Iodine Deficiency

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Iodine deficiency has multiple adverse effects in humans, termed iodine deficiency disorders, due to inadequate thyroid hormone production. Globally, it is estimated that 2 billion individuals have an insufficient iodine intake, and South Asia and sub-Saharan Africa are particularly affected. However, about 50% of Europe remains mildly iodine deficient, and iodine intakes in other industrialized countries, including the United States and Australia, have fallen in recent years. Iodine deficiency during pregnancy and infancy may impair growth and neurodevelopment of the offspring and increase infant mortality. Deficiency during childhood reduces somatic growth and cognitive and motor function. Assessment methods include urinary iodine concentration, goiter, newborn TSH, and blood thyroglobulin. But assessment of iodine status in pregnancy is difficult, and it remains unclear whether iodine intakes are sufficient in this group, leading to calls for iodine supplementation during pregnancy in several industrialized countries. In most countries, the best strategy to control iodine deficiency in populations is carefully monitored universal salt iodization, one of the most cost-effective ways to contribute to economic and social development. Achieving optimal iodine intakes from iodized salt (in the range of 150–250 μg/d for adults) may minimize the amount of thyroid dysfunction in populations. Ensuring adequate iodine status during parenteral nutrition has become important, particularly in preterm infants, as the use of povidone-iodine disinfectants has declined. Introduction of iodized salt to regions of chronic iodine deficiency may transiently increase the incidence of thyroid disorders, but overall, the relatively small risks of iodine excess are far outweighed by the substantial risks of iodine deficiency. **(*Endocrine Reviews* 30: 376–408, 2009)**

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Abbreviations: AI, Adequate intake; BMIC, breast milk iodine concentration; CI, confidence interval; DALY, disability-adjusted life year; DIT, diiodotyrosine; EAR, estimated average requirement; FT4, free T_4; IDD, iodine deficiency disorder; IGFBP, IGF binding protein; IIH, iodine-induced hyperthyroidism; IMR, infant mortality rate; MIT, monoiodotyrosine; NIS, sodium/iodide symporter; PII, plasma inorganic iodide; PN, parenteral nutrition; RDA, recommended dietary allowance; RIC, renal iodine clearance; RNI, recommended nutrient intake; Tg, thyroglobulin; TPO, thyroperoxidase; UI, urinary iodine concentration; USI, universal salt iodization.

adequate range recommended by WHO of 150–249 μg/liter, the lower 95% CI was less than 150 μg/liter (222). Because of this uncertainty, until additional data are available, the American Thyroid Association recommends that women receive 150 μg iodine supplements daily during pregnancy and lactation and that all prenatal vitamin/mineral preparations contain 150 μg of iodine (222).

Adequate iodine supply should continue after parturition because the iodine requirement of a woman who is fully breastfeeding her infant is likely even higher than that during pregnancy. Gushurst *et al.* (223) reported that the median BMIC in U.S. women who used noniodized salt or consumed low or high amounts of iodized salt was 113, 143, and 270 μg/liter, respectively. Pretell *et al.* (224) administered 950 mg iodine as injected iodized oil to pregnant women; median BMIC at 18–36 months postpartum increased to 70 μg/liter, compared with 2 μg/liter in untreated women. In Algeria, Chaouki and Benmiloud (136) gave 240 mg iodine as oral iodized oil either 1–3 months before pregnancy or in the first or third trimester. At delivery and 6 months postpartum, mean BMIC increased significantly compared to untreated women. In Danish mothers (n □ 147), median BMIC on the fifth day postpartum was significantly higher (57 μg/liter) in those receiving supplementation with 150 μg/d of oral iodine, compared with those not supplemented (34 μg/liter) (225). In Germany, 60 mothers who received 200 μg/d of oral iodine had significantly higher mean iodine concentrations in breast milk (76 μg/liter) than untreated (55 μg/liter) (226). Thus, iodine supplementation of breastfeeding women can significantly improve iodine supply to the newborn.

X. Enteral and Parenteral Nutrition

A. Infancy

Balance studies in healthy preterm infants have suggested that iodine intakes of at least 30 μg/kg body weight/d are required to maintain positive balance, and experts generally recommend iodine intakes of 30 to 60 μg/kg · d for this group (227–229). Formula milks for preterm infants contain 20 to 170 μg iodine/liter, and, depending on the dietary iodine intake of the mother, breast milk generally contains 50 to 150 μg/liter (97, 226, 230). Thus, particularly during the first postnatal weeks when feed volumes are often low, enterally fed preterm infants may not achieve the recommended intake of iodine (228, 230).

Oral absorption of iodine is efficient; in adults, oral iodine bioavailability is typically 90–95% (11, 12). This suggests that iodine dosages via the enteral or parenteral route should be nearly equivalent. However, commercially available parenteral nutrition (PN) solutions contain much less iodine than breast milk or preterm formula milks (230). U.S. and European clinical nutrition societies recommend parenteral iodine intakes of 1 μg/kg body weight/d (231, 232), far below fetal accretion rates (228, 229). This conservative recommendation assumes that parenterally fed preterm infants will absorb iodine through the skin from topical iodinated disinfectants and also receive small amounts of adventitious iodine in other infusions. This assumption is supported by the study of Moukarzel *et al.* (233), who found in 18 infants receiving long-term total PN without iodine supplementation that thyroid function test results were normal and serum iodide concentrations were significantly higher than in control children. The authors estimated that adventitious iodine in total PN solutions and fat emulsions accounted for about 50% of the iodine intake and assumed that skin absorption of topical iodinated disinfectant accounted for the remaining intake. They concluded that it was unnecessary to supplement iodine even in children receiving long-term total PN without added iodine. Moreover, frequent use of iodinated antiseptics in infants can result in transcutaneous absorption of at least 100 μg iodine per day, iodine excess, and neonatal hypothyroidism (234).

Because of concerns over possible iodine excess and the potential advantages of chlorhexidine-based antiseptics (235), use of iodinated antiseptics in infants may be decreasing, putting infants at risk of iodine deficiency. If parentally fed preterm infants are not exposed to adventitious sources of iodine, they may receive only 1–3 μg iodine/kg body weight/d and be in negative iodine balance during the first few postnatal weeks (228, 229). In the study of Ibrahim *et al.* (229), preterm infants (n □ 13) had a mean iodine intake of 3 μg/kg body weight/d at PN rates of 150 ml/kg/d. All 13 infants had negative iodine balances on d 1, 12 remained in negative balance at d 6, but only three infants remained in negative balance on d 28.

Several authors have argued that iodine deficiency should be avoided during this period because it may transiently lower thyroid hormone levels in the first weeks of life (228, 229). Transient hypothyroxinemia in preterm infants has been linked to impaired neurodevelopment (236–238), but the potential role of iodine in this phenomenon has been investigated in only one randomized controlled trial (239). Infants born before 33 wk gestation (n □ 121) were randomized to receive either iodine-supplemented formula milk (272 μg iodine/liter) or the same formula without iodine supplementation (68 μg iodine/liter) until 40 wk postconceptional age. These provided daily iodine intakes of approximately 40–50 and 12–16 μg per kg body weight in the treatment and control groups, respectively. There was no statistically significant

effect on thyroid function or in the incidence of chronic lung disease (239).

However, the study had several limitations. Although transient hypothyroxinemia is most closely associated with adverse outcomes in extremely preterm infants, only 14% of subjects had a birth weight below 1000 g. Second, the intervention began only after the infants had established enteral feeding, usually 2 wk after birth, but in preterm infants iodine balance is often negative, and transient hypothyroxinemia is established in the first 1–2 postnatal weeks. Finally, the trial was likely underpowered to assess a potential effect on neurodevelopment. A recent review concluded that the available data are insufficient to support supplementation of preterm infants with iodine (240). Moreover, although subgroup analyses in a single controlled trial suggested that T_4 replacement may prevent neurodevelopmental morbidity in extremely preterm infants (241), the overall data are insufficient to recommend prophylactic thyroid hormone treatment in preterm infants (242).

B. Childhood

A daily dose of 1 μg iodine/kg body weight is also recommended for children receiving PN (231, 232). A recent study assessed the iodine and thyroid status of children aged 1 to 17 yr (n □ 15; mean age, 76 months) on long-term PN (243). Nine children had short bowel syndrome, and six had other intestinal diseases. Ten were on total PN, and five were on partial PN for 14 to 84 wk. There was a significant inverse correlation between duration of PN and UI, and after 12 wk all children had a UI less than 100 μg/liter, with eight less than 50 μg/liter (moderate deficiency) and seven less than 20 μg/liter (severe deficiency). However, despite apparently low iodine intakes, there was no significant increase in thyroid size or signs of thyroid dysfunction in the children. If needed, parenteral trace element additives containing iodine are available for pediatric use. An example is Peditrace solution (Fresenius Kabi, Bad Homburg, Germany), which contains KI (1.3 μg/ml KI equivalent to 1 μg iodide/ml). The manufacturer's recommended dosage (244) for infants and children weighing 15 kg or less and 2 d old or older is 1 ml/kg body weight/d; the recommended daily dose is 15 ml for children weighing more than 15 kg.

C. Adulthood

Commercially available products for enteral nutrition generally supply 75–110 μg iodine per serving (245). Daily iodine requirements in adult patients receiving total enteral nutrition or total PN are estimated to be 70–150 μg (246). A recent technical review of PN by the American Gastroenterological Association recommended iodine intakes of 70–140 μg/d (247). Although most PN formulations do not contain iodine, deficiency is not likely to occur because of cutaneous absorption from iodine containing disinfectants and other adventitious sources of iodine. Iodine deficiency symptoms have not been reported with in-hospital iv nutrition support (248). Thyroidal iodine stores may be adequate to meet the needs of patients requiring total PN for less than 3 months (246); in iodine-sufficient adults, thyroidal iodine content is 15–20 mg (18). Iodine status and thyroid hormone levels were adequate in Brazilian adults with intestinal malabsorption secondary to short gut syndrome who were receiving long-term total PN without iodine (251). For these reasons, many experts do not recommend supplemental iodine routinely for subjects receiving total PN (249, 250). If needed, iv sodium iodide solutions are available. For example, Iodopen (APP Pharmaceuticals, Schaumberg, IL) contains 100 μg iodine/ml. According to the manufacturer's specifications (252), the usual adult dosage for prophylaxis or treatment of iodine deficiency is 1 to 2 μg iodine/kg of body weight/d. For children and pregnant/lactating women, the recommended dosage is 2 to 3 μg iodine/kg of body weight/d.

XI. Increasing Iodine Intakes in Populations and Iodine Excess

More than two thirds of the 5 billion people living in countries affected by iodine deficiency now have access to iodized salt (4). Iodine excess is occurring more frequently, particularly when salt iodine levels are too high or are poorly monitored. For example, in Brazil, Armenia, and Uganda, median UI is more than 300 μg/liter, whereas in Chile it is above 500 μg/liter (191). High dietary iodine can also rarely come from natural sources, such as seaweed in coastal Japan (253, 254), iodine-rich drinking water in China (255, 256), and iodine-rich meat and milk in Iceland from fish products used for animal feed (257). The median UI in primary school-aged children in the United States is 229 μg/liter (90), as a result of iodine-containing agents used in dairying and food preparation (9, 258), together with iodine from fortified salt.

European (259) and U.S. (8) expert committees have recommended tolerable upper intake levels for iodine (Table 6) but caution that individuals with chronic iodine deficiency may respond adversely to intakes lower than these. In monitoring populations consuming iodized salt, the WHO/ICCIDD recommendations (54) for the median UI that indicates more than adequate and excess iodine intake are shown in Table 2. Acute iodine poisoning caused by ingestion of many grams causes gastrointestinal irritation, abdominal pain, nausea, vomiting, and diar-

ism increased only in the area with previous moderate iodine deficiency. The increase occurred in young and middle-aged adults. Similarly, new cases of overt hyperthyroidism in these two areas of Denmark before and for the first 6 yr after iodine fortification were identified. The overall incidence rate of hyperthyroidism increased [baseline, 102.8/100,000/year; after salt iodization 138.7/100,000/year (*P* for trend □0.001)]. Hyperthyroidism increased in both sexes and in all age groups, but in contrast to IIH where most cases occur in older individuals, many of the new cases were observed in young subjects—the increase was highest in adults aged 20–39 yr—and were presumably of autoimmune origin. The authors suggested that further monitoring is expected to show a decrease in the number of elderly subjects suffering from nodular hyperthyroidism.

XII. Conclusions

Concerns about potential increases in iodine-induced thyroid disease continue to delay or limit the implementation of iodine prophylaxis in iodine-deficient populations. Are these concerns justified? Looking at the benefits *vs.* the risks of iodine prophylaxis, it is clear that severe iodine deficiency in pregnancy can cause hypothyroidism, poor pregnancy outcome, cretinism, and irreversible mental retardation. Mild-to-moderate iodine deficiency *in utero* and in childhood results in less severe learning disability, poor growth, and diffuse goiter. In adults, mild-to-moderate iodine deficiency appears to be associated with higher rates of more aggressive subtypes of thyroid cancer and increases risk for nontoxic and toxic nodular goiter and associated hyperthyroidism.

However, increasing iodine intakes in deficient populations is not without risk. Mild iodine deficiency may be associated with a decreased risk of overt and subclinical hypothyroidism, as well as autoimmune thyroiditis. In China, chronic excess iodine intakes are associated with a small increase in subclinical hypothyroidism and autoimmune thyroiditis, but not overt hypo- or hyperthyroidism. In contrast, in Denmark, correcting mild-to-moderate deficiency modestly increased rates of hypo- and hyperthyroidism. The differing effects of varying iodine intakes in these studies may be related to differences in underlying thyroid autonomy, genetic susceptibility, or other environmental variables.

More prospective data on the epidemiology of thyroid disorders caused by changes in iodine intake in other countries would be valuable. But it appears that achieving optimal iodine intakes (in the range of 150–250 μg/d for adults) can minimize the amount of thyroid dysfunction in populations (285). Iodine prophylaxis with periodic monitoring is an extremely cost-effective approach to help control thyroid disorders, compared with clinical diagnosis and treatment. If programs of iodine prophylaxis are carefully monitored for both iodine deficiency and excess, the relatively small risks of iodine excess are far outweighed by the substantial risks of iodine deficiency—pregnancy loss, goiter, and mental retardation, which continue to affect up to one third of the global population (191).

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