

Iodine deficiency: Clinical implications

ABSTRACT

Iodine is crucial for thyroid hormone synthesis and fetal neurodevelopment. Major dietary sources of iodine in the United States are dairy products and iodized salt. Potential consequences of iodine deficiency are goiter, hypothyroidism, cretinism, and impaired cognitive development. Although iodine status in the United States is considered sufficient at the population level, intake varies widely across the population, and the percentage of women of childbearing age with iodine deficiency is increasing. Physicians should be aware of the risks of iodine deficiency and the indications for iodine supplementation, especially in women who are pregnant or lactating.

KEY POINTS

Adequate iodine intake during pregnancy is critical for normal fetal development.

Major sources of dietary iodine in the United States are dairy products and iodized salt.

The daily iodine requirement for nonpregnant adults is 150 µg, and for pregnant women it is 220 to 250 µg. Pregnant and lactating women should take a daily iodine supplement to ensure adequate iodine intake.

Assessing the risk of iodine deficiency from clinical signs and from the history is key to diagnosing iodine deficiency. Individual urine iodine concentrations may vary from day to day. Repeated samples can be used to confirm iodine deficiency.

A 65-year-old woman is found to have a goiter. She is clinically euthyroid. She is a strict vegan and only uses noniodized Himalayan salt for cooking. Her thyroid gland is diffusely enlarged with no nodules. The estimated weight of the thyroid gland is 50 g (normal 10–20 g) based on ultrasonography. Her thyroid-stimulating hormone (TSH) level is 2.95 mU/L (reference range 0.5–5 mU/L), and her free thyroxine level is 0.8 ng/dL (0.7–1.8 ng/dL). Testing for TSH receptor antibody is negative. Her 24-hour urine iodine is undetectable (urine iodine concentration < 10 µg/L with urine volume 3,175 mL). What may be the cause of her goiter?

IODINE IS AN ESSENTIAL ELEMENT needed for the production of thyroid hormone, which controls metabolism and plays a major role in fetal neurodevelopment. Its ionized form is called iodide. Iodine deficiency results in impairment of thyroid hormone synthesis and may lead to several undesirable consequences. Physicians should be aware of the risks iodine deficiency poses, especially during pregnancy, and should be familiar with approaches to testing and current indications for iodine supplementation.

SOURCES OF IODINE AND SALT IODIZATION

The major environmental source of iodine is the ocean. Elemental iodine in the ocean volatilizes into the atmosphere and returns to the soil by rain. The effects of glaciation, flooding, and leaching into soil have resulted in the variable geographic distribution of iodine. Mountainous areas (eg, the Alps, Andes, Himalayas) and areas with frequent flooding typically have iodine-deficient soil due to slow iodine cycling.¹ Seafood is a good source

of iodine because marine plants and animals concentrate iodine from seawater. The iodine content of other foods varies widely, depending on the source and any additives.

In the United States, the major sources of dietary iodine are dairy products (due to livestock iodine supplements and use of iodophors for cleaning milk udders) and iodized salt.^{1,2} Seafood contains a higher amount of iodine by weight than dairy products but is consumed far less than dairy.^{3,4} Further, the iodine content of milk can range from 88 to 168 µg per 250 mL (about 1 cup), depending on the product manufacturer. Also, iodine content is often omitted from the food label. Even if it is reported, the package labeling may not accurately predict the iodine content.⁵

Less common sources of iodine are radiographic contrast, bread with iodate dough conditioners, red food coloring (erythrosine), and drugs such as amiodarone.¹

Using iodized salt is an effective and stable way to ensure adequate iodine intake. In the United States, only table salt is iodized, and the salt typically used in processed food has only minimal iodine content.⁶ Nearly 70% of the salt we ingest is from processed food. Table salt provides only 15% of dietary salt intake, and only 70% of consumers choose iodized salt for home cooking.⁷

■ IODINE REQUIREMENTS

Daily requirements of iodine suggested by the World Health Organization (WHO) and by the US Institute of Medicine are in the range of 90 to 150 µg/day.^{8,9} The iodine requirement is higher in pregnancy (220–250 µg/day) because of increased maternal thyroid hormone production required to maintain euthyroidism and increased renal iodine clearance, and it is even higher in lactating women (250–290 µg/day).

■ IODINE STATUS IN POPULATIONS

Since the establishment of universal salt iodization programs under the influence of the WHO and the International Council for Control of Iodine Deficiency Disorders (ICCID) in 1990, global iodine status has continued to improve. Yet only 70% of households worldwide currently have access to adequately io-

dized salt, because many countries lack a national program for iodine supplementation. The population of the United States was historically iodine-deficient, but since the introduction of salt iodization in the 1920s, the iodine status in the United States has been considered adequate.¹

The WHO defines iodine status for a population by the median spot urinary iodine concentration. Because a urinary iodine concentration of 100 µg/L represents an iodine intake of about 150 µg/day, the WHO uses a median urinary iodine concentration of 100 to 199 µg/L to define adequate iodine intake for a nonpregnant population.⁹

The National Health and Nutrition Examination Survey (NHANES) found that the median urinary iodine concentration decreased by more than 50% from the 1970s to the 1990s, indicating declining iodine status in the US population.² Of particular concern, the percentage of women of childbearing age with moderate iodine deficiency increased from 4% to 15% over this period.² Still, the NHANES survey in 2009–2010 indicated that the overall US population is still iodine-sufficient (median urinary iodine concentration 144 µg/L).¹⁰ The decline in the US iodine status may be due to reduction of iodine content in dairy products, increased use of noniodized salt by the food industry, and recommendations to avoid salt for blood pressure control.

Although US iodine status has been considered generally adequate, iodine intake varies greatly across the population. Vegans tend to have iodine-deficient diets, while kelp consumers may have excessive iodine intake.¹¹ Individuals with lactose intolerance are at risk of iodine deficiency, given that dairy products are a major source of iodine in the United States. Physicians should be aware of these risk factors for iodine deficiency.

■ PREGNANCY AND LACTATION

It is crucial to maintain euthyroidism during pregnancy. In early gestation, maternal thyroid hormone production increases 50% due to an increase in thyroid-binding globulin and stimulation by human chorionic gonadotropin. The glomerular filtration rate increases by

Dairy products and iodized salt are the main sources of dietary iodine in the United States

Iodine deficiency leading to hypothyroidism in pregnancy can cause irreversible fetal brain damage

30% to 50% during pregnancy, thus increasing renal iodine clearance. Fetal thyroid hormone production increases during the second half of pregnancy, further contributing to increased maternal iodine requirements because iodine readily crosses the placenta.¹²

Women with sufficient iodine intake before and during pregnancy generally have adequate intrathyroidal iodine storage and can adapt to the increased demand for thyroid hormone throughout gestation. But in the setting of even mild iodine deficiency, total body iodine stores decline gradually from the first to third trimester of pregnancy.¹³

The fetal thyroid gland does not begin to concentrate iodine until 10 to 12 weeks of gestation and is not controlled by TSH until the full development of the pituitary-portal vascular system at 20 weeks of gestation.¹² Therefore, the fetus relies on maternal thyroid hormone during this critical stage of neurodevelopment. Thyroid hormone is essential for oligodendrocyte differentiation and myelin distribution¹⁴ as well as fetal neuronal proliferation and migration in the first and second trimesters. Iodine deficiency leading to maternal hypothyroidism can result in irreversible fetal brain damage.

Because of the greater requirement during pregnancy, the WHO recommends using a median urinary iodine concentration of 150 to 249 µg/L to define a population that has no iodine deficiency.⁹ The NHANES data from 2007 to 2010 showed that pregnant US women were mildly iodine-deficient (median urinary iodine concentration 135 µg/L),¹⁰ and the National Children's Study of 501 pregnant US women during the third trimester in 2009 to 2010 showed they had adequate iodine intake (median urinary iodine concentration 167 µg/L). Interestingly, pregnant non-Hispanic blacks were the only ethnic group with a median urinary iodine concentration less than 150 µg/L, suggesting that race or ethnicity is a predictor of iodine status in pregnant women.¹⁰

Iodine requirements during lactation

During lactation, thyroid hormone production and renal iodine clearance return to the prepregnancy state. However, a significant amount of iodine is excreted into breast milk at a concentration 20 to 50 times greater than

that in plasma.¹⁵ It is recommended that lactating women continue high iodine intake to ensure sufficient iodine in breast milk to build reserves in the newborn's thyroid gland.

The iodine requirement during lactation is 225 to 350 µg/day.¹⁶ Breast milk containing 100 to 200 µg/L of iodine appears to provide adequate iodine to meet Institute of Medicine recommendations for infants.¹⁷ The amount of iodine excreted into breast milk depends on maternal iodine intake. In the setting of iodine sufficiency, the iodine content of breast milk is 150 to 180 µg/L, but it is much lower (9–32 µg/L) in women from iodine-deficient areas, eg, the "goiter belt," which included the Great Lakes, the Appalachians, and northwestern states. While iodized salt has virtually eliminated the goiter belt, the risk of iodine deficiency remains for people who avoid iodized salt and dairy.¹⁵

To ensure adequate iodine intake, the American Thyroid Association recommends that women receive iodine supplementation daily during pregnancy and lactation.¹¹ However, the iodine content of prenatal multivitamins is currently not mandated in the United States. Only half of marketed prenatal vitamins in the United States contain iodine, in the form of either potassium iodide or kelp. Though most iodine-containing products claim to contain at least 150 µg of iodine per daily dose, when measured, the actual iodine content varied between 33 and 610 µg.¹⁸

CONSEQUENCES OF IODINE DEFICIENCY

Goiter

Goiter in iodine-deficient areas is considered to be an adaptation to chronic iodine deficiency. Low iodine intake leads to reduced thyroid hormone production, which in turn stimulates TSH secretion from the pituitary. TSH increases iodine uptake by the thyroid, stimulates thyroid growth, and leads to goiter development.

Initially, goiter is characterized by diffuse thyroid enlargement, but over time it may become nodular from progressive accumulation of new thyroid follicles. Goiter in children from iodine-deficient areas is diffusely enlarged, whereas in older adults it tends to be multinodular.

Iodine deficiency and chronic TSH stimulation may play a role in TSH receptor-activating mutations of thyroid follicles. These “gain-of-function” mutations are more common in the glands of patients with goiter in areas of iodine deficiency but are relatively rare in areas of iodine sufficiency.¹⁹ Toxic multinodular goiter may eventually develop, and hyperthyroidism may occur if iodine deficiency is not severe.

Goiter generally does not cause obstructive symptoms, since the thyroid usually grows outward. However, a very large goiter may descend to the thoracic inlet and compress the trachea and esophagus. The obstructive effect of a large goiter can be demonstrated by having a patient raise the arms adjacent to the face (the Pemberton maneuver). Signs suggesting obstruction are engorged neck veins, facial plethora, increased dyspnea, and stridor during the maneuver. Computed tomography of the neck and upper thorax may provide information on the degree of tracheal compression.²⁰

Hypothyroidism

A normal or low triiodothyronine (T_3), a low serum thyroxine (T_4), and a variably elevated TSH are features of thyroid function tests in iodine deficiency.^{11,21,22} As long as daily iodine intake exceeds 50 $\mu\text{g}/\text{day}$, the absolute uptake of iodine by the thyroid gland usually remains adequate to maintain euthyroidism. Below 50 $\mu\text{g}/\text{day}$, iodine storage in the thyroid becomes depleted, leading to hypothyroidism.¹

The clinical manifestations of hypothyroidism from iodine deficiency are similar to those of hypothyroidism from other causes. Because of thyroid hormone’s role in neural and somatic development, the manifestations of hypothyroidism differ among age groups (Table 1).

Cretinism

Before the development of fetal thyroid tissue in the 10th to 12th week of gestation, the fetus is dependent on maternal thyroid hormone, which crosses the placenta to support general and neural development. Iodine deficiency leading to maternal hypothyroidism (in early gestation) or inadequate fetal thyroid hormone production (in late gestation) may

TABLE 1

Clinical manifestations of iodine-deficiency disorder by age group

Age group	Clinical manifestations
Fetus	Abortion Stillbirth Increased risk of perinatal death Cretinism
Infant	Goiter Hypothyroidism Mental retardation Intellectual impairment
Child, adolescent	Goiter Hypothyroidism Intellectual impairment Impaired physical development
Adult	Goiter Toxic multinodular goiter Increased risk of iodine-induced hyperthyroidism Hypothyroidism Intellectual impairment

Adapted from reference 9.

result in various degrees of mental retardation or lower than expected IQ.

Severe iodine deficiency during gestation typically results in cretinism, characterized by severe mental retardation accompanied by other neurologic or physical defects. Cretinism is divided into two subtypes according to clinical manifestations (neurologic and myxomatous cretinism; Table 2), which may reflect the different timing of intrauterine insult to the developing fetal nervous system and whether the iodine deficiency continues into the postnatal period. Both types can be prevented by adequate maternal iodine intake before and during pregnancy.^{23,24}

Although mild gestational iodine deficiency does not result in cretinism, it nevertheless has an adverse impact on fetal neurodevelopment and subsequent functioning. Children of mothers with mild gestational iodine deficiency were found to have reductions in spelling, grammar, and English literacy performance despite growing up in iodine-replete environments.²⁵

If intake is < 50 $\mu\text{g}/\text{day}$, iodine stored in the thyroid becomes depleted, leading to hypothyroidism

TABLE 2

**Cretinism:
Comparative features of neurologic and myxomatous subtypes**

	Neurologic cretinism^a	Myxomatous cretinism^a
Period of intrauterine iodine deficiency	Early in pregnancy (maternal hypothyroidism)	Late in pregnancy
Continuing postnatal iodine deficiency	No	Yes
Deaf-mutism	Often present	Absent
Neurologic deficits Gait disturbances Spasticity Squinting	Often present	Absent
Growth	Normal	Growth retardation Epiphyseal dysgenesis
Physical signs of hypothyroidism Coarse, dry skin Hoarseness Delayed relaxation of reflexes	Absent	Present
Effect of thyroid hormone replacement	No effect	Improvement

^aThe features of the two subtypes may overlap, depending on the duration and magnitude of postnatal hypothyroidism.

**Research
is needed
on the effects
of mild iodine
deficiency
and iodine
supplements
on cognitive
function**

Impaired cognitive development

Reduction in IQ has been noted in affected youth from regions of severe and mild iodine deficiency. A meta-analysis of studies relating iodine deficiency to cognitive development suggested that chronic moderate to severe iodine deficiency reduced expected average IQ by about 13.5 points.²⁶

The effects of mild iodine deficiency during childhood are more difficult to quantify. The results of one study suggested that mild iodine deficiency was associated with subtle neurodevelopmental deficits and that iodine supplementation might improve cognitive function in mildly iodine-deficient children.²⁷

In a 2009 randomized, placebo-controlled study in New Zealand, 184 children ages 10 to 13 with mild iodine deficiency (median urinary iodine concentration of 63 µg/L) received iodine supplementation (150 µg/day) or placebo for 28 weeks. Iodine supplementation increased the median urinary iodine concentration to 145 µg/L and significantly improved perceptual reasoning measures and overall cognitive score compared with placebo.²⁸

These findings suggest that correcting mild iodine deficiency in children could improve certain components of cognition. More research is needed to understand the effects of mild iodine deficiency and iodine supplementation on cognitive function.

■ ASSESSING IODINE STATUS

The diagnosis of iodine deficiency is based on clinical and laboratory assessments. Clinical manifestations compatible with iodine deficiency and careful history-taking focused on the patient's dietary iodine intake and geographic data are keys to the diagnosis.

Four main methods are used to assess iodine status at a population level: urinary iodine, serum thyroglobulin, serum TSH, and thyroid size. Urinary iodine is a sensitive marker for recent iodine intake (within days); thyroglobulin represents iodine nutrition over a period of months and thyroid size over a period of years.¹

Urinary iodine

Most dietary iodine is excreted into the urine within 24 hours of ingestion, and the 24-hour

urinary iodine is considered a reference standard for the measurement of individual daily iodine intake. However, the process of collection is cumbersome, and the 24-hour urinary iodine can vary from day to day in the same person, depending on the amount of iodine ingested.

A study in healthy women from an iodine-sufficient area suggested that 10 repeated 24-hour urine collections estimated the person's iodine status at a precision of 20% because of variable daily iodine intake.²⁹ Therefore, when necessary, several 24-hour urine iodine determinations should be performed.

A single, random, spot urinary iodine is expressed as the urinary iodine concentration and is affected by the amount of iodine and fluids the individual ingests in a day, thus resulting in high variation both within an individual person and between individuals. Expressing the urinary iodine concentration as the ratio of urine iodine to creatinine is useful in correcting for the influence of fluid intake. The ratio of urine iodine to creatinine can be used to estimate 24-hour urine iodine with the following formula: *urine iodine (μg/L)/creatinine (g/L) × age- and sex-specific estimated 24-hour creatinine excretion (g/day)*. Another clinical use of the spot urine iodine is to screen for exposure to a large amount of iodine from a source such as radiographic contrast.³⁰

Although individual urine iodine excretion and urine volume can vary from day to day, this variation tends to even out in a large number of samples. In study populations of at least 500, the median value of the spot urinary iodine concentration is considered a reliable measure of iodine intake in that population.³⁰ The spot urine iodine test is convenient, making it the test of choice to study iodine status in a large cohort. The WHO recommends using the median value of the spot urine iodine to evaluate the iodine status of a population.⁹

Thyroglobulin

Thyroglobulin is a thyroid-specific protein involved in the synthesis of thyroid hormone. Small amounts can be detected in the blood of healthy people. In the absence of thyroid damage, the amount of serum thyroglobulin depends on thyroid cell mass and TSH stimulation. The serum level is elevated in iodine

TABLE 3

Degrees of iodine deficiency based on total goiter rate in school-age children

Total goiter rate (%)	Severity of iodine deficiency
0.0–4.9	None
5.0–19.9	Mild
20.0–29.9	Moderate
≥ 30	Severe

deficiency as a result of chronic TSH stimulation and thyroid hyperplasia. Thus, thyroglobulin can serve as a marker of iodine deficiency.

Serum thyroglobulin assays have been adapted for use on dried whole-blood spots, which require only a few drops of whole blood collected on filter paper and left to air-dry. The results of the dried whole-blood assay correlate closely with those of the serum assay.³¹ An established international dried whole-blood thyroglobulin reference range for iodine-sufficient school-age children is 4 to 40 μg/L.³² A median level of less than 13 μg/L in school-age children indicates iodine sufficiency in the population.³³

Thyroid-stimulating hormone

Iodine deficiency lowers serum T₄, which in turn leads to increased serum TSH. Therefore, iodine-deficient populations generally have higher TSH than iodine-sufficient groups. However, the TSH values in older children and adults with iodine deficiency are not significantly different from values of those with adequate iodine intake. Therefore, TSH is not a practical marker of iodine deficiency in the general population.

In contrast, TSH in newborns is a reasonable indicator of population iodine status. The newborn thyroid has limited iodine stores compared with that of an adult and hence a much higher iodine turnover rate. TSH from the cord blood is markedly elevated in newborns of mothers with moderate to severe iodine deficiency.³⁴ A high prevalence of newborns with elevated TSH should therefore reflect iodine deficiency in the area where the mothers of the newborns live.

TSH is now routinely checked in newborns

TSH is not a practical marker of iodine deficiency in the general population

TABLE 4

Tolerable upper intake levels for iodine^a

Age	Male	Female	Pregnancy	Lactation
Birth to 1 year	Not possible to establish ^b	Not possible to establish ^b		
1–3	200 µg	200 µg		
4–8	300 µg	300 µg		
9–13	600 µg	600 µg		
14–18	900 µg	900 µg	900 µg	900 µg
≥ 19	1,100 µg	1,100 µg	1,100 µg	1,100 µg

^a These data refer to chronic ingestion of the specified iodine concentrations.

^b Formula and food should be the only sources of iodine for infants.

Adapted from reference 8.

Supplement with iodized salt or a daily multivitamin that contains iodine

to screen for congenital hypothyroidism. TSH is typically checked 2 to 5 days after delivery to avoid confusion with transient physiologic TSH elevation, which occurs within a few hours after birth and decreases rapidly in 24 hours. The WHO has proposed that a more than 3% prevalence of newborns with TSH values higher than 5 mU/L from blood samples collected 3 to 4 days after birth indicates iodine deficiency in a population.¹ This threshold appears to correlate well with the iodine status of the population defined by the WHO's median urinary iodine concentration.^{35,36}

But several other factors can influence the measurement of newborn TSH, such as prematurity, time of blood collection, maternal or newborn exposure to iodine-containing antiseptics, and the TSH assay methodology. These potential confounding factors limit the role of neonatal TSH as a reliable monitoring tool for iodine deficiency.^{35,37}

Thyroid size

The size of the thyroid gland varies inversely with iodine intake. Thyroid size can be assessed by either palpation or ultrasonography, with the latter being more sensitive. The goiter rate in school-age children can be used to determine the severity of iodine deficiency in the population (Table 3). A goiter rate of 5% or more in school-age children suggests the presence of iodine deficiency in the community.

Although thyroid size is easy to estimate by palpation, it has low sensitivity and specificity to detect iodine deficiency and high interobserver variation. Thyroid ultrasonography provides a more precise measurement of thyroid gland volume. Zimmermann et al³⁸ provided reference data on thyroid volume stratified by age, sex, and body surface area of school-age children in iodine-sufficient areas.³⁸ Results of ultrasonography in a population is then compared with these reference data. The higher the percentage of the population with thyroid volume exceeding the 97th percentile of the reference range, the more severe the iodine deficiency. However, the WHO does not specify how to grade the degree of iodine deficiency based on the thyroid volume obtained with ultrasonography. Follow-up studies showed no significant correlation between urinary iodine concentration and thyroid size.^{39,40}

Thyroid size decreases slowly after iodine repletion. Therefore, the goiter rate may remain high for several years after iodine supplementation begins.^{1,9}

TREATMENT AND PREVENTION

Treatment of iodine deficiency should be instituted at the levels recommended by the Institute of Medicine and the WHO. The tolerable upper intake levels for iodine are outlined in Table 4. In a nonpregnant adult, 150 µg/day is sufficient for normal thyroid function.

Iodine intake should be higher for pregnant and lactating women (250 µg/day according to the WHO recommendation).

Iodine supplementation is easily achieved by using iodized salt or an iodine-containing daily multivitamin.

In patients with overt hypothyroidism from iodine deficiency, we recommend initiating levothyroxine treatment along with iodine supplementation to restore euthyroidism, with consideration of possible interruption in 6 to 12 months when the urine iodine has normalized and goiter size has decreased. Thyroid function should be reassessed 4 to 6 weeks after discontinuation of levothyroxine.

At the population level, iodine deficiency can usually be prevented by iodization of food products or the water supply. In developing countries where salt iodization is not practical, iodine deficiency has been eradicated by adding iodine drops to well water or by injecting people with iodized oil.

TAKE-HOME POINTS

Iodine is essential for thyroid hormone synthesis. It can be obtained by eating iodine-

containing foods or by using iodized salt. The WHO classifies iodine deficiency based on the median urinary iodine concentration. Iodine nutrition at the community level is best assessed by measurements of urinary iodine, thyroglobulin, serum TSH, and thyroid size.

Adequate iodine intake during pregnancy is important for fetal development. Iodine deficiency is associated with goiter and hypothyroidism. Severe iodine deficiency during pregnancy is associated with cretinism.

There is evidence that mild to moderate iodine deficiency can cause impaired cognitive development and that correcting the iodine deficiency can significantly improve cognitive function.

CASE FOLLOW-UP

This patient had been following a strict vegan diet with very little intake of iodized salt. Her dietary history and the presence of goiter suggested iodine deficiency. She was instructed to take an iodine supplement 150 µg/day to meet her daily requirement. After 2 months of iodine supplementation, her urine iodine concentration had increased to 58 µg/L. She remained biochemically euthyroid.

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