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Excess iodine intake: sources, assessment, and effects on thyroid function

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Iodine is essential for thyroid hormone synthesis. High iodine intakes are well tolerated by most healthy individuals, but in some people, excess iodine intakes may precipitate hyperthyroidism, hypothyroidism, goiter, and/or thyroid autoimmunity. Individuals with preexisting thyroid disease or those previously exposed to iodine deficiency may be more susceptible to thyroid disorders due to an increase in iodine intake, in some cases at intakes only slightly above physiological needs. Thyroid dysfunction due to excess iodine intake is usually mild and transient, but iodine-induced hyperthyroidism can be life-threatening in some individuals. At the population level, excess iodine intakes may arise from consumption of overiodized salt, drinking water, animal milk rich in iodine, certain seaweeds, iodine-containing dietary supplements, and from a combination of these sources. The median urinary iodine concentration (UIC) of a population reflects the total iodine intake from all sources and can accurately identify populations with excessive iodine intakes. Our review describes the association between excess iodine intake and thyroid function. We outline potential sources of excess iodine intake and the physiological responses and consequences of excess iodine intakes. We provide guidance on choice of biomarkers to assess iodine intake, with an emphasis on the UIC and thyroglobulin.

Keywords: iodine; iodine excess; thyroglobulin; thyroid autoimmunity; iodized salt

Introduction

Iodine is a nutrient essential for thyroid hormone (TH) synthesis. The consequences of iodine deficiency are well documented,[1–3] and the global strategy to correct iodine deficiency through universal salt iodization (USI) has remarkably improved the health of populations worldwide.[4] Yet, the relationship between iodine intake and thyroid disorders is U-shaped and both inadequate and excessive iodine intakes may provoke thyroid dysfunction.[5–7]

In 2017, while 123 countries reported adequate iodine nutrition in school-age children, 11 countries recorded "excessive" intakes: intakes higher than those required to prevent iodine deficiency.[8] Adverse consequences of excess iodine intakes have been reported,[9] but thyroid dysfunction may also occur at lower intake levels.[7] Transient increases in the incidences of hypothyroidism or thyroid autoimmunity in previously iodine-deficient areas may occur even during careful implementation of USI,[6,10–12] and iodine-induced hyperthyroidism has been observed at daily iodine intakes of less than 300 μg.[13,14]

The aim of our paper is to review the association between excess iodine intake and thyroid function, including the etiology, physiological responses, and consequences of excess iodine intakes. In addition, we provide guidance on the relevant biomarkers that are used to assess excess iodine intake in population monitoring, with an emphasis on the UIC and Tg. We include new data on Tg concentrations in populations across the life cycle who are exposed to excessive iodine intakes.

Methods

We searched relevant databases, including PubMed, Web of Science, Scopus, TRIP, Epistemonikos, and the ETH Bibliothek, using the search terms "iodine excess" AND (any of the following): "thyroglobulin

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OR Tg," autoimmune*, "thyroid autoimmunity," "thyroglobulin antibody," "Hashimoto's thyroiditis," "Graves' disease," biomarker, urine, "TSH OR thyrotropin OR "thyroid stimulating hormone," "thyroxine OR T4," water, food, diet*, and combinations thereof. Selected articles were not limited by type or year of publication, but were limited to English or French language. Reference lists of selected articles were screened for further papers. This search strategy was first conducted in June 2017 and updated in July and September 2018.

Dietary reference values for excessive iodine intake

The recommended daily iodine intake for schoolchildren is 120 μg, and for adults is 150 μg.[15,16] Recommendations are increased for pregnant and lactating women to 250 μg iodine/day to reflect their additional needs.[15,16]

International reference values for upper intakes of iodine are given in Table 1. These values are based upon an interpretation of three small pharmacokinetic dose−response studies evaluating the effects of subchronic iodine exposures in euthyroid adults.[17–19] In these short-term studies, though thyroid function tests generally remained within normal ranges despite exposure to up to 4500 μg/day,[18] iodine intakes of ≥500 μg/day over several weeks can induce subtle, reversible changes in the pituitary−thyroid function in adults, probably by inhibiting TH synthesis and/or release.

The lowest observed adverse effect level (LOAEL) proposed for iodine intakes based on these studies is 1700−1800 μg/day, based on a mild increase in thyroid-stimulating hormone (TSH) that was not associated with clinical adverse effects.[20] To obtain a tolerable upper intake level (UL) from an LOAEL, an uncertainty factor (UF) is applied to compensate for a lack of precision and accuracy across study results and account for differences between populations or varying environmental conditions. The United States Institute of Medicine used a UF of 1.5, bringing the UL to 1100 μg/day,[21] whereas the European Union Scientific Committee on Food used a UF of 3 to reach a UL of 600 μg/day,[20] due to differences in interpretation of the LOAEL effect. In 1988, the Joint Food and Agriculture Organization of the United Nations and WHO Expert Committee on Food Additives suggested the maximal UL from all iodine sources of 1 mg/day would be safe for most of the population except those with iodine sensitivity or underlying thyroid disorders.[16,22]

Intake extrapolations using reference body weights for children and adolescents and based on the conservative European Union UL generally agree with the WHO upper safe threshold for population assessment of iodine intakes.[15,16]

Potential sources of excessive iodine exposure

Iodine exists in a natural cycle of evaporation from seawater and condensation onto land, but soils in many regions are iodine deficient.[23] Most foods have low native iodine content and contribute little to dietary intakes. Population iodine sufficiency is generally maintained through iodine fortification of salt.[15]

Iodized salt

The USI is a safe and cost-effective mass fortification strategy that, if properly implemented, can meet the needs of all population groups.[4,24,25] At a salt intake of about 10 g/day, WHO recommends salt fortification at 20−40 mg/kg, and iodization of ≥15 mg/kg at consumption is adequate to prevent population iodine deficiency but not the risk of excess intakes in vulnerable groups.[4,15,25] The risk of localized excess iodine intakes may increase if legislation stipulates salt iodine fortification above the recommended level or if salt is overiodized at production.[24,26] Salt fortification should be adapted to the actual salt intake and the cumulative coverage of iodized salt, including coverage in staple processed foods, such as bread or bouillon.[27–29]

Food and food products

Though most foods are poor in native iodine, foods from the sea, particularly certain seaweeds, are rich in iodine, though the content is variable.[30] Seaweed ingestion is central to some cultures, including in Japan,[30,31] Korea,[32,33] and elsewhere in East Asia. Daily consumption of iodine at mg doses in these regions is well tolerated by most of the population. However, thyroid disorders triggered by excessive iodine intakes from seaweed have been reported in school-age children and adults,[9,31] preterm neonates,[32] and breastfed infants.[33] Unprocessed meat is generally low in iodine,[28] but accidental thyroid tissue found in beef burgers has caused thyrotoxicosis (hamburger thyrotoxicosis).[34–36]

Table 1. Recommended upper intake levels for iodine

Age group	IOM (μg/day)	SCF (μg/day)	WHO (μg/kg/day)
Premature infants	ND	ND	100
0–6 months	ND	ND	150
7–12 months	ND	ND	140
1–3 years	200	200	50
4–6 years	300 (4–8 years)	250	
7–10 years	600 (9–13 years)	300	50 (7–12 years)
11–14 years		450	30 (>13 years)
15–17 years	900 (14–18 years)	500	
Adult	1100	600	
Pregnant and lactating women	1100	600	40

Sources: IOM, the United States Institute of Medicine;[21] SCF, the European Union Scientific Committee on Foods;[20] WHO, the World Health Organization.[16]
ND, not determined.

Milk products are a major contributor of iodine to many diets, and depending on dairy practice, can be iodine rich.[37,38] Iodinated cattle fodder and mineral supplements are routinely given to dairy herds in excess of their dietary requirements,[39] and iodophor udder disinfectants, used to prevent mastitis infections, contribute to milk iodine content either directly through contamination or by transdermal uptake by the cow.[37] Other animal milks, including goat and camel milk, have been reported to be rich in iodine and are major contributors to local dietary intakes in some settings.[40–42]

The food dye erythrosine contains high amounts of iodine.[29] Though permitted for use in Europe,[43] it is no longer widely used in the United States.[29] Iodate added to bread as a conditioner (not as a fortificant) can contribute to intakes, but this use of iodate is declining.[29]

Breast milk and infant formulae

Iodine is a critical micronutrient during the first 1000 days of life.[3,4,15,44–46] Iodine in breast milk is highly variable depending upon maternal iodine intake.[47,48] In iodine-sufficient populations, if iodine intake is borderline, iodine is preferentially partitioned into breast milk to safeguard infant requirements.[47] High breast milk iodine concentration (BMIC) is reported in areas with excess iodine intakes.[26,42,48,49] Whether there is an active down-regulation of iodine secretion into breast milk at elevated maternal iodine intakes remains unclear.

Infant formula milk, with very few exceptions, must contain iodine to mimic breast milk composition. Levels are strictly mandated: in the United States, infant formulas contain 5–75 μg/100 kcal,[50] whereas EU directives state a tighter range of 15–29 μg/100 kcal.[51] The final iodine content of the formula administered to the infant can also be influenced by the iodine content of the water used for reconstitution.[52]

Water

Drinking water typically has an iodine content of approximately 1–10 μg/L.[53] Groundwater high in iodine is increasingly reported in the literature, including in Algeria,[40,41] Argentina,[54] China,[55–57] Denmark,[58] Djibouti,[26] Ethiopia,[59] and Kenya.[26,60] Concentrations are linked primarily to proximity to a marine environment, the bedrock type through which the water has been filtered, and the depth of the well.[23,53] Iodine-rich water may be the principal source of dietary iodine for some populations, such as in Djibouti,[26] Somalia,[61] and regions in China,[56,62] and has been associated with an increased prevalence of thyroid dysfunction and goiter in some regions[55,63–65] but not in others.[26,61]

Isolated cases of thyroid dysfunction have been associated with drinking water purified with iodine, including in a relief worker population in Nigeria[66] and the U.S. astronauts.[67]

Dietary supplements

Prenatal supplements containing iodine are recommended during pregnancy and lactation in women with inadequate dietary intake,[15] but if maternal consumption becomes excessive, the risk of fetal or neonatal complications increases.[68] In the European Union, dietary supplements are regulated as

foods, and a harmonized legislation regulates the substances that can be used in dietary supplements and their sources.[69] In the United States, the Food and Drug Administration has been granted authority to establish regulations regarding dietary supplement manufacturing, health claims, and labeling.[70] However, regulation of dietary supplements is not harmonized internationally and may put the consumer at risk. An Italian survey[71] found that labeled iodine content was incorrect in more than half of dietary supplements tested, with some supplements exceeding the tolerable upper level. A survey of the U.S. prenatal multivitamins found significant discordance between label information and laboratory assay; 25 brands containing kelp contained between 33 and 610 μg per daily dose, the latter being almost three times the 220 μg recommended daily intake.[72] This may be explained by the natural variations in kelp iodine content,[30] and for this reason, kelp supplements should generally be avoided, and potassium iodide should be used in vitamin preparations.[7]

Iodine in pharmaceuticals and disinfectants

Some pharmaceuticals containing iodine may risk iodine toxicity with chronic use. Amiodarone, an antiarrhythmic drug, liberates 7−21 mg iodide daily depending on dosage.[73] Povidone, iodine skin disinfectant, may be toxic to burn patients and neonates,[7] the use of iodine-containing preparations in neonates being particularly critical (see below).[74] Iodine-containing contrast media can contain up to 370 mg/mL and is a common clinical source of excess iodine exposure.[75] Large doses of iodine are also used in response to nuclear emergencies to reduce the uptake of radioiodines into the thyroid;[76] however, this particular use is beyond the scope of our review.

Human biomarkers of iodine excess

Urinary iodine concentration

The urinary iodine concentration (UIC) is the recommended biomarker of population iodine status.[15] Excretion of iodine in the urine reflects recent iodine intake. In healthy, iodine-replete adults, >90% of dietary iodine is absorbed from the small intestine and >90% is excreted within 24−48 hours.[1] The ingested amount of iodine can, therefore, be estimated from the UIC.[1,15,77] The UIC is conventionally expressed as a population median in μg/L.[15] Assessment of individual iodine status using spot urine samples is not recommended due to intradiurnal variations in intake.[78,79] At the population level, variations are considered to even out with adequate sample size.[1,15]

A median UIC in the range 100−299 μg/L indicates adequate iodine intakes in school-age children; the mUIC below this cutoff indicates inadequate iodine intakes, and above, more than the amount required to prevent and control iodine deficiency.[15,24] The upper threshold for iodine excess is, therefore, mUIC ≥ 300 μg/L in school-age children, or ≥500 μg/L in pregnant women.[15] These thresholds are lowered (≥200 μg/L) in areas of previous endemic deficiency (Table 2). No threshold for excessive iodine intake has been defined in nonpregnant, nonlactating adults nor infants.

Thyroglobulin

Tg is a 660 kDa glycoprotein, synthesized in the thyrocyte and secreted into the thyroid colloid. It is integral to thyroid function and regulation, being both the framework for TH synthesis and an important intracellular regulator.[80–82] Both the synthesis of Tg in the thyrocyte and its secretion into the colloid are controlled by TSH and other factors, including insulin-like growth factor-1[83] and Tg itself.[80]

Healthy euthyroid glands release Tg into the circulation in small amounts via the endocytic transporter−mediated pathway involving megalin.[84,85] In euthyroid populations with a sufficient iodine intake, median serum Tg is normally <10 μg/L, though reference ranges are assay specific.[84] Upon hyperstimulation of the thyroid by TSH or thyroid-stimulating antibodies, production and release of Tg is elevated due to either thyroid hyperplasia,[86] or the upregulation of megalin, whose expression is also controlled by TSH.[80,85] The megalin pathway avoids lysosomal denaturation of Tg in the thyrocyte,[85] thereby regulating the liberation of excessive TH under changes in iodine intake. The relative concentrations of iodinated or noniodinated Tg may differ depending upon the thyroid disease state.[87] *In vitro* studies suggest that poorly iodinated Tg is preferentially transcytosed to preserve richly iodinated Tg for storage or hormone synthesis,[88] though this mechanism may also explain the release of highly iodinated Tg into the circulation as a

Table 2. Iodine status biomarkers and thresholds for iodine sufficiency and excess

Biomarker	Population assessment	Threshold for sufficiency	Thresholds for excess	Notes	Reference
UIC	Iodine status	In schoolchildren: mUIC 100–299 μg/L <20% of a sample population should have UIC <50 μg/L In nonpregnant, nonlactating adult women: mUIC >100 μg/L In pregnant women: mUIC 150–249 μg/L	Population median: ≥300 μg/L in school children ≥500 μg/L in pregnant women ≥200 μg/L in populations with longstanding iodine deficiency and rapid increases in iodine intake	Reflects recent iodine intake	15
Tg	Iodine status Iodine intakes during preceding ~month Thyroid activity	Serum: Iodine-sufficient adults: 3−40 μg/L (a) DBS: Schoolchildren: 4−40 μg/L (b) Pregnant women: 0.3−43.5 μg/L (c)	Schoolchildren: >3% of values >40 μg/L	Reference range may vary by specimen type, assay, or population Some reports of confounding due to TgAb	95 for (a) 93 for (b) 90 for (c)
TSH	Population risk of iodine deficiency (using neonatal TSH screening data)	In neonatal TSH screening programs: <3% of values >5 mIU/L	NA	Reference range may vary by specimen type, assay, or population Neonatal TSH data may reflect population risk of moderate-to-severe iodine deficiency during pregnancy Maybe confounded by the use of iodine-containing antiseptics at birth	15
TgAb	Prevalence of autoimmune thyroiditis Increased risk of thyroid dysfunction in a sample population	Reference range may vary by specimen type, assay, or population. Can be measured in serum or on DBS	NA	Strong genetic and environmental influences on antibody development may confound interpretation	NA
TPOAb	Predictor of increased risk of hypothyroidism[104]	Reference range may vary by specimen type, assay, or population. Can be measured in serum or on DBS	NA	Strong genetic and environmental influences on antibody development may confound interpretation	NA
TGR/Tvol	Iodine sufficiency	Schoolchildren: <5% TGR in a sample population	Not established	Undertaken by palpation or ultrasound Interobserver variation is high	15

Note: T3/T4 and TSHAb are not included in this table as they are not recommended for use in population surveys to assess iodine status or iodine excess.

DBS, dried blood spot; NA, not applicable; PPT, postpartum thyroiditis; Tg, thyroglobulin; TgAb, thyroglobulin autoantibodies; TGR, total goiter rate; TPOAb, thyroid peroxidase autoantibodies; TSH, thyroid-stimulating hormone (thyrotropin); Tvol, thyroid volume; UIC, urinary iodine concentration; mUIC, median UIC.

homeostatic mechanism under conditions of excess iodine intake.

Tg is a sensitive population indicator of both low and excess iodine intake, following a U-shaped association with the UIC, as shown in schoolchildren (Fig. 1A),[89] pregnant women,[90,91] and infants.[46] Elevated Tg normalizes in school-age children after iodine repletion.[92,93] Due to high day-to-day variability, however, the utility of Tg as an individual biomarker of iodine status is uncertain.[94]

Tg can be analyzed in serum or on dried whole-blood spot (DBS), which simplifies field collection and transport.[92,93] The WHO supports the use of DBS-Tg for monitoring iodine status in school-age children in addition to the UIC.[15] Table 2 shows the established DBS-Tg international reference ranges for iodine sufficiency. Table 3 lists Tg values in serum and on DBS from a range of populations exposed to excessive iodine intakes.

Thyroid-stimulating hormone

TSH, also known as thyrotropin, is secreted from the pituitary gland in response to changes in circulating TH, in an intricate negative feedback mechanism

Table 3. Thyroglobulin concentrations and/or prevalence of thyroid autoimmunity in studies reporting excess iodine intakes

Study location	Described iodine source	Population group age range	Median UIC (μg/L) [Median BMIC (μg/L)]	*n*	Tg (μg/L)	*n*	Serum/ DBS	Thyroid antibody	Prevalence	Reference
Adult, male and female										
Mexico, Mexico City	NR	18–67 years	267 (161–482)[a]	48	NR			TPOAb TgAb	9% 10.5%	97
China, Hebei province	Drinking	20–50 years	1152 (753–1539)[a]	506	NR			TPOAb TgAb	Males: 11% Females: 20% Males: 5% Females 16%	98
China, Huanghua, Hebei	Drinking	14–79 years	615 (470–768)[a]	1074	6.4 (3.6–11.4)[a]	1074	Serum	TPOAb TgAb	10.5% 9%	57
China, Huanghua, Hebei Province (2004)	Drinking water	19–83 years	635 (427–745)[a]	864	10.2 (5.9–20.4)[a]	864	Serum	NR		57
Adult, nonpregnant women										
Tanzania, Kinondoni, Dar es Salaam	Iodized salt	18–44 years	473 (321–689)[a]	298	18.1 (12.1–28.8)[a]	321	DBS	NR		46
Kenya, Kibwezi, Makindu County	Iodized salt Iodine-rich ground-water	18–44 years	289 (173–458)[a]	293	26.6 (18.9–39.8)[a]	213	DBS	NR		46
China, Liaoning Province	Drinking water	39 ± 13 years[b]	223 (128–375)[a]	211	6.9 (4.4–13.35)[a]	211	Serum	TPOAb TgAb	7% 8%	99
Pregnant women										
Kenya, Kibwezi, Makindu County	Iodized salt Iodine-rich ground-water	18–44 years	337 (198–505)[a]	162	28.1 (19.3–41.3)[a]	149	DBS	NR		46
Tanzania, Kinondoni, Dar es Salaam	Iodized salt	18–44 years	429 (270–615)[a]	306	25.8 (18.2–38.4)[a]	306	DBS	TgAb	11%	90
Nepal	Iodized salt	18–44 years	290 (162–404)[a]	156	10.7 (7.4–15.1)[a]	156	DBS	TgAb	25%	90
China, Liaoning Province	Drinking water	19–40 years	The group with UIC ≥500	229	13.6 (5.8–48.5)[a]	198	Serum[c]	TPOAb	10%	91
Lactating women and their breastfeeding infants (where applicable)										
Tanzania, Kinondoni, Dar es Salaam	Iodized salt	LW: 18–44 years	LW: 192 (120–297)[a] [BMIC: NR]	363	LW: 19.2 (13.9–27.5)[a]	366	DBS	NR		46
		BFI: 0–6 months	BFI: 515 (279–886)[a]	208	BFI: 59.4 (39.8–81.7)[a]	341	DBS			
Kenya, Kibwezi, Makindu County	Iodized salt Iodine-rich ground-water	LW: 18–44 years	LW: 245 (278–886)[a] [240 (173–346)[a]]	146 126	LW: 21.5 (15.0–31.1)[a]	147	DBS	NR		46
		BFI: 0–6 months	BFI: 546 (323–940)[a]	110	BFI: 51.1 (37.8–64.2)[a]	142	DBS			
South Africa, Townships of Potchefstroom	Iodized salt	LW: 28 ± 7 years[b]	LW: 118 (67–179)[a] [179 (126–269)[a]]	100 100	LW: 22.2 (14.4–30.7)[a]	96	DBS	NR		100
		BFI: 3 ± 1 months[b]	BFI: 373 (202.0–627.0)[a]	92	BFI: 77.0 (56.3–105.7)[a]	66	DBS			
Algeria, Saharawi refugee camps	Drinking water and animal milk	BFI: 31.4 ± 5.9 years[b]	350 (208–533)[a] [479 (330–702)[a]]	111 111	NR for the complete sample		Serum	TPOAb and/or TgAb	17%	42
China, Pingyao, Jicun	Drinking water	LW: 25 ± 3 years[b]	LW: 823 (558–1508)[a] [942 (739–1359)[a]]	125 99	LW: 16.3 (7.8–28.6)[a]	133	Serum	TPOAb TgAb	13% 16%	48
		BFI: NR	BFI: 1222 (787–1995)[a]	124	BFI: NR			BFI: NR		
Infants and young children										
Tanzania, Kinondoni, Dar es Salaam	Iodized salt	6–24 months, receiving breast milk and complementary foods	551 (272–987)[a]	204	50.1 (35.3–74.3)[a]	199	DBS	NR		46

Continued

Table 3. *Continued*

Study location	Described iodine source	Population group age range	Median UIC (μg/L) [Median BMIC (μg/L)]	*n*	Tg (μg/L)	*n*	Serum/ DBS	Thyroid antibody	Prevalence	Reference
Kenya, Kibwezi, Makindu County	Iodized salt Iodine-rich groundwater	6–24 months, receiving breast milk and complementary foods	536 (332–1136)[a]	202	56.1 (43.4–74.6)[a]	294	DBS	NR		46
Algeria, Saharawi refugee camps	Drinking water and animal milk	31.4 months (25.3–35.1)[a], previously breastfed, receiving breast milk and complementary foods, or fully weaned	458 (275–1026)[a]	289	38.4 (10.7–158.0)[a]	289	Serum	NR		49
Nepal, Eastern	Iodized salt	6–24 months, receiving breast milk and complementary foods, or fully weaned	407 (312–491)[a]	630	21.7 (20.4–22.9)[d]	563	Serum	NR		101
Burkina Faso, Dandé Health District	Iodized salt	9 months, receiving breast milk and complementary foods	276 (192–397)[d]	80	33.2 (28.8–37.9)[d]	83	Serum	NR		102
Burkina Faso, Dandé Health District		18 months, receiving breast milk and complementary foods	310 (227–425)[d]	80	26.1 (23.3–29.0)[d]	83	Serum	NR		102
School-age children and adolescents										
Tanzania, Kinondoni, Dar es Salaam	Iodized salt	6–12 years	520 (329–760)[a]	317	32.1 (21.7–44.8)[a]	310	DBS	NR		46
Kenya, Kibwezi, Makindu County	Iodized salt Iodine-rich groundwater	6–12 years	424 (294–598)[a]	284	37.4 (25.0–53.0)[a]	253	DBS	NR		46
Korea, national	NR	6–19 years	449 (15–21,905)[e]	1288	NR			TPOAb	2%	103
Philippines, Tuguegarao	Iodized salt	6–12 years	375 (348–395)[f]	404	17.3 (11.1–27.1)[a]	371	DBS	NR		4
China, Shandong Province, Ningjin County	Drinking water	7–14 years	190 (119–418)[a,g]	397	14.4 (9.3–22.8)[a]	411	Serum	TPOAb and/or TgAb	4%	56
China, Shandong Province, Lingxian County	Drinking water	7–14 years	203 (107–363)[a,g]	522	15.5 (9.6–23.2)[a]	567	Serum	TPOAb and/or TgAb	13%	56
China, Shandong Province, Gaotang County	Drinking water	7–14 years	784 (494–978)[a,g]	495	18.1 (10.7–32.7)[a]	506	Serum	TPOAb and/or TgAb	11%	56
China, Shandong Province, Dongchangfu District	Drinking water	7–14 years	620 (424–887)[a,g]	718	16.6 (10.2–26.6)[a]	740	Serum	TPOAb and/or TgAb	3%	56
Tanzania, Kinondoni, Dar es Salaam	NR	6–12 years	338 (6–1883)[e]	173	17.6 ± 14.3[h]	173	DBS	NR		89

Continued

Table 3. *Continued*

Study location	Described iodine source	Population group age range	Median UIC (μg/L) [Median BMIC (μg/L)]	*n*	Tg (μg/L)	*n*	Serum/ DBS	Thyroid antibody	Prevalence	Reference
Kenya, Kibwezi, Makindu County	Iodized salt Iodine-rich groundwater	6−12 years	624 (437–939)[a]	342	24 (16–37)[a]	342	Serum	NR		104
Various locations with UIC >300 μg/L	NA	6−12 years	UIC >300	477	17.4 ± 18.0[h]	477	DBS	TPOAb	0.5%	89
China, Zhangwu, Liaoning Province	Iodized salt	7−10 years	338[i]	110	7.7 ± 7.2[b]	50	Serum	TPOAb TgAb	1% 1%	105
China, Huanghua, Hebei Province	Drinking water	6−11 years	631[i]	112	13.7 ± 22.8[b]	50	Serum	TPOAb TgAb	3% 0%	105

BFI, breastfeeding infant; BMIC, breast milk iodine concentration; DBS, dried blood spot; LW, lactating women; *n*, sample size; NR, not reported/not measured; Tg, thyroglobulin; TgAb, thyroglobulin antibody positive titer; TPOAb, thyroid peroxidase antibody positive titer; UIC, urinary iodine concentration.
[a]Median (IQR)
[b]Arithmetic mean ± SD
[c]Measurement of Tg only made in TgAb negative women
[d]Geometric mean (95% CI)
[e]Median (range)
[f]Median (bootstrapped 95% CI)
[g]First spot urine result reported
[h]Geometric mean ± SD
[i]mean (with no measure of variation reported)

involving the hypothalamic−pituitary−thyroid (HPT) axis. Within a normal range of iodine intakes, small changes occur within TSH concentrations; however, differences are not significant and there is a wide overlap between individual TSH values (Fig. 1B). TSH is therefore not a sensitive biomarker of neither iodine deficiency nor excess. Yet, TSH is routinely measured in many countries as part of neonatal congenital hypothyroidism screening programs, usually by heel prick, and data obtained by these screening programs may be used to assess population iodine status: a prevalence of >3% of TSH values >5 mIU/L in newborns indicates iodine deficiency in a population.[15] Neonatal TSH may reflect moderate-to-severe iodine deficiency during pregnancy, but its value in mild iodine deficiency and iodine excess is uncertain.[106,107]

In addition to newborn screening, TSH is routinely used in clinical practice as a sensitive marker for hypo- and hyperthyroidism and can be used as a diagnostic tool (alone or in conjunction with other tests) for thyrotoxicosis.[108]

Thyroxine and triiodothyronine

3,5,3′,5′-L-tetraiodothyronine (thyroxine, T4) and its biologically active counterpart 3,5,3′-L-triiodothyronine (T3) circulate mainly as protein-bound hormones (>99%).[77] Very little T3 is secreted by the thyroid gland itself (10%), being principally formed in the peripheral tissues by T4 deiodination.[109] Iodine comprises 65% and 59% of T4 and T3, respectively.[77] Under conditions of excess iodine substrate, T4 is synthesized and preferentially secreted over T3, to permit autonomous regulation of intrathyrocyte iodide concentration (in iodine deficiency, the opposite occurs.) Total TH titer is measured in serum or DBS and reported as total or free hormone concentration, for example, the proportion of free hormone is estimated given the total hormone concentration and the measures of hormone binding.[77] Though TH is a direct indicator of thyroid function, they are generally not used to assess iodine status in population iodine surveys, as values are often within the normal range during mild-to-moderate iodine deficiency, and only fall in severe deficiency (Fig. 1C).[77]

Thyroid autoimmunity

Tg has several different antigenic domains (epitopes) on its structure to which antibodies bind.[87,110] In persons with developed autoimmunity, thyroglobulin autoantibodies (TgAb)

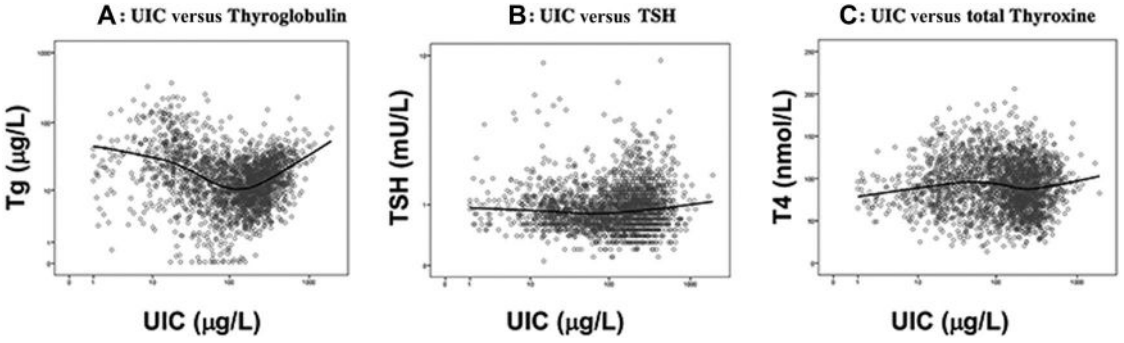

Figure 1. **The relationship between thyroglobulin and iodine intake. Scatterplots (using individual values of 2512 schoolchildren aged 6–12 years from 12 countries) of thyroglobulin (A), TSH (B), and total thyroxine (C) versus the UIC with a Loess smoothed line added to show the best fit. Data are presented on a log scale on both axes. Adapted from Zimmermann *et al.*[89] with permission.**

recognition is typically restricted to certain domains on the Tg molecule.[87,110] The observed immunogenicity is induced by stereochemical changes to the Tg structure: highly iodinated Tg may have a different confirmation and be more immunogenic than poorly iodinated Tg;[111] alternatively, reactive oxygen species-mediated proteolysis can alter the spatial structure.[112] In susceptible individuals, both reactions may be heightened with excessive iodine exposure, or abrupt increases in iodine intake in endemic deficiency, particularly if Tg titers are elevated, which is typical under both conditions.[89] The development of thyroid autoimmunity has been thoroughly reviewed elsewhere.[113–115]

While data from human studies are conflicting, they suggest that iodine intake may be a stronger predictor for elevated TgAb in the presence of genetic susceptibility (increased in Caucasian female populations, see Ref. 114) and relative environmental factors (e.g., infections or exposure to environmental toxins, such as polyaromatic hydrocarbons, see Ref. 114). In individuals, TgAb is a diagnostic serological marker of Hashimoto's thyroiditis (HT) and its epitope recognition patterns have been proposed as a disease progression marker.[110] On a population level, positive TgAb titer prevalence may predict the development of autoimmune disorders in a population. Literature suggests that the development of TgAb positivity has a strong genetic link,[6,114,116] and may also be associated with elevated Tg concentrations; but TgAb positivity may confound Tg assay measurement and concurrent assays may be considered. However, the relationship is unclear since the association between TgAb and Tg concentration in assays is poor,[117] and data to date are inconclusive.[86,118] TgAb are more routinely reported as measured in serum samples though some studies report DBS-TgAb.[90] Stinca *et al.* found no apparent interference of TgAb with population Tg results measured on DBS from pregnant women across 11 countries,[90] though other studies suggest an interference of TgAb in the metabolic clearance of Tg, and therefore its measurement.[119] TgAb are not always present in autoimmune thyroid disorders and have no proven role in their development.[117] Screening is only indicated in adults as TgAb are generally rare in children.[120]

Thyroid peroxidase autoantibodies (TPOAb) show a prevalence of between 12% and 26% in otherwise healthy populations.[96] TPOAb react against antigenic epitopes of the thyroid peroxidase (TPO) enzyme. In healthy subjects, antibodies do not block TPO activity,[121] though in persons with autoimmunity, TPOAb competitively block enzyme activity and affect the oxidative potential of the thyrocyte, fix complement, and cause thyrocyte destruction.[122] TPOAb correlate positively with TSH levels, and positive TPOAb titers may indicate the presence of risk factors for hypothyroidism.[96] Again, females are more at risk of positive titers than males.[96] Thresholds for antibody positivity are assay specific. Population analyses of TPOAb titers may elucidate future risk of thyroid disease; however, the assay is usually restricted to a clinical or research setting.

Thyroid volume

The size of the thyroid gland changes inversely in response to alterations in iodine intake, and both

deficient and excessive iodine intakes may increase thyroid volume (Tvol).[123] The differing etiology of a raised Tvol between ID and iodine excess renders it unsuitable for use as the only indicator of iodine status. Furthermore, changes in goiter prevalence lag behind changes in iodine status and therefore cannot be relied upon to accurately reflect current iodine intake. In areas of mild-to-moderate iodine deficiency and/or excess, measurement of thyroid size using ultrasound is preferable over palpation, though a cutoff for Tvol in iodine excess is not established.

Physiological responses to iodine excess

The healthy thyroid is a highly flexible organ, capable of adapting to various levels of dietary iodine, including an ability to concentrate iodine up to 80-fold if the gland is stimulated.[10] Most euthyroid adults, without underlying thyroid disease and living in iodine-sufficient areas, can tolerate a chronic excess iodine intake of up to 2 g/day without clinical effect.[10] At high intake levels, small changes in TH concentration indicate adaptation by the thyroid: serum T4 and T3 concentrations may drop by 25% and 15%, respectively, with a corresponding rise in TSH of 1−2 mIU/L; however, in most individuals, all values remain within the normal range. There are no clinical signs of thyroid dysfunction or goiter though ultrasonographic thyroid volume may slightly increase.[10] These mild adverse effects are usually reversible.

Regulation of thyroidal iodine uptake following excessive iodine exposure

In 1948, Wolff and Chaikoff demonstrated that organification of iodide in the rat thyroid was blocked when plasma concentrations were raised to a critical level,[124] and that once iodide levels dropped an "escape" from this block occurred. The precise mechanism of the acute Wolff–Chaikoff effect is not entirely understood.

More recent research has shown that TSH is the major regulator of thyroid function and, as described previously, its secretion responds to circulating TH in a negative feedback process controlled through the HPT axis.[109] As circulating TH increases with increasing iodine intake, TSH secretion falls. This regulates the synthesis of Tg and its secretion onto the thyrocyte surface where iodination takes place, thereby regulating the formation of TH,[80,83] and, further, causes a downregulation in sodium-iodide symporter (NIS) expression after about 24 hours.[125]

Research in rat models suggests that there is an earlier, initial response to iodine excess involving inhibition of the NIS once the level of organified iodine in the thyrocyte reaches a critical level.[126] In rat models, after a 5-h exposure to excess iodide, basolateral NIS expression was equivalent in iodine-exposed or control rat thyrocytes, though the uptake of iodide was 25% less in the iodide-exposed cohort.[125] Further, high intracellular iodide concentrations lead to the formation of iodopeptides that inhibit TPO activity and prevent organification.[7]

Intrathyroidal control of iodine uptake and hormone synthesis: thyroglobulin

Though Tg synthesis and secretion is controlled by TSH, Tg has direct effects on thyrocyte function and TH synthesis via an intrinsic regulatory negative feedback mechanism, which is separate to that of the HPT axis. Early *in vitro* studies demonstrated Tg suppression of mRNA for several genes coding for proteins integral to TH synthesis, including the expression of *Slc5a5* (coding for the NIS protein), thereby regulating the influx of iodine into the thyrocyte.[80,81] In a time- and dose-dependent manner, Tg also suppresses dual oxidase 2 expression, the dominant extracellular hydrogen peroxide (H_2O_2) producer,[127] reducing iodine organification by TPO.[80]

Thyroid disorders associated with iodine excess

When normal thyroidal adaptation to excess iodine exposure fails, resulting morbidities are varied and often disparate. Responses depend on prior iodine status, and the risk of morbidity increases in populations previously affected by endemic iodine deficiency.

Increased thyroidal volume and goiter

Goiter, an enlargement of the thyroid, is caused by thyrocyte hyperplasia following overstimulation by TSH, typical in regions affected by iodine deficiency. Yet, with iodine excess, goiter can occur due to failure to escape from the Wolff−Chaikoff effect, or due to persistent stimulation by thyroid-stimulating antibodies that keep the NIS activated and/or propagate lymphocytic infiltration causing an increase in thyroid size.

Iodine-induced goiter was first described in Japan in the 19th century,[31] though a large epidemiological study conducted between 1960 and 1964 in coastal Hokkaido was the first to receive international attention.[9,31] The local population consumed on average 20 mg iodine/day, mainly from seaweed.[9] The adult goiter rate was 9%, compared with 1% in an inland community. More recently, high Tvol were also recorded in school-age children in coastal Hokkaido: median Tvol was 4.9 mL^2 in coastal Hokkaido, compared with 2.9 mL^2 in noncoastal Hokkaido.[128]

In a multicountry study, Tvol increased in school-age children when iodine intakes were more than twice those recommended, equivalent to mUIC ≥ 500 μg/L.[128] Data from China from areas with excessive iodine exposure due to iodine-concentrated potable water suggest that Tvol increases from an iodine intake in schoolchildren >150 μg/day.[129] In another recent study in Chinese school-children, the odds ratio (OR) for total goiter rate per 50 μg iodine intake increments rose from 0.9 (95% CI: 0.2–3.9) at an estimated daily iodide intake of 150–199 μg, to 14.2 (95% CI: 4.8–42.7) at >600 μg iodine/day.[56] A recent meta-analysis that compiled data from 43 Chinese studies, grouped them by iodine status, found a lower prevalence of thyroid nodules in the excessive iodine intake group compared with those with adequate or deficient intakes (7%, 25%, and 22%, respectively).[130]

Goiter has been associated with excessive iodine intakes in Sudan,[131] Ethiopia,[132] Algeria,[132–134] and China.[56,62–65] Lv *et al.* investigated the reversibility of iodine-induced goiter following the initiation of a Chinese policy to remove iodized salt from regions with a high water iodine concentration.[135] Before discontinuation of iodized salt, the mUIC among 8−10-year-olds was 518 μg/L and goiter prevalence 33%. Though mUIC remained high following salt discontinuation (416 μg/L), goiter rate fell to 7%.[135]

Hypothyroidism

Overt and subclinical hypothyroidism are described in Table 4. In subjects with an underlying thyroid disorder, acute excessive iodine intakes may lead to temporary overt or subclinical hypothyroidism that resolves when iodine intakes decrease.[136] Vulnerable individuals may have an increased risk of failing to adapt to the acute Wolff−Chaikoff effect. Predisposing factors are underlying autoimmune thyroiditis (AT), treatment of the thyroid with radioactive iodine and history of external thyroid irradiation, previous subtotal thyroidectomy, postpartum or subacute thyroiditis, and some medications, such as lithium, which interferes with iodine organification and TH release.[136] Subclinical hypothyroidism is a risk factor for the development of overt hypothyroidism. Depending upon antibody status and TSH concentrations, the progression of subclinical to overt hypothyroidism will affect between 1% and 5% of cases per year,[137] although one study reported remission of 60% of cases of subclinical hypothyroidism over 5 years.[137]

The prevalence of subclinical and overt hypothyroidism is generally higher in areas of optimum or chronic excessive iodine intake than in settings of mild-to-moderate iodine deficiency.[5,130,138] In the meta-analysis by Weng *et al.*,[130] across 43 Chinese studies, the authors found the highest prevalence of subclinical hypothyroidism in the group with excessive iodine intake compared with the adequate or deficient intake groups (8%, 3%, and 2%, respectively). Another recent meta-analysis of international studies in adults reported an OR for overt and subclinical hypothyroidism of 2.8 (95% CI: 1.5–5.3) and 2.0 (95% CI: 1.6–2.6) between adequate and excessive iodine intakes, respectively.[5]

Even small increases in iodine intake are associated with a small increase in the prevalence of subclinical hypothyroidism, particularly if the iodine intake increases from deficient to more than adequate within a short time. In a hospital-based retrospective study of 885 Slovenian adults, an increase in the incidence of iodine-induced hypothyroidism was observed from 5% in 2 years before to 20% in 10 years following a mandatory increase in salt iodization levels from 10 to 25 mg/kg in 1999.[139]

The development of hypothyroidism following chronic excess iodine exposure may be due to increased thyroid autoimmunity, the presence of elevated antithyroid antibodies.[57,130,140]

Thyroid autoimmunity

Excessive iodine consumption has been widely described as a risk factor for the development of thyroid autoimmunity.[6,97,116,141,142] The association between autoimmunity and disease is complex; a diagnosis of autoimmune disease is made using positive antibody titers, yet individuals may have positive titers of autoantibodies and no

Table 4. Definitions of thyroid function disorders

Disease state	TSH criteria	T4 criteria
Overt hypothyroidism:	Above upper threshold or >10 mU/L	Below lower threshold or normal
Raised TSH		
Low T4		
Subclinical hypothyroidism	Above upper threshold	Normal
Overt hyperthyroidism	Below lower threshold	Above upper threshold
Subclinical hyperthyroidism	Below lower threshold	Normal
Isolated hypothyroxinemia	Normal	Below lower threshold
Elevated thyroxine[a]	Normal	Above upper threshold
Secondary hypothyroidism[a]	Below lower threshold	Below lower threshold
Secondary hyperthyroidism[a]	Above upper threshold	Above upper threshold

[a]Mostly extrathyroidal disorders and not usually associated with excess iodine intakes.

disease, or disease and a negative titer.[6] Autoimmune, Hashimoto's, or chronic lymphocytic thyroiditis are the most frequent causes of hypothyroidism in iodine-sufficient areas.[2] Lymphocytic infiltration of the thyroid and the stimulation by antithyroid antibodies can increase the risk of chronic inflammation of the thyroid gland and subsequent hypothyroidism.[116] Though lymphocytic infiltration of the thyroid may be a more critical factor than the detection of circulating antibodies since despite having an elevated TSH many individuals exposed to excess iodine will not have a positive antibody titer.[6] Risk of developing AT is elevated due to a genetic predisposition[142,143] in females[142,144,145] and Caucasian populations.[145] Positive antibodies are said to peak at 45−55 years,[142] with hypothyroidism associated with AT more prevalent with increasing age.[142,144–146] The risk of developing autoimmunity and subsequent hypothyroidism may increase after improvements in iodine intakes, such as after implementation of USI or other iodine fortification, particularly in populations previously exposed to iodine deficiency.

In repeated cross-sectional studies in rural Italy,[147] 15 years after the availability of iodized salt, there was an increased incidence of thyroid antibody positivity and a corresponding rise in the prevalence of HT, which increased progressively with age. The frequency of hypothyroidism was also elevated and was mainly subclinical hypothyroidism in children under 15 years old. However, the prevalence of autonomously functioning nodules decreased in subjects younger than 45 years (see below). Ten years after an increase in salt fortification levels in Slovenia, the incidence of HT more than doubled, while that of autonomous thyroid nodules decreased by 27%.[148] Increased incidence of thyroid autoimmunity following the introduction of iodized salt has similarly been observed in Polish adults,[149] Sri Lankan school-age girls,[150] and younger adults in Greece.[151–153] In cross-sectional population studies in adults in Denmark before and 4−5 years after salt iodization, the prevalence of positive TPOAb increased from 14% to 24% and the prevalence of positive TgAb increased from 14% to 20%.[154] In a 5-year prospective Chinese study,[57,155] the cumulative incidence of AT (albeit at low titers) was significantly higher in the cohort with excessive iodine intake. In the same study, euthyroid participants positive for TPOAb and TgAb at baseline exposed to iodine above requirements developed thyroid disorders more frequently than individuals who were antibody negative.

However, other studies report no increase or a reduction in thyroid autoimmunity with time following fortification.[113,154,156–158] The analysis of epidemiological data from a mildly iodine-deficient population in Tasmania found no association between iodine supplementation and an increase of thyroid autoimmunity between 1995 and 2013.[158]

Improved diagnostic criteria and increasing the use of screening technologies for the thyroid (particularly thyroid ultrasound) have led to increased detection of mild thyroid disorders; this has likely contributed to an increase in the incidence of thyroid disorders and biased comparison over time.[159,160] This makes drawing conclusions on temporal trends linking changes in iodine intake and changes in the incidence of thyroid disorders challenging. More evidence from longer term observational studies is needed to resolve this issue.

Postpartum thyroiditis

Postpartum thyroiditis is a thyroid dysfunction characterized by lymphocytic infiltration of the thyroid gland within the first year postpartum in women who were euthyroid before pregnancy,[161,162] or a new occurrence of thyroid autoimmunity (excluding Graves' disease (GD)) postpartum. The classical presentation is a hyperthyroid phase followed by a hypothyroid phase, with a return to euthyroidism within the following year. Alternative presentations may include isolated hypothyroxinemia or isolated thyrotoxicosis.[162] In healthy populations, the incidence of postpartum thyroiditis is about 5%, but it is sharply elevated, to 50%, in women with preexisting autoimmunity and positive TPOAb or TgAb titers in the first trimester.[161,162]

Three small randomized studies have examined the effects of prenatal iodine supplementation on postpartum thyroiditis, but none of the studies observed a difference in frequency or severity of the condition.[163–165] In a randomized trial, pregnant women were given 200 μg iodine/day or placebo until delivery; no differences were observed in maternal thyroid function tests, thyroid volume, or TPOAb between groups during pregnancy and at 6 weeks postpartum.[166] Autoimmune thyroid disease during pregnancy has been recently reviewed in depth.[115]

Iodine-induced hyperthyroidism

Iodine-induced hyperthyroidism, also known as the Jod–Basedow effect, is most frequently observed following iodine supplementation or fortification in areas of very low iodine intake, where the risk of nodular goiter is increased.[6] When the thyroid gland is under iodine-deficient conditions for a considerable period, TSH hyperstimulation may occur as an adaptive response to the limited iodine supply. This can promote autonomous growth and function of thyrocyte clusters,[6] possibly due to mutations promoted by H_2O_2.[167] Following an increase in iodine exposure such as during the introduction of iodized salt, these nodules may escape the control of TSH and act autonomously to overproduce TH, causing hyperthyroidism. The iodine exposure triggering such a reaction in susceptible individuals does not need to be "excessive"; even modest increases in iodine intake below 300 μg/day can trigger this phenomenon, such as initiation or incremental increases in salt iodization. The definition of iodine "excess" in these individuals, therefore, depends upon previous iodine status. Older persons with nodular goiter having had a longer exposure to iodine deficiency are at highest risk,[10,14,138] and living in an iodine-deficient area has been proposed as a risk factor per se.[141,168] The degree of effect depends upon the longevity and severity of iodine deficiency, and the degree of increased exposure to iodine.[13]

Incidence of iodine-induced hyperthyroidism with implementation of iodine fortification or supplementation has been reported.[11,14,154,169–172] The incidence increase is generally considered transient: exposed populations show a 5-to-7-year increase in incidence of iodine-induced hyperthyroidism; however, with time, both the prevalence of iodine-induced hyperthyroidism and nodular goiters decreases to levels below those observed before iodine overexposure. In Switzerland, in 1980, the yearly incidence of toxic nodular goiter and GD together rose by 27% following the correction of iodine deficiency, but from 1980 to 1996, the incidence of both thyroid disorders decreased to levels lower than the baseline annual incidence of about 35 cases per 100,000: toxic nodular goiter decreased to 6.9 per 100,000, and GD to 20.6 per 100,000.[11] A similar pattern of iodine-induced hyperthyroidism, a transient rise followed by a decrease to incidence levels lower than before the increase in iodine intake has been reported in Sweden[173] and Denmark.[14] Overt and subclinical hyperthyroidism are described in Table 4.

Graves' disease

Though nodular goiter is one of the major causes of hyperthyroidism in iodine-deficient or previously endemic areas, GD is the most common cause of hyperthyroidism in iodine-sufficient regions, affecting 0.5% of the population, particularly younger adults.[174–176] In GD, the hyperthyroid state is not linked to autonomously functioning thyroid tissue; rather, it is due to abnormal stimulation of the TSH receptor on thyrocytes by IgG antibodies. Diffuse goiter may be present due to thyroid hyperplasia, and TSH mimicry stimulates increased liberation of TH.[176] Triggers for the development of autoimmunity of GD are multifactorial and considered having a genetic proponent[174,177,178] that may induce sensitivity to environmental factors, including smoking, stress, irradiation, infection,

iodine-containing drug use (e.g., amiodarone), and iodine overload.[176–179]

In a cross-sectional study comparing iodine-deficient adults in Denmark with adults in Iceland with excessive iodine intakes, the incidence of GD was higher in Iceland, particularly among younger age groups.[138] In Denmark, over 6 years following salt fortification in 1998, the incidence of overt hyperthyroidism increased in younger adults (20−39 years) compared with older age groups (40−59 and >60 years).[12] Further follow-up studies monitoring the use of antithyroid medication prescribed for hyperthyroidism indicated that the prevalence had fallen back to baseline levels,[180] suggesting that increases in incidence may be transient following fortification, similar to the prevalence of nodular goiter. However, since this was not reported in other populations,[11,173] further long-term data are required for firm conclusions.[6]

Under situations of sustained iodine sufficiency, dietary iodine intake has little influence on the onset of GD,[177] and a recent systematic review could not establish an association between iodine excess itself and hyperthyroidism.[5] Whether chronic excessive iodine exposure induces the onset of autoimmunity linked to GD remains unclear.

Thyroid cancer

Thyroid cancer rates have increased dramatically in the last decade; however, this may be due in part to progress in the early detection of microcarcinomas rather than a true increase in incidence.[159,160,181] A link between thyroid cancer and excess iodine intakes has been proposed,[160] possibly due to increased oxidative DNA damage.[141] However, to date, there are few data to support this theory. A comprehensive review on thyroid cancer[181] concluded that iodine excess may be a weak promoter; a recent meta-analysis of 16 studies reported an OR of 1.4 (95% CI: 1.1–1.9) between exposure to excessive iodine intakes and risk of papillary thyroid carcinoma, a tendency that was more pronounced when considering only studies conducted in high iodine intake regions (OR 2.2; 95% CI: 1.4–3.5).[182] Finally, Cao *et al.*[183] found that an iodine intake >300 μg/day decreased the risk of thyroid cancer (OR 0.74; 95% CI: 0.6–0.9). Thyroid cancer is the most prevalent malignancy of the endocrine system, and more long-term data from large case–control studies with an accurate estimation of iodine intake are needed to assess the potential relationship with excessive iodine intakes.

Vulnerable groups

Pregnancy, lactation, and the neonate

During pregnancy, increased iodine intake is required to provide for both maternal and fetal needs and to account for increased maternal losses due to an increased maternal glomerular filtration rate.[3] However, the upper acceptable limits for iodine intake during pregnancy are uncertain (Table 3) and the consequences of iodine excess during pregnancy are poorly understood. Although capable of iodine organification starting from 16 to 20 gestational weeks, the developing fetal thyroid may not be able to escape from the Wolff−Chaikoff effect until about 36 weeks.[184] Sequelae due to maternal−fetal excess iodine exposure include, in severe cases, fetal goiter that can obstruct the neonatal airway at delivery,[185,186] or congenital hypothyroidism.[184,187] Although most reported cases have been due to medications, supplements, or seaweed, in some individuals even mildly excessive maternal intakes may cause maternal hypothyroidism or isolated hypothyroxinemia,[45] and this could potentially affect cognitive development of the offspring.[188]

An international study comparing pregnant women across a range of iodine intakes from deficient to more than adequate indicated a U-shaped curve between the UIC and circulating Tg, indicating increased thyroid stress at extremes of intake.[90] Though the prevalence of thyroid disorders in women in the highest intake population was generally low, a 16% prevalence of isolated hypothyroxinemia (Table 4) was observed. This was lower than that seen in populations considered to have an optimal iodine intake, and there was no clear association between iodine intake and thyroid function disorders.[90] A large cross-sectional study of TgAb-negative pregnant women in China showed a U-shaped association between the UIC and Tg.[91] In this study, women with UIC ≥ 500 μg/L had a significantly higher risk of isolated hypothyroxinemia. At a study site in Kenya with adequate salt iodization levels and high iodine in local groundwater, iodine intakes were above requirements and although the prevalence of overt thyroid disorders was low, the prevalence of isolated hypothyroxinemia was 10%.[26]

Breast milk is the principal route to assure infant iodine intakes in both exclusively breastfed infants and those also receiving complementary foods (see above). Mothers with excessive iodine intake typically have a high BMIC.[26,32,42,48,189,190] Excess iodine consumption during lactation may not only increase the maternal susceptibility to thyroid dysfunction, but case reports also suggest the risk of subclinical and clinical hypothyroidism in their infants induced by excess BMICs.[184,189,190] The risk is likely higher in preterm infants with immature thyroid function control mechanisms, particularly with daily iodine intakes of more than 100 μg iodine/kg body weight/day.[32]

However, the susceptibility to excess iodine intake during infancy is uncertain. In a Japanese study of 26 infants exposed to excessive quantities of iodine in breast milk from lactating mothers receiving iodine therapy for GD (see above), only 1 out of 26 infants showed any thyroid dysfunction, which resolved with cessation of the mother's treatment.[191] The authors suggest that the infants in this study could maintain euthyroidism via initiation and then successful escape from the Wolff–Chaikoff effect. In infants exposed to excess iodine during medical procedures,[74] despite application of iodine contrast media at an extremely high dose, no permanent thyroid dysfunction was observed.

Toddlers and young children

TH turnover is markedly increased in infants and children compared with adults, with serum concentrations decreasing throughout childhood and early adolescence.[120] Yet, serum Tg reaches concentrations similar to those of adults by about aged 6 months.[120] The changes in thyroid physiology during infancy may increase the vulnerability of infants to extremes of iodine intake.

A study assessing thyroid function in 6–18-month-old infants across seven sites with low to high iodine intakes observed that infants with the lowest intakes may be at a higher risk of subclinical hyperthyroidism, though no infant had a suppressed TSH.[46] In infants consuming optimal iodine intakes or those above requirements, no increase in thyroid dysfunction was observed.[46] In contrast, in a study assessing 18–48-month-olds in long-established refugee camps in Western Algeria, mUIC was 458 μg/L, serum Tg elevated in 14% of children, and 9% had subclinical hypothyroidism.[49] In 6–24-month-olds in Nepal with mUIC >400 μg/L, the prevalence of overt hypothyroidism was <1% but 7% for subclinical hypothyroidism.[101] Thyroid antibodies are rare in children and are unlikely to explain these phenomena.[120] Therefore, long-term effects of chronic excessive iodine intakes on thyroid function and somatic growth and development in infants and young children remain uncertain.[46]

Conclusion

The spectrum of thyroid disorders with respect to iodine intake is U-shaped, and initiatives to optimize population iodine intakes should focus on the maintenance of levels within an optimal range. Though iodine excess is generally well tolerated, it may induce physiological changes in susceptible groups, particularly those previously exposed to iodine deficiency, pregnant women, or infants. In most cases, thyroid function resolves with either time or a return to iodine intakes within recommendations; however, long-term consequences, particularly in the offspring of women exposed to excessive iodine intake during gestation, are unclear.

Iodine intakes are cumulative and may arise from a variety of sources, and monitoring and surveillance initiatives should emphasize the consideration of all-source intakes. The prevention of iodine deficiency generally outweighs the risks from iodine excess. Careful deliberation should be used during the revision of salt iodization policy when population iodine excess is observed, as current thresholds to define iodine excess are equivocal and do not cover all population groups. Monitoring and surveillance for salt iodization programs should be extended to routinely include human biomarkers in conjunction with the assessment of salt iodine concentrations. The UIC measured in spot urine samples is the most sensitive biomarker of excessive iodine intakes to date; however, the use of Tg shows promise as an adjunct measure in population assessment.

Statement

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is being published individually but will be consolidated with other manuscripts as a special issue of *Annals of the New York Academy of Sciences*, the coordinators of which were Drs. Maria Nieves Garcia-Casal and Juan Pablo Peña-Rosas. The special issue is the responsibility of the editorial staff of *Annals of the New York Academy of Sciences*, who delegated to the coordinators preliminary supervision of both technical conformity to the publishing requirements of *Annals of the New York Academy of Sciences* and general oversight of the scientific merit of each article. The workshop was supported by WHO, the United States Agency for International Development (USAID), and the Bill & Melinda Gates Foundation. The authors alone are responsible for the views expressed in this paper; they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated or the decisions, policies, or views of the WHO. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors, publisher, or editorial staff of *Annals of the New York Academy of Sciences*.

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Author contributions

J.F. conducted the literature searches and drafted the manuscript. M.B.Z. and M.A. contributed to content and provided revisions. All authors reviewed and agreed on the final manuscript.

Competing interests

The authors declare no competing interests.

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