodine and only 1–2% is excreted in feces and in sweat [7]. While renal iodine clearance is fairly constant, thyroid clearance varies with iodine intake. In conditions of adequate iodine supply, no more than 10% of absorbed iodine is taken up by the thyroid. In chronic iodine deficiency, this fraction can exceed 80% [8, 9]. The salivary glands, gastric mucosa, small intestine, and choroid plexus take up small amount of iodine. The lactating mammary gland also concentrates iodine to provide iodide into the milk for thyroid hormone biosynthesis by the nursing newborn [10, 11]. Under normal circumstances, plasma iodine has a half-life of approximately 10 h, but this time is shortened if the thyroid is overactive, as in iodine deficiency or hyperthyroidism. In iodine-sufficient areas, the adult thyroid traps about 60 μg of iodine per day to balance losses and maintain thyroid hormone synthesis [12].

The Na^+/I^- symporter (NIS) is the plasma membrane glycoprotein that mediates active I^- transport into the thyroid and other tissues. NIS transfers iodide into the thyroid at a concentration gradient 20–50 times that of plasma [13] and mediates the uptake of iodide into the thyroid follicular cells using the electrochemical gradient generated by the Na^+/K^+ ATPase [14–16]. Iodide efflux into the follicular lumen is mediated in part by pendrin (SLC26A4), which is a coupled electroneutral iodide/chloride, iodide/bicarbonate, and chloride/bicarbonate exchanger [17–19]. At the intraluminal side, iodide is oxidized, a reaction that requires hydrogen peroxide (H_2O_2) and is mediated by thyroid peroxidase (TPO), which is located at the apical surface of the thyrocyte [20].

TPO and hydrogen peroxide oxidize iodide and attach it to tyrosyl residues on thyroglobulin (Tg), to produce monoiodotyrosine (MIT) and diiodotyrosine (DIT), the precursors of thyroid hormones. TPO then catalyzes the coupling of the phenyl groups of the iodotyrosines through a di-ether bridge to form the thyroid hormones [21]. In the thyroid, mature Tg, containing 0.1–1.0% of its weight as iodine, is stored extracellularly in the luminal colloid of the thyroid follicle [21, 22]. After endocytosis, endosomal and lysosomal proteases digest Tg and release T4 and T3 into the circulation where the half-life of T4 and T3 is 5–8 days and 1.5–3 days, respectively. Degradation of T4 and T3 in the periphery releases iodine that enters the plasma iodine pool and can be taken up by the thyroid or excreted by the kidney.

1.2.1 Iodine Requirements and Tolerable Upper Levels

Since iodine cannot be stored for long periods by the body, tiny amounts are needed regularly. Iodine turnover, thyroidal radioiodine uptake, and balance studies in euthyroid adults have suggested that the average daily requirement for iodine is 91–96 μg/day [12, 23, 24]. Therefore, according to the U.S. Institute of Medicine (IOM), the estimated average requirement (EAR) for iodine for men and nonpregnant, nonlactating women has been set at 95 μg/day [25]. EAR represents the daily iodine intake that meets the requirement of half of the healthy individuals in a particular life stage. The corresponding Recommended Dietary Allowance (RDA), calculated as the EAR plus twice the coefficient of variation in the population (rounded to the nearest 50 μg) is 150 μg/day [25]. RDA corresponds to the WHO recommendation for adequate daily iodine intake (AI) of 150 μg/day for men, nonpregnant, nonlactating women [26]. In other words, international groups have made recommendations which are fairly similar. Iodine Global Network (IGN, formerly ICCIDD), WHO, and UNICEF recommend the following daily amounts: age 0–5 years: 90 μg/day; age 6–12 years: 120 μg/day; older than 12 years: 150 μg/day; pregnant and lactating women: 250 μg/day.

The Food and Nutrition Board, Institute of Medicine also set the tolerable upper limits of the daily iodine intake as 1.1 mg (1100 μg) for adults, with proportionately lower levels for younger age groups [25], while lower are the tolerable upper limits set by WHO [27] (Table 1.1).

1.2.2 Thyroidal Adaptation to Iodine Deficiency

The body of a healthy adult contains 10–20 mg of iodine, of which 70–80% is in the thyroid. In chronic iodine deficiency, the iodine content of the thyroid may fall to <10 mg. Specifically, thyroidal adaptation to low iodine intake (50–100 μg/day) is mediated by an increased secretion of thyroid stimulating hormone (TSH) which

Table 1.1 Tolerable upper intake level for iodine

	Upper tolerable levels (μg/day)	
Life-stage group	European Commission Scientific Committee on Food	U.S. Institute of Medicine
1–3 years	200	200
4–6 years	250	300
7–10 years	300	300
11–14 years	450	300
15–17 years	500	900
Adult	600	1100
Pregnant and lactating women	600	1100

Table 1.2 Thyroidal adaptation to iodine deficiency

Daily iodine intake	Mechanisms of adaptation	Iodine content in the thyroid	Synthesis of thyroid hormones
50–100 μg/day	↑ TSH	Still in the normal limits (10–20 mg)	Preferential synthesis and release of T3
	↑ I^- uptake by the thyroid		
	↑ Tg breakdown		
	↓ UIC		
<50 μg/day	↑ TSH	Below the normal limits (<10 mg)	Reduced synthesis of thyroid hormones
	↑ I^- uptake by the thyroid		
	↑ Tg breakdown		
	↓ UIC		

increases iodine uptake by the thyroid through stimulation of NIS expression. As a greater fraction of circulating iodide is cleared by the thyroid, there is a progressive reduction in renal iodide excretion. TSH also stimulates breakdown of Tg and preferential synthesis and release of T3 into the blood [28]. Below 50 μg/day, despite a high fractional clearance of plasma inorganic iodine by the thyroid, absolute iodine intake falls, the iodine content of the thyroid is depleted, and many individuals develop goiter (Table 1.2) [9, 29].

The effects of iodine deficiency on the development of goiter and thyroid hypofunction are extremely variable among populations and individuals, even in endemic areas. Dietary, environmental, and/or genetic factors may account for this variability [30–33]. Initially, goiter is characterized by diffuse, homogeneous enlargement, but nodules often develop over time. Many thyroid nodules derive from a somatic mutation and are of monoclonal origin [34]. Although iodine deficiency produces diffuse goiter in all age groups, it is also associated with a high occurrence of multinodular toxic goiter, mainly in women older than 50 years [35].

1.3 Iodine Deficiency in Pregnancy and Fetal Brain

Iodine requirements during pregnancy are substantially increased compared to the nonpregnant state because of changes in maternal thyroid economy that occur as pregnancy establishes [36]. Three events are mainly responsible for a trend toward a reduction in maternal iodide pool during pregnancy: (1) an increased iodide consumption; (2) an increased renal clearance of iodide; and (3) transfers of iodine from mother to fetus [37].

Maternal T4 production during pregnancy is roughly estimated to exceed by 50% of the normal hormone synthesis in the nonpregnant population, which implies that additional 50–100 μg of iodine/day is needed to cope with the increased functional demands imposed by pregnancy.

Early in pregnancy, iodide losses are augmented because of an increase in renal blood flow and glomerular filtration. In addition, the placenta transfers iodine from the maternal circulation to the fetal placental unit, which is estimated at about 50–75 μg/day toward the end of gestation, but it is likely more minimal in the first trimester. Overall considered, these factors are responsible for an additional dose of iodine needed to provide an adequate substrate for both maternal and fetal needs that is quantified in around 150 μg/day [36]. In accordance, recommended iodine intake in pregnancy based on a technical consultation on behalf of the WHO is 250 μg/day [38], roughly corresponding to a urinary iodine excretion of 185 μg/L [39]. This goal is reasonably achievable through universal salt iodization (USI), provided that this measure has been in effect for at least 2 years, and iodized salt is consumed by more than 90% of households. By contrast, in countries where a USI program is lacking, daily iodine intake is assumed to be insufficient to meet the increased requirements for pregnancy, and both women of child-bearing age and pregnant women should be given a daily iodine supplementation in order to start pregnancy with enough iodine stored in their thyroid [38].

An iodine intake below the threshold of 250 μg/day is considered insufficient, and both the mother and fetus are simultaneously exposed to the potentially severe consequences of iodine deficiency. These include different degrees of both maternal and fetal thyroid failures, which in turn may compromise pregnancy outcome and affect fetal neuro-intellectual outcome [40].

1.3.1 Maternal Thyroid Adaptation to Iodine Deficiency

The first biochemical alteration occurring when gestational iodine intake is not sufficient to maintain the intrathyroidal iodine pool is a decrease in maternal T4 production, which soon becomes inappropriately low relative to the increasing thyroxine-binding globulin (TBG) concentrations. This event leads to the progressive desaturation of TBG by T4, which ultimately results in steadily declining free T4 concentrations [37]. Conversely, circulating T3 remains within the normal range, or is even slightly over the upper limit, because of a switch toward a preferential secretion of T3 over T4. This mechanism of adaptation to iodine deficiency is mainly aimed to save iodine and is reflected by an elevated total T3-to-T4 molar ratio, along with TSH concentrations that are maintained within the normal range [41]. As a result, the women are clinically maintained euthyroid by T3, even when T4 is reduced (isolated hypothyroxinemia). Notably, this mechanism, though beneficial to the mother, does not prevent the fetus to be exposed to insufficient maternal thyroid hormone, as it is primarily T4 that crosses the placenta and is delivered to the fetus [40]. If iodine supply persists to be insufficient, also the compensatory mechanism of preferential T3 secretion fails, because of the inability of the maternal iodine pool to guarantee even T3 maternal euthyroidism. Finally, this leads to overt hypothyroidism, due to reduction in total and free T3 concentrations and subsequent increase in serum TSH [42, 43].

As a result of maternal thyroid stimulation by TSH, an enlargement of the maternal thyroid may lead to a transient gestational goiter, which is an additional adaptive mechanism to this condition and is paralleled by progressive increase in serum Tg over the course of pregnancy [37].

1.3.2 Fetal Consequences of Maternal Iodine Deficiency

Unlike the mother, a fetus cannot rely on preferential thyroidal secretion of T3 to face the insufficiency of iodine, because this autoregulatory mechanism only becomes fully operative after birth. Consequently, an insufficient iodine supply to the fetus can result in a reduction in both T4 and T3 production by the fetal thyroid, and clinical and biochemical fetal hypothyroidism occur. In addition, fetal goiter may develop because of sustained TSH stimulation on fetal thyroid in conditions of low iodine intake during pregnancy [40].

The most severe consequences of gestational iodine deficiency are due to inadequate thyroid hormone supply for fetal neurodevelopment [40]. Prior to the onset of fetal thyroid function, the only source of thyroid hormone for the developing brain is the mother, whereas from weeks 16 to 20 post-conception onward both the mother and fetus cooperate to make-up the fetal thyroid hormone pool [40, 44]. Thus, any impairment of maternal and fetal thyroid function—occurring either independently or concomitantly—can result in brain damages and neuro-intellectual disorders in the offspring.

Thyroid hormone influences all stages of brain development by acting through specific gestational time windows during which early and late phases of brain development occur. In particular, early gestation neurogenesis and neuronal migration are under the control of thyroid hormone from the mother, which is the unique source of thyroid hormone at that time. Conversely, neuronal and glial cell differentiation, myelination, and synaptogenesis, which occur from the second trimester of gestation onward, result from a cooperation of both maternal and fetal thyroid hormone contribution [44].

Thyroid hormone actions on the brain are mostly due to the interaction of the biologically active T3 with its specific nuclear receptors and the regulation of related gene expression [45]. In the brain, only a small part of T3 derives from circulation, the vast majority of this hormone being generated from local 5′-deiodination of T4 by type 2 deiodinase (D2) within the astrocytes [46]. Both T4 and T3 cross the blood–brain barrier by means of specific transmembrane transporters, such as the organic anion transporter polypeptide 1c1 (OATP1c1) and the monocarboxylate transporter 8 (MCT8) [47, 48]. Mutations of the latter have been reported to be responsible for the Allan–Herndon–Dudley syndrome, a rare disease characterized by severe mental retardation and neurological impairment due to deficient thyroid hormone transport to the brain [49]. The role of thyroid hormone on brain development is also demonstrated by the evidence of variable degrees of brain damage occurring in patients affected with resistance to thyroid hormone syndromes [50].

Apart from the above rare conditions involving thyroid hormone transport and action, maternal and fetal thyroid insufficiency due to iodine deficiency still remains the leading cause of preventable brain damage. The spectrum of iodine-deficiency neurological damages encompasses several clinical manifestations, from endemic cretinism, which is the most severe manifestation of iodine deficiency, to subtle cognitive deficits, observed in association with even mild to moderate iodine deficiency in pregnancy [51, 52].

Cretinism is characterized by mental retardation in combination with: (1) predominant defects of hearing and speech and characteristic disorders of stance and gait of varying degree (neurological cretinism); or (2) predominant hypothyroidism and growth retardation (myxedematous cretinism); or (3) a combination of the two above syndromes (mixed cretinism) observed in some areas [53]. Cretinism has been typically reported to occur in severely iodine-deficient regions (i.e., median UIC < 20 μg/L in school-age children) and is related to both maternal and fetal hypothyroidism occurring from early gestation onward [40]. Indeed, pivotal intervention studies carried out in populations with high levels of endemic cretinism clearly showed that iodine supplementation before or early in pregnancy is associated with a sharp reduction in the incidence of the condition [9]. Even mild to moderate iodine deficiency (median UIC values of 20–99 μg/L in school-age children) may be associated with altered child neurobehavioral development, likely because of a reduced maternal thyroid hormone availability during early phases of brain development [52].

1.3.3 Iodine Supplementation During Pregnancy

Overall, evidence has been provided that strongly suggests that maternal iodine supplementation started well in advance of conception improves maternal thyroid function and is effective in preventing early maternal thyroid failure [54]. By contrast, no significant changes in maternal thyroid parameters have been reported with iodine supplementation started during pregnancy. Nonetheless, the evidence of a significantly lower thyroid volume and a reduction in neonatal serum thyroglobulin and TSH concentrations in the newborns of iodine supplemented mothers compared with non-supplemented controls is suggestive of improved fetal iodine status with gestational iodine supplementation [9, 55].

With regard to the effects of prenatal iodine supplementation on child neurodevelopment, findings of both observational and intervention studies in mild to moderate iodine deficiency are mixed [56, 57], with some reporting no benefits on child neurobehavioral development [58, 59] and others showing a possible improvement in psychomotor development with prenatal supplementation [60, 61]. Possible explanations for these conflicting results include the use of different tests to measure developmental domains, differences in study inclusion criteria, and, not least, the timing of iodine supplementation during gestation. In this regard, a recent meta-analysis of individual participant data from three prospective population-based

European birth cohorts showed that a lower maternal urinary iodine during pregnancy was associated with lower verbal IQ score in children, but this effect was evident up to the 14th week of gestation only [62]. This finding suggests that, in order to guarantee optimal fetal brain supply of thyroid hormone, iodine supplementation in women with mild to moderate iodine deficiency should be started not later than the first trimester to be effective on child neurodevelopment.

1.3.4 Iodine and Lactating Mothers

Since the mammary gland during lactation is able to concentrate iodine, iodine supply to the newborn via the breast milk may be maintained even in the face of maternal iodine deficiency [63, 64]. This explains why, in areas of iodine deficiency, breast milk iodine concentrations are often greater than expected based on the UIC of the lactating mother [65, 66]. However, there is no consensus on what an adequate breast milk iodine concentration is, and WHO has not made a recommendation on this issue because available studies aimed at evaluating breast milk iodine concentration in iodine-sufficient areas have been conducted in nonrepresentative too small samples [39].

Regarding median UIC in lactating women that indicates adequate iodine nutrition, it is important to underline that, although the iodine requirement is high in lactating women (250 μg/L according to WHO recommendation), after accounting for iodine losses into breast milk, the median UIC that indicates adequate iodine nutrition is the same as that of nonpregnant, nonlactating women (≥100 μg/L) [26].

1.4 Iodine Deficiency in Infancy and Childhood

The WHO recommends an iodine intake of 90 μg/day in early infancy, indicating that a median UIC of at least 100 μg/L in infants is sufficient [26]. These recommendations are currently debated because, assuming a urine volume of 300–500 ml/day, such a daily iodine intake would provide a higher UIC cutoff of 180 μg/L. Iodine balance studies by Delange [67] showed that the average iodine retention of full-term infants was 6.7 μg/kg/day. With an average of fetal weight of 3 kg, the mean retention of a fully developed fetus would be approximately 22 μg/day. These data are consistent with a more recent study in which UIC was measured in a representative national sample of healthy, full-term, iodine-sufficient, euthyroid, breast feeding Swiss infants in the first week after birth [68]. A median UIC of 77 μg/L was found. Therefore, assuming a urine volume of 300–500 ml/day, extrapolating from this median UIC suggests that the mean daily iodine intake in iodine-sufficient Swiss newborns in the first week of life is 30–50 μg/day. These findings suggest that further studies are necessary to establish optimal UIC reference range for iodine-sufficient newborns and to facilitate the use of UIC as an indicator of iodine status in this age group.

Currently, the only indicator used to assess iodine status in newborns is neonatal TSH [69, 70], which is used in many countries for routine newborn screening of congenital hypothyroidism [26]. Since the newborn thyroid has limited iodine stores, even mild deficiency during pregnancy will compromise neonatal secretion of both T4 and T3, with a consequent increased pituitary TSH secretion [71]. It has also been demonstrated that newborn TSH, obtained with the use of a sensitive assay on samples collected 3–4 days after birth, is a sensitive indicator of even marginal iodine nutrition in pregnancy [72].

Besides elevated TSH levels, both transient and permanent forms of congenital hypothyroidism are more frequently observed in iodine-deficient than in iodine-sufficient areas [73, 74]. It has also been demonstrated that, after the correction of iodine deficiency, the time needed to observe a decrease in the incidence of permanent congenital hypothyroidism is about a decade under a condition of iodine sufficiency. This time may be explained by the need to achieve a long-lasting adequate iodine status in the population before observing an effect on the incidence of the disease [74]. In this regard, it has been shown that sustained salt iodization can maintain adequate iodine status in all population groups, even in pregnant women despite their higher requirements [39].

During childhood, iodine deficiency has been linked to reduced intellectual and motor performance [75, 76]. It has been reported that mild iodine deficiency impairs cognition in children, and moderate to severe iodine deficiency in a population reduces the intelligence quotient by 10–15 points [9]. In this regard, it is important to underline that in children born and raised in areas of iodine deficiency, cognitive impairment is at least partially reversible by iodine repletion [77].

Iodine status may influence growth through its effects on the thyroid axis, as demonstrated by the fact that administration of T4 to hypothyroid children increases their growth. Thyroid hormone promotes GH secretion and modulates the effects of GH at its receptor. In iodine-deficient children, impaired thyroid function and goiter are inversely correlated with IGF-I and IGFBP-3 concentrations [78]. In addition, iodine repletion in iodine-deficient children was found to be associated with increase in IGF-I and IGFBP-3 concentrations and improved somatic growth [79, 80].

As iodine intake falls, secretion of TSH increases in an effort to maximize uptake of available iodine, and TSH stimulates thyroid hypertrophy and hyperplasia. If this adaptation is successful and the iodine deficiency is not too severe, the person may escape with only an enlarged thyroid and no other apparent damage from the iodine deficiency. Goiters in children are usually small, soft, and diffuse, but over time, thyroid follicles may fuse and become encapsulated, a condition termed nodular goiter.

Chronic iodine deficiency increases the TSH concentration and may also produce a thyroid hormone pattern consistent with subclinical hypothyroidism [80]. In children, subclinical hypothyroidism may be associated with a more atherogenic lipid profile [81]. An uncontrolled study reported iodine treatment of goitrous German adolescents decreased plasma cholesterol concentrations [82]. Another study reported that iodine treatment of moderately iodine-deficient children with elevated TSH concentrations due to iodine deficiency improves their lipid profile and reduces their insulin (C-peptide) levels compared with control [83]. This

previously unrecognized benefit of iodine prophylaxis may be important because iodine deficiency remains common in many countries with increasing rates of obesity and cardiovascular disease.

1.5 Iodine Deficiency in Adults and Elderly

The consequences of iodine deficiency have been so far regarded as conditions mostly involving specific subset of population such as fetuses, newborns, pregnant women, and lactating mothers, for whom a definitely large number of clinical and biochemical data are now available in the literature. Basically, this is due to the fact that iodine deficiency during pregnancy and lactation is known to irreversibly affect brain development and explains why studies on iodine deficiency are mainly targeted to pregnant and lactating women. Conversely, in the elderly and adults, data on dietary iodine status are still relatively limited.

Few observational studies aimed at verifying the status of iodine nutrition over the course of life in the general population from different geographic areas overall demonstrated a significant decline in daily iodine intake later in life [84–87]. Explanations for this trend include a reduction in milk consumption, particularly evident among females, a reduction in salt consumption, and a major condition of global undernourishment in the elderly [88].

The importance of the population iodine intake and of related different thyroid abnormalities in elderly subjects was studied in several reports from over the world. Either uni- or multi-nodular goiter is the more common consequence of iodine deficiency at all ages, even in mild to moderate iodine-deficient areas. In fact, the reduction in thyroid hormone synthesis due to inadequate iodine availability triggers TSH-driven goiter growth and nodularity, which, at least initially, is accompanied by biochemical euthyroidism. In long-standing multi-nodular goiter, because of the persistently increased thyroid cell replication rate, somatic point mutations of the TSH receptor (TSHR) may occur, which result in a constitutive activation of the TSHR and the development of autonomously functioning thyroid nodules [89, 90]. This finally leads to hyperthyroidism, either subclinical or overt, with related cardiac risks of atrial fibrillation, embolism, and congestive cardiac failure [91]. Indeed, thyroid hormones play a central role on heart function, through both genomic and nongenomic effects. Thyroid hormone excess results in deep changes of both cardiac function and cardiovascular hemodynamics, with increase in resting heart rate, blood volume, stroke volume, myocardial contractility, and ejection fraction. All these events may precipitate a “high output heart failure” and arrhythmia such as atrial fibrillation with related risk of embolic complications, especially in the elderly [91]. The relationship between iodine deficiency and hyperthyroidism due to multinodular goiter is evident from studies carried out in both iodine-deficient and iodine-sufficient areas, showing higher prevalence of hyperthyroidism (subclinical or overt) in the former and higher prevalence of hypothyroidism in iodine-sufficient populations [1]. Notably, after implementation of iodine prophylaxis programs, the

incidence of hyperthyroidism may transiently increase, as a consequence of iodine-induced thyrotoxicosis in elderly subjects with preexisting autonomously functioning nodule(s).

While long-term effects of iodine deficiency in early life on neurodevelopment are well acknowledged, little evidence is presently available regarding the impact of iodine deficiency occurring in elderly on brain function. Pioneering researches involving adults residing in areas with severe iodine deficiency showed that correction of iodine deficiency by means of iodized oil injections dramatically reverted the state of lethargy observed in endemic populations in these villages, likely because of a restoration of brain thyroid hormone levels [92]. In fact, thyroid hormones are required for brain function throughout life, and both hypo- and hyperthyroidism occurring in adults can manifest with a wide range of mood disorders and cognitive decline. Typically, these changes regress with euthyroidism restoration, thus indicating that, contrary to what is observed in early life, thyroid hormone alterations of adult onset are not associated with permanent brain damages [93]. Nonetheless, some evidence has been recently provided suggesting a link between low iodine intake in older adults and inner brain atrophy as evaluated by brain structural magnetic resonance imaging scans [94]. Further studies specifically addressing the relationship between long-lasting iodine deficiency, structural brain abnormalities, and cognitive abilities would be useful, for specific preventive strategies be adopted also in elderly people.

In conclusion, the elderly is a rapidly growing segment of the population. It is a high public health priority to ensure older adults having sufficient iodine intake to maintain optimal thyroid function and reduce the burden on health care resources. Recommendations to monitoring iodine nutritional status in elderly should be reinforced and iodine deficiency corrected with the same attention already reserved to other population subsets.

1.6 Prevention of Iodine Deficiency Disorders

Iodine deficiency disorders (IDD) still represent a global health threat to individuals and societies. To eradicate IDD, the WHO recommended USI as the preferred strategy [95]. Over the years, voluntary or mandatory programs of salt iodization have been implemented in many countries. Salt is considered an appropriate vehicle for fortification with iodine, for the following reasons: (1) it is widely consumed by virtually all population groups in all countries; (2) in many countries, salt production is limited to a few centers, facilitating quality control; (3) the technology needed for salt iodization is well established, inexpensive, and relatively easy to transfer to countries around the world; (4) addition of iodate or iodide to salt does not affect the taste or smell of the salt or foods containing iodized salt; (5) iodine (mainly from iodate) remains in processed foods that contain salt; and (6) iodization is inexpensive (the cost of salt iodization per year is estimated at US$0.02–0.05 per individual covered, and

even less for established salt-iodization programs) [96]. Additionally, the concentration of iodine in salt can easily be adjusted to meet policies aimed at reducing the consumption of salt in order to prevent cardiovascular disease. The WHO recommends combining strategies of salt/sodium reduction with parallel salt iodization programs [97]. To make both prevention programs effective, iodine prophylaxis programs should be adapted to the actual salt intake of the population by increasing iodine concentration of iodized salt, when necessary, and by promoting the use of iodized salt in processed food production.

Every year, the IGN, which is a nonprofit, nongovernment organization for the sustainable elimination of iodine deficiency worldwide (www.ign.org), releases a global scorecard of iodine nutrition in populations based on median urinary iodine concentration in school-age children as a proxy for the general population. Based on the most recent scorecard [98, 99], 115 countries are classified as having optimal iodine nutrition, while 23 countries are still classified as iodine deficient (in Europe: Finland, Germany, and Norway). It is worth to note that the iodine intake in several countries formerly classified as optimal has declined, including Cambodia, Nicaragua, Tajikistan, and Germany, which reflects the risk of program backsliding and the need for vigilance and continuous monitoring. The scorecard also indicates that the iodine intake is classified as excessive in 14 countries, which reinforces the need for measures to reduce the excessive iodine exposure in these countries.

1.6.1 Monitoring of Iodine Prophylaxis Programs

Achieving optimal iodine nutrition at the population level is necessary but maintaining it through careful monitoring is equally important. Assessing iodine nutrition at the population level is usually done by (1) determining salt iodine levels, (2) estimating household coverage of adequately iodized salt, (3) measuring the urinary iodine concentration and estimating the prevalence of goiter in schoolchildren.

As mentioned in the first part of this chapter, most iodine absorbed in the body eventually appears in the urine. Therefore, urinary iodine excretion is a good marker of very recent dietary iodine intake. In individuals, urinary iodine excretion can vary somewhat from day to day and even within a given day. However, this variation tends to even out among populations. Conversely, goiter assessment by thyroid ultrasound in schoolchildren is an indicator of a long-lasting iodine intake in a population. In fact, it has been demonstrated that iodine prophylaxis is able to prevent the development of goiter in children born after the implementation of iodized salt and to control thyroid enlargement in older children, although it is less effective in reducing goiter size in children exposed to iodine deficiency in the first years of life [100]. However, the prevalence of goiter in monitoring iodine status in populations may be difficult to estimate because of the lack of consensus on international reference values for thyroid volume [101, 102].

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