Facts of Iodine Supplementation

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Introduction on Iodine Metabolism and Deficiency

Synthesis of thyroid hormones in sufficient quantities to meet the physiologic demands requires supply of adequate amounts of exogenous iodine. It is estimated that a minimum daily intake of 100 µg iodine is essential to eliminate all signs of iodine deficiency, though the daily requirement varies between different age groups.[1] While iodine is required at all ages, the most critical stages of iodine requirement are during fetal stage and early childhood due to rapid neurological development which takes place at that time. Deficiency of iodine will result in reduced formation of thyroid hormones affecting growth, development and metabolism of various tissues. It was estimated in 1999 that nearly 38% of world population spread across 130 countries were affected by IDD making IDD the most common endocrine disorders world wide.[2] Out of an estimated world population of 5.8 billion in different regions, 3.8% are estimated to be suffering from iodine deficiency in some form, though only 12% is affected by goitre. The manifestations arising from iodine deficiency in a community is termed 'Iodine Deficiency Disorders' (IDD) and encompasses a broad spectrum of disorders as shown in Table 1.

Iodine is ingested in several chemical forms. Iodide is rapidly and nearly completely absorbed in the stomach and duodenum. Iodate, 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%

The Sequence of Events After Absorption of Iodides from Food

At the apical surface of the thyrocyte, the enzymes thyroperoxidase (TPO) and hydrogen peroxide oxidize iodide and attach it totyrosyl residues on thyroglobulin to produce monoiodotyrosine (MIT) and diiodotyrosine (DIT), the precursors of thyroid hormone. TPO then catalyzes the coupling of the phenyl groups of the iodotyrosines through a diether bridge to form the thyroid hormones.[3] Linkage of two DIT molecules produces T_4 and linkage of a MIT and DIT produces T_3. Thus, T_3 is structurally identical to T_4 but has one less iodine (at the 5' position on the outer ring). Iodine comprises 65 and 59% of the weights of T_4 and T_3, respectively. In the thyroid, mature thyroglobulin (Tg), containing 0.1 to 1.0% of its weight as iodine, is stored extracellularly in the luminal colloid of the thyroid follicle. After endocytosis, endosomal and lysosomal proteases digest Tg and release T_4 and T_3 into the circulation. Degradation of T_4 and T_3 in the periphery—the half-life of circulatingT_4 is 5–8 days, and for T_3, 1.5 to 3 days—releases iodine that enters the plasma iodine pool and can be taken up by the thyroid or excreted by the kidney. More than 90% of ingested iodine is ultimately excreted in the urine, with only a small amount appearing in the faeces.

Recommendations for Iodine Intake (µG/D) by Age or Population Group

The estimated average requirement (EAR) is the daily iodine intake that meets the requirement of half of the healthy individuals in a particular life stage. The EAR is not meant to be used in the assessment of intake in individuals, but it can be used for groups. The recommended dietary allowance (RDA) for iodine is the average daily intake sufficient to meet the iodine requirement of 97–98%of healthy individuals in a life stage. It can be used as a goal for daily iodine intake by individuals. The RDA is derived from the EAR, considering the estimated variability in individual requirements. The adequate intake (AI) is given if there is insufficient scientific evidence to calculate an EAR. For example, the AI for iodine in infancy is based on observed mean iodine intakes by healthy full-term breastfed infants in iodine-sufficient areas. The AI is expected to meet or exceed the amount of iodine needed in "essentially all" individuals in the specified population group and it can be used as a goal for individual intake (Table 2).

Table 1 : Iodine deficiency disorders

Fetus	Neonate	Infant/Child/Adolescent	Adult
Spontaneous abortions	Goitre	Goitre	Goitre and its compilations
Stillbirths	Overt or subclinical hypothyroidism	Subclinical or overt hypothyroidism	Hypothyroidism
Congenital anomalies	Cretinism	Mental retardation	Endemic mental retardation
Increased perinatal and infant mortality		Retarded physical development	Decreased fertility
Endemic cretinism		Increased susceptibility of the thyroid gland to nuclear radiation	Spontaneous hyperthyroidism in the elderly
			Increased susceptibility of the thyroid to nuclear radiation

Table 2 : Dietary intake of iodine

Age or population group	IOM EAR	AI or RDA	Age or population group	WHO RNI
Infants 0–12 months		110–130	Children 0–5 yr	90
Children 1–8 yr	65	90	Children 6–12 yr	120
Children 9–13 yr	73	120		
Adults ≥ 14 yr	95	150	Adults >12 yr	150
Pregnancy	160	220	Pregnancy	250
Lactation	200	290	Lactation	250

Goitrogens

Dietary substances that interfere with thyroid metabolism can aggravate the effect of iodine deficiency, and they are termed goitrogens.

- **Cruciferous vegetables** including cabbage, kale, cauliflower, broccoli, turnips, and rapeseed, containing lucosinolates; their metabolites compete with iodine for thyroidal uptake. Lima beans, linseed, sorghum, and sweet potato contain

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cyanogenic glucosides; these may be metabolized to thiocyanates that compete with iodine for thyroidal uptake.

- **Cigarette smoking** is associated with higher serum levels of thiocyanate that may compete with iodine for uptake via the NIS into both the thyroid and the secretory epithelium of the lactating breast; smoking during the period of breast feeding is associated with reduced iodine levels in breast milk.
- **Soy and millet** contain flavonoids that may impair TPO activity. Use of soy-based formula without added iodine can produce goitre and hypothyroidism in infants, but in healthy adults, soy-based products appear to have negligible effects on thyroid function.
- **Unclean drinking water** may contain humic substances that block thyroidal iodination, and industrial pollutants, including resorcinol and phthalic acid, may also be goitrogenic
- **Deficiencies of selenium, iron, and vitamin A** exacerbate the effects of iodine deficiency. Glutathione peroxidase and the deiodinases are selenium-dependent enzymes. In selenium deficiency, accumulated peroxides may damage the thyroid and deiodinase deficiency impairs thyroid hormone metabolism, and these effects have been implicated in the etiology of myxedematous cretinism. Iron deficiency reduces heme-dependent TPO activity in the thyroid and impairs production of thyroid hormone. In goitrous children, iron deficiency anaemia blunts the efficacy of iodine prophylaxis whereas iron supplementation improves the efficacy of iodized oil and iodized salt. Pregnant women are highly vulnerable to iron deficiency anaemia, and poor maternal iron status predicts both higher TSH and lower T_4 concentrations during pregnancy in an area of borderline iodine deficiency. Vitamin A deficiency in iodine-deficient children increases TSH stimulation and risk for goitre through decreased vitamin A-mediated suppression of the pituitary TSH β-gene.

Thyroidal Adaptation to Iodine Deficiency

The thyroid adapts to low intakes of dietary iodine by marked modification of its activity, triggered by increased secretion of TSH by the pituitary. In most individuals, if iodine intake falls below approximately 100 µg/d, TSH secretion is augmented, which increases plasma inorganic iodide clearance by the thyroid through stimulation of NIS expression. TSH exerts its action at the transcription level of the NIS gene through a thyroid-specific enhancer that contains binding sites for the transcription factor Pax8 and a cAMP response element-like sequence. 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 T_3 into the blood. As long as daily iodine intake remains above a threshold of approximately 50 µg/d, despite a decrease in circulating plasma inorganic iodine, absolute uptake of iodine by the thyroid remains adequate, and the iodine content of the thyroid remains within normal limits (≈10–20 mg).Below this threshold, despite high fractional clearance of plasma in organic iodine by the thyroid, absolute intake falls, the iodine content of the thyroid is depleted, and many individuals develop goitre.

In large colloid goitre, the configuration of Tg is abnormal, reducing the efficiency of thyroid hormone synthesis. Initially, goitres are characterized by diffuse, homogeneous enlargement, but over time, nodules often develop. Many thyroid nodules derive from a somatic mutation and are of monoclonal origin; the mutations appear to be more likely in nodules under the influence of a growth promoter, such as iodine deficiency. Although iodine deficiency produces diffuse goitre in all age groups, it is also associated with a high occurrence of multi-nodular toxic goitre mainly seen in women older than 50 yrs. The characteristic pattern of circulating thyroid hormones in children in areas of moderate-to-severe iodine deficiency is a variably elevated TSH, a low serum T_4, and a normal or high-normal T_3;this pattern is also seen in adults, but less predictably, and it may not be present .The serum Tg concentration is typically elevated. Thyroid failure and cretinism usually develop only in regions of chronic, severe iodine deficiency where individuals show low circulating T_4 and T_3 and dramatically elevated TSH. It should be emphasized that the effects of iodine deficiency on the development of goitre and thyroid hypo function are extremely variable among populations and individuals, even in endemic areas. The dietary, environmental, and/or genetic factors that account for this variability in the expression of iodine deficiency from one locality to the next remain largely undefined.

Methods to Assess Iodine Status

Four methods are generally recommended for assessment of iodine nutrition in populations: urinary iodine concentration (UI), the goitre rate, serum TSH, and serum Tg. These indicators are complementary, in that UI is a sensitive indicator of recent iodine intake (days) and Tg shows an intermediate response (weeks to months), whereas changes in the goitre rate reflect long-term iodine nutrition (months to years).

Thyroid size

Two methods are available for measuring goitre:

1. Neck inspection and palpation
2. Thyroid ultrasonography

By palpation, a thyroid is considered goitrous when each lateral lobe has a volume greater than the terminal phalanx of the thumbs of the subject being examined. In the classification system of WHO:

- Grade 0 is defined as a thyroid that is not palpable or visible
- Grade 1 is a goitre that is palpable but not visible when the neck is in the normal position (i.e., the thyroid is not visibly enlarged)
- Grade 2 goitre is a thyroid that is clearly visible when the neck is in a normal position. Goitre surveys are usually done in school-age children.

However, palpation of goitre in areas of mild iodine deficiency has poor sensitivity and specificity; in such areas, measurement of thyroid volume by ultrasound is preferable. Thyroid ultrasound is subjective and requires judgment and experience. Differences in technique can produce inter observer errors in thyroid volume as high as 26%.WHO recommends that the total goitre rate be used to define severity of iodine deficiency in populations using the following criteria: below 5%, iodine sufficiency; 5.0–19.9%, mild deficiency; 20.0–29.9%, moderate deficiency; and above 30%, severe deficiency.

Urinary iodine concentration

More than 90% of dietary iodine eventually appears in the urine therefore urinary iodine (UI) is an excellent indicator of recent iodine intake. UI can be expressed as a

Table 3 : Epidemiological criteria from the WHO for assessment of iodine nutrition in a population based on median or range of UI

UI (µg/l)	Iodine intake	Iodine nutrition			
School-aged children					
<20	Insufficient	Severe iodine deficiency			
20–49	Insufficient	Moderate iodine deficiency			
50–99	Insufficient	Mild iodine deficiency			
100–199	Adequate	Optimum			
200–299	More than adequate	Risk of iodine-induced hyperthyroidism in susceptible groups			
>300	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid disease)			
Pregnant women		Lactating women[2]		Children less than 2 yr of age	
<150	Insufficient	<100	Insufficient	<100	Insufficient
150–249	Adequate	≥100	Adequate	≥100	Adequate
250–499	More than adequate				
≥500[1]	Excessive				

concentration (µg/l), in relationship to creatinine excretion (µg iodine/g creatinine), or as 24-h excretion (µg /day). For populations, because it is impractical to collect24-h samples in field studies, UI can be measured in spot urine specimens from a representative sample of the target group and expressed as the median, in µg/l. Although the median UI does not provide direct information on thyroid function, a low value suggests that a population is at higher risk of developing thyroid disorders.

There is no information about iodine nutrition for pregnant and lactating women in the WHO assessment table, and the upper limits of the median UI for lactating women and children less than two years of age were not specified (Table 3).

1. The term excessive means in excess of the amount needed to prevent and control iodine deficiency.
2. In lactating women, the numbers for median UI are lower than the iodine requirements because of the iodine excreted in breast milk

However, the median UI is often misinterpreted. Individual iodine intakes and, therefore, spot UIs are highly variable from day to day and a common mistake is to assume that all subjects with a spot UI less than 100 µg/l are iodine deficient. Daily iodine intake for population estimates can be extrapolated from UI, using estimates of mean 24-h urine volume and assuming an average iodine bioavailability of 92% using the formula: urinary iodine (µg/l) x 0.0235 x body weight (kg) = daily iodine intake. Using this formula, a median UI of 100µg/l corresponds roughly to an average daily intake of 150 µg.

Thyroid stimulating hormone

Serum TSH is determined mainly by the level of circulating thyroid hormone, which in turn reflects iodine intake, TSH can be used as an indicator of iodine nutrition. However, in older children and adults, although serum TSH may be slightly increased by iodine deficiency, values often remain within the normal range. TSH is therefore a relatively insensitive indicator of iodine nutrition in adults. In contrast, TSH is a sensitive indicator of iodine status in the newborn period.

Thyroglobulin

Tg is synthesized only in the thyroid and is the most abundant intra thyroidal protein. In iodine sufficiency, small amounts of Tg are secreted into the circulation, and serum Tg is normally less than 10 µg/l. In areas of endemic goitre, serum Tg increases due to greater thyroid cell mass and TSH stimulation. Serum Tg is well correlated with the severity of iodine deficiency as measured by UI. Commercially available assays measure serum Tg, which requires venipuncture, centrifugation, and frozen sample transport, which may be difficult in remote areas.

Thyroid hormone concentrations

In contrast, thyroid hormone concentrations are poor indicators of iodine status. In iodine-deficient populations, serum T_3 increases or remains unchanged, and serum T_4 usually decreases. However, these changes are often within the normal range, and the overlap with iodine-sufficient population is large enough to make thyroid hormone levels an insensitive measure of iodine nutrition

Assessing status during pregnancy

According to the WHO/International Council for the Control of Iodine Deficiency Disorders (ICCIDD)/UNICEF for evaluating the status of iodine nutrition in pregnant women, evaluating the median urinary iodine concentration (UI) is recommended. The recommended daily iodine intake can be used to extrapolate the expected UI in µg/l. This assumes the median 24-h urine volume for girls in the age group of 7-15 years to be 0.9 ml/h/kg; for adult women to be 1.5 l; and the mean iodine bioavailability to be 92%. Using this model, the UI during pregnancy is derived to be approximately 135-150 µg/l, corresponding to the recommended daily iodine intake of 220-250 µg for the period of pregnancy. It may also be necessary to take into account the variations in age of pregnant women, particularly in developing countries, where adolescent pregnancy in not uncommon. For example, for a 15-yr-old weighing 50 kg, the UI value comes about to be approximately 185-215µg/l, considering the recommended daily intake of 220-250µg. However, given the physiological alterations during pregnancy, an increase in the glomerular filtration rate and possibly renal iodine clearance (RIC)), this estimation of UI may stand less valid. These uncertainties were reflected in the recent WHO expert group report, which recommended an adequate iodine intake in pregnancy to be 150-249µg, and suggested that the UI be extrapolated from this value.

Assessing status during lactation

Since the mammary gland 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. Iodine supply to the infant may be maintained even in cases of maternal iodine deficiency because of the ability of the mammary glands to concentrate iodine. This may explain the higher values of BMICs than expected (based on UI) that are observed in lactating mothers in areas of iodine deficiency. The full-term infant's iodine requirement is approximately 7µg/kg body weight. Assuming that the iodine in breast milk is 95% absorbed, and the mean breast milk excretion of iodine is 0.781 in the first six months post-childbirth, the minimum BMIC required to fulfil the infant's iodine requirement (of 50µg/day) is 80µg/l until introduction of food. Although maternal iodine requirement during lactation is high (200-290µg/day), the median UI that indicates adequate iodine nutrition status in a lactating woman is the same as that of a non-pregnant, non-lactating woman, keeping in mind the amount of iodine lost in breast milk. [13-15]

Assessing status during infancy

WHO recommendations state that a median UI of at least 100µg/l in infants is sufficient. At the same time, they recommend an iodine intake of 90µg/d during infancy and suggest extrapolating from this to a median UI assuming a urine volume of 300–500 ml/d, but this would produce a higher cut-off of at least 180µg/l.[12]

Concerns of Iodine Supplementation

Thyrotoxicosis

Iodine induced thyrotoxicosis (IIT) was first reported from Tasmania and has since been observed in several other countries with most of iodisation programs. Studies from India also did not reveal any excess occurrence of hyperthyroidism after prolonged iodine prophylaxis.[4-7] It appears that while benefits of iodisation are overwhelming, it could result in IIT especially in the early phase, in individuals with pre existing nodular disease, in the absence of adequate monitoring of the programs.[8,9]

Goitre and autoimmunity

It has been suggested that iodine supplementation could induce/aggravate autoimmunity resulting in goitre and thyroid dysfunction as evident from animal studies, experimental studies on humans and population studies. A study on school children from Delhi, India also reported direct correlation between urinary iodine excretion (UIE) and autoimmunity with goitre and autoimmunity with thyroid dysfunction (subclinical hypothyroidism).[10] In China, autoimmune thyroiditis was found to be associated with more than adequate or excess iodine but no such relation of iodine status with thyroid antibodies alone.[11]

Iodine nutrition and thyroid dysfunction

Some studies point to increasing thyroid dysfunction with increased iodine intake possibly due to iodine directly suppressing thyroid function as well as iodine inducing autoimmune thyroiditis. Other studies, however, do not corroborate the above evidence linking iodine with thyroid.

Iodine nutrition and goitre

It is suggested that excessive iodine could cause goitre due to iodine induced increase in autoimmune thyroiditis as well as iodine induced block of thyroid hormone release causing increase in TSH and goitre.

Iodine and thyroid neoplasia

The existence of a relationship between occurrence of thyroid cancer and iodine status continues to be debated. Available evidence from animal experiments, epidemiological studies and from the introduction of iodine prophylaxis has demonstrated a relationship between iodine intake and the types of thyroid carcinoma, while no clear evidence exists for a relationship between the overall cancer incidence and iodine intake. All the studies are in general hampered by difficulty in comparing populations since many factors have to be considered other than the iodine intake, such as ethnicity, other dietary factors (e.g., selenium), histological examination and radiation. Knowledge of all these factors has an influence also on the diagnostic work-up and management of patients in each population.[16]

Conclusion

- Minimum daily intake of 100 µg iodine is essential to eliminate all signs of iodine deficiency, though the daily requirement varies between different age groups.
- The effects of iodine deficiency on the development of goitre and thyroid hypo function are extremely variable among populations and individuals, even in endemic areas.
- Four methods are generally recommended for assessment of iodine nutrition in populations: urinary iodine concentration (UI), the goitre rate, serum TSH, and serum Tg.
- Thyroid gland palpation and thyroid ultrasonographic examination are used to assess thyroid enlargement.

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