Iodine deficiency (ID) has multiple adverse effects on growth and development due to inadequate thyroid hormone production. Methods for assessment of iodine nutrition in individuals include the urinary iodine concentration (UI), thyroid size and thyroid function tests. The UI measured in several repeat 24-h urine samples can detect inadequate iodine intake in individuals receiving enteral or parenteral nutrition (PN) and allow for iodine supplementation before the onset of hypothyroidism. A daily dose of 1 μg iodine/kg body weight is currently recommended for children receiving PN, but this is far below their requirements. Daily iodine requirements in adults receiving enteral nutrition or PN are estimated to be 70–150 μg, but most PN formulations do not contain iodine. Despite this, ID has been unlikely because absorption from iodine-containing skin antiseptics and other adventitious sources can provide sufficient iodine. However, if chlorhexidine replaces iodine-containing antiseptics for catheter care, ID may occur during long-term PN, and periodic testing of UI and thyroid function may be prudent. Infants may be particularly vulnerable to ID because of their small thyroidal iodine store. In this review, we describe three recent patients (an infant, a child and an adult) who developed ID and thyroid hypofunction during PN.

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Dietary sources, absorption and metabolism

Iodine (atomic weight 126.9 g/atom) is an essential component of the hormones produced by the thyroid gland. Thyroid hormones, and therefore iodine, are essential for mammalian life. The native iodine content of most foods and beverages is low, and most commonly consumed foods provide 3–80 μg per serving. Major dietary sources of iodine in the U.S. and Europe are bread and milk. Iodine content in foods is also influenced by iodine-containing compounds used in irrigation, fertilisers, livestock feed, dairy industry disinfectants and bakery dough conditioners. Recommendations for iodine intake by age and population group are shown in Table 1.

Iodide is rapidly and nearly completely absorbed (>90%) in the duodenum; the sodium/iodide symporter (NIS) on the apical membrane of enterocytes mediates active iodine uptake. Thyroid clearance of circulating iodine varies with iodine intake: in conditions of adequate iodine supply, 10% of absorbed iodine is taken up by the thyroid. In chronic iodine deficiency (ID), this fraction can exceed 80%. Under normal circumstances, plasma iodine has a half-life of approximately 10 h, but this is reduced in ID. The body of a healthy adult contains 15–20 mg of iodine, of which 70–80% is in the thyroid. In chronic ID, the iodine content of the thyroid may fall to <20 μg. In iodine-sufficient areas, the adult thyroid traps approximately 60 μg of iodine per day to balance losses and maintain thyroid hormone synthesis; the NIS transfers iodide into the thyroid at a concentration gradient 20–50 times that of plasma. Iodine comprises 65% and 59% of the weights of thyroxine (T4) and triiodothyronine (T3), respectively. Turnover is relatively slow: the half-life of T4 is approximately 5 days and for T3, 1.5–3 days. The released iodine enters the plasma iodine pool and can be taken up again by the thyroid or excreted by the kidney. More than 90% of ingested iodine is ultimately excreted in the urine.

Assessment

Methods recommended for assessment of iodine nutrition are the urinary iodine concentration (UI), thyroid size and thyroid function tests, including thyroglobulin (Tg). These indicators are complementary, in that UI is a sensitive indicator of recent iodine intake (days), Tg and other thyroid function tests shows an intermediate response (weeks to months), while changes in the goitre rate reflect long-term iodine nutrition (months to years).

Urinary iodine concentration

Because >90% of ingested iodine is excreted in the urine, UI is generally an excellent indicator of recent iodine intake. In iodine-depleted patients receiving daily low-dose iodine supplementation, UI may remain low for several days to weeks after supplementation begins, as thyroid stores are replenished. UI can be expressed as a concentration (μg l⁻¹), in relationship to creatinine excretion (μg iodine/g creatinine), or as 24-h excretion (μg/day). For populations, because it is impractical to collect 24-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⁻¹ (Table 2). However, because

<table>
<thead>
<tr>
<th>Age or population group</th>
<th>U.S. Institute of Medicine (ref.5)</th>
<th>Age or population group</th>
<th>World Health Organization (ref.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 0–12 months</td>
<td>110–130</td>
<td>Children 0–5 years</td>
<td>90</td>
</tr>
<tr>
<td>Children 1–8 years</td>
<td>90</td>
<td>Children 6–12 years</td>
<td>120</td>
</tr>
<tr>
<td>Children 9–13 years</td>
<td>120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults ≥14 years</td>
<td>150</td>
<td>Adults &gt;12 years</td>
<td>150</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>220</td>
<td>Pregnancy</td>
<td>250</td>
</tr>
<tr>
<td>Lactation</td>
<td>290</td>
<td>Lactation</td>
<td>250</td>
</tr>
</tbody>
</table>

a Adequate Intake for infants <12 months; Recommended Daily Allowance for children >1 year.
b Recommended Nutrient Intake.
individual iodine intakes, and, therefore, spot UI concentrations are highly variable from day to day.\textsuperscript{13} A common mistake is to assume that subjects with a spot UI $< 100 \text{ mg/L}$ are iodine deficient. To estimate iodine intakes in individuals, 24-h collections are preferable. The mean UI measured in three 24-h urine samples collected over a week during which the typical diet is consumed can provide an estimate of usual iodine intake in an individual. An alternative is to use the age- and sex-adjusted iodine:creatinine ratio in adults, but this also has limitations.\textsuperscript{14} For individuals, daily iodine intake can be estimated from the UI in 24-h urine samples, assuming an average iodine bioavailability of 92%, as follows: \( \text{UI (mg/L)} / 0.92 = \text{daily iodine intake} \). Using this formula, a mean UI of 100 mg/L in 24-h urine samples from an individual would suggest an average dietary iodine intake of approximately 110 mg per day. For populations, daily iodine intake can be extrapolated from the median UI in spot urine samples using estimates of mean 24-h urine volume and assuming an average iodine bioavailability of 92% as follows: \( \text{UI (mg/L)} / 0.0235 \times \text{body weight (kg)} = \text{daily iodine intake} \). Using this formula, a median UI of 100 mg/L in 24-h urine samples corresponds roughly to an average daily intake of 150 mg.

**Thyroid size**

Two methods are available for measuring goitre: neck inspection and palpation, and 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.\textsuperscript{2} However, palpation of goitre in mild ID has poor sensitivity and specificity and measurement of thyroid volume (Tvol) by ultrasound is preferable.\textsuperscript{15} Interpretation of Tvol data requires valid reference criteria and age- and gender-specific references are available for 6- to 12-year-old children,\textsuperscript{15} but there are no established reference values for adults. Mean thyroid volume ($\pm$SD) measured by ultrasonography in 50 healthy Dutch adults (age 20–70 years) was $10.7 \pm 4.6 \text{ ml}$ (range: 2.7–20.4 ml), with the mean value in males ($12.7 \pm 4.4 \text{ ml}$) significantly greater than in females ($8.7 \pm 3.9 \text{ ml}$).\textsuperscript{16} In healthy Spanish adults ($n = 268$) the mean thyroid volume in men was 9.19 ml (95% confidence interval (CI): 9.09, 10.65 ml) and in women was 6.19 ml (95% CI: 6.22, 9.92 ml).\textsuperscript{17}

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**Table 2**

Epidemiological criteria for assessing iodine nutrition in a population based on median and/or range of UI concentrations.

<table>
<thead>
<tr>
<th>Median UI (mg/L)</th>
<th>Iodine intake</th>
<th>Iodine nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>School-aged children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>Insufficient</td>
<td>Severe iodine deficiency</td>
</tr>
<tr>
<td>20–49</td>
<td>Insufficient</td>
<td>Moderate iodine deficiency</td>
</tr>
<tr>
<td>50–99</td>
<td>Insufficient</td>
<td>Mild iodine deficiency</td>
</tr>
<tr>
<td>100–199</td>
<td>Adequate</td>
<td>Optimal</td>
</tr>
<tr>
<td>200–299</td>
<td>More than adequate</td>
<td>Risk of iodine-induced hyperthyroidism in susceptible groups</td>
</tr>
<tr>
<td>&gt;300</td>
<td>Excessive</td>
<td>Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid disease)</td>
</tr>
<tr>
<td>Pregnant women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150</td>
<td>Insufficient</td>
<td></td>
</tr>
<tr>
<td>150–249</td>
<td>Adequate</td>
<td></td>
</tr>
<tr>
<td>250–499</td>
<td>More than adequate</td>
<td></td>
</tr>
<tr>
<td>&gt;500</td>
<td>Excessive\textsuperscript{a}</td>
<td></td>
</tr>
<tr>
<td>Lactating women\textsuperscript{b}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>Insufficient</td>
<td></td>
</tr>
<tr>
<td>&gt;100</td>
<td>Adequate</td>
<td></td>
</tr>
<tr>
<td>Children less than 2 years old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>Insufficient</td>
<td></td>
</tr>
<tr>
<td>&gt;100</td>
<td>Adequate</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from reference 2.

\textsuperscript{a} The term “excessive” means in excess of the amount required to prevent and control iodine deficiency.

\textsuperscript{b} In lactating women, the figures for median UI are lower than the iodine requirements because of the iodine excreted in breast milk.
Because serum thyroid-stimulating hormone (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. TSH is a sensitive indicator of iodine status in the newborn period. Compared with the adult, the newborn thyroid contains less iodine but has higher rates of iodine turnover. Particularly when iodine supply is low, maintaining high iodine turnover requires increased TSH stimulation. Serum TSH concentrations are therefore increased in iodine-deficient infants for the first few weeks of life. If >3% of newborn TSH values are above the threshold of 5 mIU l⁻¹ whole blood collected 3–4 days after birth, this suggests ID in the population.

Thyroglobulin

Tg is synthesised only in the thyroid and is the most abundant intrathyroidal protein. In iodine sufficiency, small amounts of Tg are secreted into the circulation, and serum Tg is normally <10 μg l⁻¹. In ID, serum Tg increases due to greater thyroid cell mass and TSH stimulation. Serum Tg is well correlated with the severity of ID as measured by UI. Tg falls rapidly with iodine repletion, and it is a more sensitive indicator of iodine repletion than TSH or T4.

A new assay for Tg has been developed for dried blood spots taken by a finger prick, simplifying collection and transport. In prospective studies, dried blood spot Tg has been shown to be a sensitive measure of iodine status and reflects improved thyroid function within several months after iodine repletion.

Thyroid hormone concentrations

In adults, thyroid hormone concentrations (T4 and T3) are generally poor indicators of iodine intake, because in ID serum T3 may increase or remain unchanged and serum T4 usually falls but often remains within the normal range. Using thyroid hormone concentrations to assess iodine status in patients receiving enteral nutrition (EN) or parenteral nutrition (PN) may also be complicated by the ‘euthyroid sick syndrome’. This syndrome is often seen in patients with sepsis, trauma, burns and surgery, as well as in cardiovascular, renal and liver disease. It is characterised by low circulating levels of thyroid hormone but seemingly inappropriately low or normal TSH, suggesting central hypothyroidism.

Effects of deficiency

ID has multiple adverse effects on growth and development due to inadequate thyroid hormone production. Thyroid enlargement (goitre) is the classic sign of ID, and can occur at any age, even in the newborn. It is a physiologic adaptation to chronic ID. As iodine intake falls, secretion of TSH increases in an effort to maximise uptake of available iodine, and TSH stimulates thyroid hypertrophy and hyperplasia. The most serious adverse effect of ID is damage to the foetus. Maternal thyroxine crosses the placenta before onset of fetal thyroid function at 10–12 weeks and represents up to 20–40% of T4 measured in cord blood at birth. Normal levels of thyroid hormones are required for neuronal migration and myelination of the foetal brain, and lack of iodine irreversibly impairs brain development. Maternal subclinical hypothyroidism (an increased TSH in the second trimester) and maternal hypothyroxinaemia (a free T4 concentration <10th percentile at 12 weeks' gestation) are associated with impaired mental and psychomotor development of the offspring. However, in these studies, the maternal thyroid abnormalities were unlikely due to ID. In Europe, randomised controlled trials of iodine supplementation in mild-to-moderately iodine-deficient pregnant women have produced equivocal results and been done with no clear impact on maternal and newborn total or free thyroid hormone concentrations. Cross-sectional studies of moderate-to-severely iodine-deficient children have generally reported impaired intellectual function and fine motor skills; two meta-analyses estimated that populations with chronic ID experience a reduction in IQ of 12.5–13.5 points.
A controlled trial in 10- to 12-year-old moderately iodine-deficient children found that iodine treatment significantly improved several measures of cognition. In iodine-deficient children, impaired thyroid function is associated with lower insulin-like growth factor (IGF-1) and insulin-like growth factor binding protein (IGFBP-3) concentrations. Recent controlled trials found iodine repletion increased IGF-1 and IGFBP-3 and improved somatic growth in children.

**Requirements across the age spectrum**

Recommendations for iodine intake by age and population group, as defined by the U.S. Institute of Medicine (IOM) and the World Health Organization (WHO), are shown in Table 1. Recommendations for daily iodine intake during PN by age group are shown in Table 4.

**Infants**

The newborn requirement for T4 and, consequently, for iodine, is high whereas the calculated thyroidal store of thyroid hormone is small, particularly in preterm infants and when maternal iodine status is poor. However, the newborn thyroid is also extremely sensitive to the inhibitory effect of excess iodine, which can cause transient neonatal hypothyroidism.

The IOM recommended iodine intake for infants is based on iodine content of human milk in the United States in 1984, when U.S. iodine intakes were excessive. Because breast milk iodine concentrations are strongly influenced by maternal iodine intakes, balance studies are a more accurate reflection of iodine requirements in infancy. In healthy preterm infants, iodine intakes of at least 30 μg kg⁻¹ body weight per day are required to maintain positive balance. Increasing enteral intake to 40–50 μg iodine kg⁻¹ per day in mature preterm infants does not alter serum thyroid hormone levels. Experts generally recommend iodine intakes of 30–60 μg kg⁻¹ per day for this group.

**Children**

The iodine requirement in children is higher per kilogram body weight than in adults. The IOM recommended intake for children 1–8 years of age is based on balance studies; however, there are limited data in children older than 8 years and adolescents. Thus, the IOM requirements in this group of children are extrapolated from adult data. The median UI for girls in the most recent U.S. National Health and Nutrition Examination Survey (NHANES) was lower than that for boys; however, this most likely represents differences in diet rather than in iodine requirements between sexes.
In general, iodine requirements are consistent across adulthood. Greater iodine requirements exist during pregnancy due to the critical need for sufficient maternal iodine status to support in utero neurodevelopment. Similarly, iodine requirements are higher in lactating mothers to provide sufficient iodine intake to the developing infant.

### Iodine in enteral nutrition

#### Human Milk

Iodine content of human milk can vary depending on maternal iodine status and dietary intake as well as geographic location, with higher iodine concentrations in countries with salt iodisation. Colostrum contains the greatest amount of iodine, with concentrations as high as 200–400 μg l⁻¹, and then iodine content decreases in mature human milk to generally between 50 and 150 μg l⁻¹.

#### Enteral Formulas

Iodine content has been measured in preterm, term, follow-up and special formulas from 13 countries. Formulas from Canada, France, Greece, Japan, Switzerland and the U.S. tend to have higher iodine content than formulas from Austria, Denmark, Germany, Italy and Spain. In general, infant formulas have less iodine content than human milk. Preterm infant formulas contain 20–170 μg iodine l⁻¹, 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.

In the U.S., the measured iodine content of 17 brands of infant formula ranged from 84 to 224 μg l⁻¹ and differences existed between labelled and measured iodine content. While the labelled (100 μg l⁻¹) and measured (84–122 μg l⁻¹) content of soy-based infant formulas were similar, labelled (40–100 μg l⁻¹) and measured (102–224 μg l⁻¹) content of cow’s milk-based infant formulas were considerably different. Commercially available enteral products for use in adults generally supply 75–110 μg iodine per serving.

### Iodine in PN

Oral absorption of iodine is efficient; in adults, oral iodine bioavailability is typically 90–95%. This suggests iodine dosages via the enteral or parenteral route should be nearly equivalent. However, PN solutions contain much less iodine than enteral formulas. For infants, the U.S. and European clinical nutrition societies recommend parenteral iodine intakes of 1 μg kg⁻¹ body weight per day, far below the foetal accretion rates or the amount provided by human milk. This conservative recommendation assumes that parenterally fed infants will absorb iodine through the skin from topical

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**Table 4**

Recommendations for daily iodine intake during parenteral nutrition by age group.

<table>
<thead>
<tr>
<th>Age group</th>
<th>ASCN (ref.55) a,c</th>
<th>ESPGHAN/ESPEN (ref.56) b,c</th>
<th>AGA (ref. 61) d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>1 μg/kg body weight</td>
<td>1 μg/kg body weight</td>
<td>70–140 μg</td>
</tr>
<tr>
<td>Children</td>
<td>1 μg/kg body weight</td>
<td>1 μg/kg body weight</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>-</td>
<td>-</td>
<td>70–140 μg</td>
</tr>
</tbody>
</table>

* a Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition (ASCN).
* b European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN).
* c Assumes parenterally-fed infants and children will absorb iodine through the skin from topical iodinated antiseptics and also receive small amounts of adventitious iodine in other infusions.
* d American Gastroenterological Association (AGA).
Iodinated antiseptics and also receive small amounts of adventitious iodine in other infusions. This assumption is supported by the study of Moukarzel et al., who found normal thyroid function tests and significantly higher serum iodide concentrations in 18 infants receiving long-term PN without iodine supplementation compared with control children. The authors estimated adventitious iodine in PN solutions and fat emulsions accounted for about 50% of the iodine intake, and assumed that skin absorption of topical iodinated antiseptics accounted for the remaining intake. They concluded that it was unnecessary to supplement iodine even in children receiving long-term PN without added iodine.

A daily dose of 1 μg iodine kg⁻¹ body weight is also recommended for children receiving PN. Daily iodine requirements in adult patients receiving total EN or PN are estimated to be 70–150 μg. A recent technical review of PN by the American Gastroenterological Association recommended iodine intakes of 70–140 μg per day.

In iodine-sufficient adults, thyroidal iodine content is 15–20 mg. Thus, it has been suggested that thyroidal iodine stores are often adequate to meet the needs of adult patients requiring total PN for less than 3 months. Furthermore, many individuals on long-term PN are able to eat and drink limited amounts and have a functioning duodenum and thus may absorb dietary iodine. For these reasons, many experts do not recommend supplemental iodine routinely for subjects receiving PN. Iodine status and thyroid hormone levels were adequate in Brazilian adults with intestinal malabsorption secondary to short bowel syndrome, who were receiving long-term PN without supplemental iodine and consuming a normal diet. The patients had an estimated mean daily dietary iodine of 658 ± 125 μg and a mean UI (±SD) of 399 ± 308 μg l⁻¹, indicating excessive dietary iodine.

Sources of iodine in the PN population

A study of PN solutions and fat emulsions given to children 4–18 years of age found an iodine contaminant of 0.4–1.2 μg dl⁻¹ in PN solutions and 1.4–2.3 μg dl⁻¹ in fat emulsions. This contaminant iodine resulted in the provision of approximately 0.5 μg kg⁻¹ per day in the children studied. Another source has reported that PN solutions may contain as much as 15–25 μg iodine as contaminant. Iodine contamination has also been found in intravenous medications commonly given to hospitalised infants.

Other adventitious sources of iodine are available to patients receiving PN. Medications, notably amiodarone, have been associated with iodine excess and hyperthyroidism. In addition, the use of iodinated contrast for radiographic studies or to visualise central venous catheter placement can provide a significant source of iodine. Most likely the greatest source of iodine in patients receiving PN has been from percutaneous absorption of iodine-containing skin antiseptics. In infants receiving PN, use of iodinated contrast agents and iodine-containing skin antiseptics have been associated with excess iodine intake and hypothyroidism. In preterm neonates, due to a thin and immature stratum corneum, transdermal iodine absorption is high and there is increased risk of toxicity. Frequent use of iodine-containing antiseptics in infants can result in transcutaneous absorption of >100 μg iodine per day, iodine excess and neonatal hypothyroidism. Thus, careful control of iodine exposure in newborns is critical to maintain normal thyroid function.

Historically, povidone–iodine has been the mainstay of therapy for skin antisepsis during central line placement, routine central line care and dressing changes. Over the past decade, however, chlorhexidine-based antiseptics have largely replaced povidone–iodine due to their greater efficacy in decreasing catheter-related infections. Due to concerns over chemical burns with alcohol-containing skin products, including chlorhexidine, in low-birth-weight infants, published guidelines for prevention of catheter-related infections have refrained from making specific recommendations on the appropriate use of chlorhexidine in infants less than 2 months of age. Thus, most infants receiving PN have continued to receive povidone–iodine skin care for at least the first 2 months of life. However, considering the risks associated with neonatal sepsis, infection control practices are changing and many institutions are now using chlorhexidine-based products in all patients regardless of age. Most revised protocols now recommend that chlorhexidine be used in premature neonates and infants less than 2 months of age, provided the chlorhexidine is applied to the skin, allowed to dry completely and then removed with normal saline.
Because of concerns over possible iodine excess and the potential advantages of chlorhexidine-based antiseptics, use of iodinated antiseptics in infants may be decreasing, putting infants at risk of ID. If parenterally fed preterm infants are not exposed to adventitious sources of iodine, they may receive only 1–3 \( \mu g \) iodine kg\(^{-1}\) body weight per day, and be in negative iodine balance during the first few postnatal weeks. In the study of Ibrahim et al., preterm infants (\( n = 13 \)) had a mean iodine intake of 3 \( \mu g \) kg\(^{-1}\) body weight per day at PN rates of 150 ml kg\(^{-1}\) per day. All 13 infants had negative iodine balances on day 1, 12 remained in negative balance at day 6 but only three infants remained in negative balance on day 28.

**Iodine status in the PN population**

Prior to the widespread use of chlorhexidine in place of iodine-containing antiseptics, ID in patients receiving PN had not been reported, and clinicians were more concerned about iodine excess from PN. Smerdely et al. found significantly greater UI and serum thyrotropin in infants receiving skin antisepsis with povidone–iodine compared to infants receiving chlorhexidine. The authors recommended avoidance of povidone–iodine in very low-birth-weight infants to prevent transient neonatal hypothyroidism.

Even without the use of iodine-containing skin antiseptics, infants on short term (4–6 weeks) PN with no supplemental iodine were able to maintain normal thyroid function tests. However, another study in preterm infants found negative iodine balance (based on UI assessment) over the first week after birth. The infants were receiving PN with 1 \( \mu g \) kg\(^{-1}\) per day iodine and no iodine-containing skin antiseptics. The balance corrected with increasing enteral intake.

A recent study assessed the iodine and thyroid status of children 1–17 years of age (\( n = 15 \), mean age: 76 months) on long-term PN. Nine children had short bowel syndrome and six had other intestinal diseases. Ten were on total PN and five on partial PN for 14–84 weeks. There was a significant inverse correlation between duration of PN and UI, and after 12 weeks all children had a UI less than 100 \( \mu g \) l\(^{-1}\), with eight less than 50 \( \mu g \) l\(^{-1}\) (moderate deficiency) and seven less than 20 \( \mu g \) l\(^{-1}\) (severe deficiency). However, despite apparently low iodine intakes, there was no significant increase in thyroid size or signs of thyroid dysfunction in the children.

Crill et al. recently reported a case of a preterm infant who developed hypothyroidism due to ID at 11 months of age. The infant was being fed almost exclusively via PN and was receiving only chlorhexidine-based skin antisepsis after 3 months of age. The hypothyroidism reversed rapidly with oral potassium iodide supplementation. Subsequently, the potassium iodide was inadvertently discontinued for approximately 10 weeks and TSH increased during this time. It then normalised again within 4 weeks of re-initiation of the potassium iodide. At the same institution, two additional patients receiving PN have since developed ID and impaired thyroid function (Table 5), as described below.

The second case of ID occurred in a 7-year-old with functional short bowel syndrome, secretory diarrhoea and PN dependence. Thyroid function tests and 24-h UI were assessed as part of routine long-term monitoring. The UI concentration (33 \( \mu g \) l\(^{-1}\)) indicated moderate ID. TSH concentration was at the upper limit of the normal range and free T4 concentration was normal (see Table 5 and Fig. 1). The patient was initially supplemented with a \( \frac{1}{4} \) teaspoon iodised salt (providing 100 \( \mu g \) iodine) per

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Diagnosis</th>
<th>Enteral History</th>
<th>TSH (mIU/L)</th>
<th>Free T4 (ng/dL)</th>
<th>Thyroid Size</th>
<th>UI (( \mu g ))</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 months</td>
<td>SBS(^b)</td>
<td>None</td>
<td>46.6</td>
<td>0.4</td>
<td>Normal (ultrasound)</td>
<td>42</td>
<td>Oral potassium iodide iodized salt, then IV sodium iodide via PN iodized salt</td>
</tr>
<tr>
<td>7 years</td>
<td>Functional SBS(^b); secretory diarrhoea</td>
<td>None</td>
<td>4.1</td>
<td>1.4</td>
<td>Normal (physical exam)</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>18 years</td>
<td>SBS(^b)</td>
<td>Minimal soft food/liquids</td>
<td>8.5</td>
<td>0.9</td>
<td>3 cm bilateral thyroid nodes (physical exam)</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Patient characteristics at the time of diagnosis.  
\(^b\) SBS = short bowel syndrome.
gastrointestinal tube for 2 months. Repeat UI concentrations during this time remained low. Iodised salt replacement was discontinued and intravenous sodium iodide $3 \mu g$ kg$^{-1}$ per day was initiated via PN and then increased after 2 months to $6 \mu g$ kg$^{-1}$ per day. The UI concentration increased to near normal at 6 months. Levothyroxine supplementation was initiated at $50 \mu g$ per day 3 months after diagnosis of ID and was increased to $75 \mu g$ per day 5 months after diagnosis to achieve free T4 concentrations above $1.2 ng dl^{-1}$.

The third case of ID occurred in an 18-year-old with a history of PN dependence due to short bowel syndrome (gastroschisis at birth). This home PN patient with a history of only minimal oral intake (soft foods and liquids) was admitted for surgical removal of gastrointestinal tube and closure of gastrocutaneous fistula. Routine assessment of TSH and free T4 suggested hypothyroidism (see Table 5), and the patient was started on levothyroxine $50 \mu g$ daily. A 24-h UI (see Table 5) conducted 3 months later suggested moderate ID. The patient was started on $\frac{1}{4}$ teaspoon iodised salt (providing $100 \mu g$ iodine) per day prior to discharge home. Ten months later, repeat thyroid function tests were within normal limits (TSH $3.2 mIU l^{-1}$ and free T4 $0.9 ng dl^{-1}$), most likely due to levothyroxine therapy because the 24-h UI remained low ($25 \mu g l^{-1}$). Other than this patient, ID has not been reported in adults receiving PN.72

**Iodine in preterm infants**

Several authors have argued that ID should be avoided during the preterm postnatal period because it may transiently lower thyroid hormone levels in the first weeks of life.43,44 Transient hypothyroxinaemia in preterm infants has been linked to impaired neurodevelopment,73–75 but the potential role of iodine in this phenomenon has been investigated in only one randomised controlled trial.40 Infants born before 33 weeks’ gestation ($n = 121$) were randomised to receive either iodine-supplemented formula ($272 \mu g$ iodine l$^{-1}$) or the same formula without iodine supplementation ($68 \mu g$ iodine l$^{-1}$) until 40 weeks post-conceptional age. The formulas provided daily iodine intakes of
approximately 40–50 μg 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 difference in length of mechanical ventilation or oxygen requirements. However, the study had several limitations. Although transient hypothyroxinaemia is most closely associated with adverse outcomes in extremely preterm infants, only 14% of subjects had a birth weight <1000 g. Second, the intervention began only after the infants had established enteral feeding, usually 2 weeks after birth, but in preterm infants, iodine balance is often negative and transient hypothyroxinaemia 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 the available data are insufficient to support supplementation of preterm infants with iodine. Moreover, although subgroup analyses in a single controlled trial suggested that thyroxine replacement may prevent neurodevelopmental morbidity in extremely preterm infants, the overall data are insufficient to recommend prophylactic thyroid hormone treatment in preterm infants.

Monitoring for ID

Monitoring for ID is important in patients receiving PN without a supplemental source of iodine. In adults and older children in areas of general iodine sufficiency, such as the United States, UI, TSH and free T4 concentrations should be checked after 1–2 months of PN, and on a regular basis thereafter. Initial assessment in infants should be earlier and the frequency of monitoring increased due to their decreased thyroidal stores and the unequivocal importance of adequate iodine status during growth and cognitive development. One study reported that children receiving PN may have low iodine intakes while their thyroid function tests are normal. Thus, the measurement of 24-h UI may detect inadequate iodine status and allow for supplementation before the onset of hypothyroidism. In patients receiving continuous PN with no enteral intake or use of iodine-containing disinfectants, day-to-day variations in iodine excretion should be minimal and spot urine collections may be an acceptable alternative to 24-h collections. In older children and adults, routine physical assessment of thyroid size and measurement of blood Tg concentration can be additional monitoring tools.

Most clinical laboratories do not routinely measure UI concentrations, therefore samples are commonly sent to referral laboratories. However, poor laboratory practice can lead to iodine losses from samples, or iodine contamination. It is important to use an experienced referral laboratory with a validated method for UI measurement. Regular external control is valuable, such as participation in the Ensuring the Quality of Iodine Procedures (EQUIP) program of the U.S. CDC (http://www.cdc.gov/labstandards/equip.htm). In the case of ID outlined in Figure 1, the hospital’s referral laboratory for UI assessment changed from one month to the next and the resulting UI concentration was almost 100-fold greater than the previous month’s concentration. Repeat 24-h UI 10 days later was sent to both of the referral laboratories and resulted in a 6.5-fold difference between the laboratories. Thus, clinicians should work closely with a laboratory experienced in UI measurement to ensure that decisions on iodine supplementation are based on accurate and reproducible results.

Iodine supplementation

Many of the multitrace element products available in Europe contain iodine. While multitrace element products containing iodine have previously been available in the U.S. for adults, none is currently available for either adult or paediatric patients. A single-entity intravenous iodine product (Iodopen®, APP Pharmaceuticals, LLC, Schaumburg, IL, USA) is available and labelled specifically as an additive to PN solutions. There are no reported stability or incompatibility problems when iodine additions are made to PN solutions. Advantages of using the single-entity iodine product include the ability to titrate the dose based on patient response and the ability to individualise trace elements rather than use multitrace products that contain predetermined amounts of chromium, copper and manganese that are known to accumulate in long-term PN patients. Commercially available iodine-containing trace element products are shown in Table 6.
Several options exist for enteral iodine supplementation (see Table 7). Iodised salt supplementation is the most economical and accessible option for iodine supplementation in patients able to take at least small-volume enteral feedings or medications. The desired dose of iodised salt can be added to food, mixed with liquids, or mixed in a small volume of water and given per gastrointestinal or nasogastric feeding tube. Iodine content of iodised salt may vary from country to country as salt iodisation programmes adjust the amount of iodine added to salt based on population UI surveillance. WHO/ICCIDD/UNICEF recommends an iodine content of 20–40 mg kg\(^{-1}\) salt,\(^2\) while the U.S. Food and Drug Administration (USFDA) recommends an iodine content of 46–76 mg kg\(^{-1}\) salt.\(^7\) \(^9\) A recent study evaluated the iodine content of iodised salt in the U.S. and found approximately 50% of salt samples studied had iodine content below USFDA recommendations, while less than 10% had iodine content exceeding the USFDA recommendations.\(^7\) \(^9\) Iodine content of salt also varied within individual containers and under storage at high humidity.\(^7\) \(^9\) Patients with ID who do not have adequate response to iodised salt therapy may need higher daily doses of salt or may require oral potassium iodide or

### Table 6
Trace element products containing iodine.

<table>
<thead>
<tr>
<th>Name</th>
<th>Product Type</th>
<th>Manufacturer</th>
<th>Iodine Content</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addamel N(^a)</td>
<td>Adult multitrace</td>
<td>Fresenius Kabi</td>
<td>Potassium iodide 16.6 µg/mL (equivalent to 12.7 µg/mL iodide)</td>
<td>Adults: 10 mL/day Children ≥ 15 kg: 0.1 mL/kg/day Children ≥ 2 days old: 0.05 mL/kg/day Adults and patients ≥ 40 kg: 40 mL/day</td>
</tr>
<tr>
<td>Decan(^b)</td>
<td>Adult multitrace</td>
<td>Aguettant</td>
<td>Sodium iodide 0.045 µg/mL (equivalent to 0.038 µg/mL iodide)</td>
<td>Infants and children ≤ 40 kg: 1 mL/kg/day Infants and children ≥ 15 kg (and ≥ 2 days old): 1 mL/kg/day Children &gt;15 kg: 15 mL/day Children and pregnant/lactating women: 2–3 µg/kg/day iodine Adults: 1–2 µg/kg/day iodine (75–150 µg/day)</td>
</tr>
<tr>
<td>Oligo-elements(^b)</td>
<td>Pediatric multitrace</td>
<td>Aguettant</td>
<td>Sodium iodide 5.91 µg/mL (equivalent to 5 µg/mL iodide)</td>
<td>Infants and children ≤ 40 kg: 1 mL/kg/day Infants and children ≥ 15 kg (and ≥ 2 days old): 1 mL/kg/day Children &gt;15 kg: 15 mL/day Children and pregnant/lactating women: 2–3 µg/kg/day iodine Adults: 1–2 µg/kg/day iodine (75–150 µg/day)</td>
</tr>
<tr>
<td>Peditrace(^a)</td>
<td>Pediatric multitrace</td>
<td>Fresenius Kabi</td>
<td>Potassium iodide 1.31 µg/mL (equivalent to 1 µg/mL iodide)</td>
<td>Infants and children ≤ 40 kg: 1 mL/kg/day Infants and children ≥ 15 kg (and ≥ 2 days old): 1 mL/kg/day Children &gt;15 kg: 15 mL/day Children and pregnant/lactating women: 2–3 µg/kg/day iodine Adults: 1–2 µg/kg/day iodine (75–150 µg/day)</td>
</tr>
<tr>
<td>Iodopen(^a)</td>
<td>Single entity</td>
<td>APP Pharmaceuticals</td>
<td>Sodium iodide providing 118 µg/mL (equivalent to 100 µg/mL iodide)</td>
<td>Infants and children ≤ 40 kg: 1 mL/kg/day Infants and children ≥ 15 kg (and ≥ 2 days old): 1 mL/kg/day Children &gt;15 kg: 15 mL/day Children and pregnant/lactating women: 2–3 µg/kg/day iodine Adults: 1–2 µg/kg/day iodine (75–150 µg/day)</td>
</tr>
</tbody>
</table>

\(^a\) Addamel\(^a\) and Peditrace\(^a\) labeling, Fresenius Kabi, Bad Homburg, Germany.

\(^b\) Decan\(^a\) and Oligo-elements\(^b\) labeling, Aguettant, Lyon, France

\(^c\) Iodopen\(^a\) labeling, APP Pharmaceuticals, Schaumberg, IL, USA.

### Table 7
Oral iodine supplements.

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Name (Manufacturer)</th>
<th>Iodine Content(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodised salt</td>
<td>Various (Upsher-Smith)(^ah)</td>
<td>Varies per manufacturer and geographic location 1 g/mL (50 mg per drop)(^h) potassium iodide 65 mg/mL (black raspberry flavored) (^5) Potassium iodide 50 mg/mL (2.5 mg per drop)(^d) iodine and 100 mg/mL (5 mg per drop)(^d) potassium iodide 65 mg and 130 mg tablets(^f)</td>
</tr>
<tr>
<td>Potassium iodide solution</td>
<td>SSKI(^b) (Upsher-Smith)(^ab), Thyroshield(^c) (Fleming)(^e)</td>
<td>65 mg/mL potassium iodide (black raspberry flavored) 50 mg/mL (2.5 mg per drop)(^d) iodine and 100 mg/mL (5 mg per drop)(^d) potassium iodide 65 mg and 130 mg tablets(^f)</td>
</tr>
<tr>
<td>Iodine strong solution</td>
<td>Various</td>
<td>65 mg/mL potassium iodide (black raspberry flavored) 50 mg/mL (2.5 mg per drop)(^d) iodine and 100 mg/mL (5 mg per drop)(^d) potassium iodide 65 mg and 130 mg tablets(^f)</td>
</tr>
<tr>
<td>(Lugol’s solution)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium iodide tablets</td>
<td>Various</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) SSKI\(^b\) labeling, Upsher-Smith Laboratories, Inc., Minneapolis, MN, USA.

\(^b\) May be mixed in water, fruit juice, or milk per product labeling.

\(^c\) Similar products available internationally.

\(^d\) Assumes 20 drops per mL (1 drop = 0.05 mL).

\(^e\) Thyroshield\(^c\) labeling, Fleming Pharmaceuticals, Fenton, St. Louis Co., MO, USA.

\(^f\) Tablets may be crushed and dissolved with water and then further mixed with a selected drink (milk, formula, juice, soda) to make a 3.25 mg/mL (using 130 mg tablet) and a 1.625 mg/mL (using 65 mg tablet) solution; see product labeling for specific instructions.
parenteral iodine via PN. Potassium iodide is available commercially in both tablet and solution dosage forms.

Deficiencies of other micronutrients may affect iodine status in patients receiving nutrition support. Iron-deficiency anaemia impairs iodine incorporation into thyroid hormone and increases risk of hypothyroidism at low iodine intakes.80 Since multivitamin products for parenteral use do not contain iron, iron status should be routinely monitored in patients receiving long-term PN, and parenteral iron replacement should be given at least monthly to provide adequate iron stores. Iron is primarily absorbed in the duodenum and proximal jejunum. Thus, in patients able to tolerate some enteral intake, oral iron supplements may be given. Vitamin A deficiency can also aggravate thyroid dysfunction due to ID.81 Vitamin A is a component of multivitamin preparations added to PN solutions; thus vitamin A deficiency should not be a concern in patients receiving PN exclusively. However, in patients receiving only partial PN support, particularly in patients with significant ileal resection and fat malabsorption, assessment of vitamin A status and supplementation with additional vitamin A, as well as other fat soluble vitamins, may be warranted. Finally, adequate selenium is important for optimal thyroid and iodine status since the iodothyronine deiodinases are selenoproteins.82 Selenium should be supplemented in long-term PN with periodic assessment of selenium status.

Excess and toxicity

Most people who are iodine sufficient are remarkably tolerant to high dietary intakes of iodine. Iodine intakes up to 1 mg per day are well tolerated by most adults, as the thyroid is able to adjust to a wide range of intakes and regulate the synthesis and release of thyroid hormones.83 Some individuals with excess iodine intakes, particularly those who were previously iodine deficient, develop hyperthyroidism (the Jod–Basedow phenomenon). However, excessive intakes may inhibit iodine uptake by the thyroid and impair thyroid hormone synthesis (the Wolff–Chaikoff effect). Thus, excess iodine may cause both hyper- and hypothyroidism. In children, chronic intakes of ≥500 µg per day are associated with increased thyroid volume, an early sign of thyroid dysfunction.84

Potential adverse acute reactions to parenteral injection of iodine include hypersensitivity reactions (angioneurotic oedema, cutaneous and mucosal haemorrhages, fever, arthralgia, lymphadenopathy, eosinophilia).85 Symptoms of chronic iodide poisoning include a metallic taste in the mouth, increased salivation, gastrointestinal tract irritation, headache, pulmonary oedema and acneiform skin lesions.86 Thyroid function should be monitored in patients exposed to frequent large amounts of iodine-containing radiographic contrast dyes or the drug amiodarone.

European87 and U.S.5 expert committees have recommended tolerable upper intake levels for iodine (Table 8), but individuals with chronic ID may respond adversely to intakes lower than these.88 For monitoring of populations using the median UI, recommendations for more than adequate and excess iodine intake are shown in Table 2.2

<table>
<thead>
<tr>
<th>Age group</th>
<th>European Commission/Scientific Committee on Food (ref. 94)</th>
<th>US Institute of Medicine (ref. 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3 years</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>4–6 years</td>
<td>250</td>
<td>300</td>
</tr>
<tr>
<td>7–10 years</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>11–14 years</td>
<td>450</td>
<td>300</td>
</tr>
<tr>
<td>15–17 years</td>
<td>500</td>
<td>900</td>
</tr>
<tr>
<td>Adult</td>
<td>600</td>
<td>1100</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>600</td>
<td>1100</td>
</tr>
</tbody>
</table>
Practice points

- A daily dose of 1 μg iodine/kg body weight is recommended for infants and children receiving PN, but this is far below their requirement, because it is assumed that iodine-containing antiseptics and/or other adventitious sources of iodine will provide sufficient iodine.
- If chlorhexidine replaces iodine-containing antiseptics for catheter care, ID may occur during long-term PN.
- In older children and adults in iodine-sufficient countries, thyroidal iodine stores may be adequate to meet the needs of patients requiring PN for up to 3 months.
- Periodic assessment of thyroid size, as well as Tg, TSH and free T4 concentrations, can be used to assess iodine status in patients receiving PN exclusively.
- Iodine concentrations in spot urine samples are highly variable and should generally not be used to diagnose ID.
- The mean UI measured in three 24-h urine samples collected over a week during which the habitual diet is consumed can provide an estimate of usual iodine intake in an individual.
- Measurement of UI concentrations in patients on PN may detect inadequate iodine and allow for supplementation before the onset of hypothyroidism.

Future research needs

- Randomised controlled trials of iodine supplementation are needed in extremely preterm and extremely low-birth-weight infants, the group at greatest risk of transient hypothyroxinaemia, with clinically important outcomes including respiratory morbidity and neurodevelopment.
- Iodine requirements for individuals on long-term PN should be better defined, particularly when chlorhexidine-based antiseptics are used in place of iodinated antiseptics. If it is demonstrated that there is increased risk of ID in such patients, the possible need for revision of current PN iodine guidelines should be considered.

Conflict of interest statement

The authors have no conflicts of interest or financial disclosures to make.

References


86. Available at: [http://www.merck.com/mmpe/sec01/ch005/ch005e.html](http://www.merck.com/mmpe/sec01/ch005/ch005e.html).
