Iodine status in intestinal failure in adults

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Purpose of review
The aim of this work is to review the recent findings on iodine nutrition in adults with intestinal failure.

Recent findings
Patients with intestinal failure who require long-term parenteral nutrition are potentially at risk for trace element deficiencies. It was considered that iodine deficiency was unlikely to occur in adults on parenteral nutrition, even if iodine is not added to parenteral nutrition, because of iodine absorption from iodine-containing antiseptics, to presence of iodine as contaminant in parenteral nutrition products and to absorption of dietary iodine, in patients eating and having a functioning duodenum. It is believed that thyroidal iodine could support thyroid function for several months during total parenteral nutrition. Clinical Nutrition Societies do not have uniform opinion about the need to supplement iodine routinely in parenteral nutrition in adults. Although very few studies have addressed this topic, inadequate iodine supply in long-term parenteral nutrition in young adults, and the increased risk of iodine deficiency in adults on long-term parenteral nutrition have recently been reported.

Summary
There is some evidence that adults with intestinal failure on long-term parenteral nutrition may be at risk of iodine deficiency. Studies carried out in large cohorts of patients are required to better define iodine requirements in long-term parenteral nutrition.

Keywords
intestinal failure, intestinal insufficiency, iodine nutrition, parenteral nutrition, thyroid function

INTRODUCTION

Intestinal failure

The European Society for Clinical Nutrition and Metabolism (ESPEN) has recently defined and classified intestinal failure as 'the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth' [1▪]. The reduction of gut absorptive function that does not require intravenous supplementation of macronutrients and/or water and electrolytes, to maintain health and/or growth, has been defined as intestinal insufficiency or deficiency [1▪]. Intestinal failure has been classified as: acute, short-term condition (Type I), prolonged acute condition requiring parenteral nutrition over weeks/months (Type II), or chronic condition that necessitates parenteral nutrition over months/years (Type III; chronic intestinal failure, CIF). Five pathophysiological mechanisms were identified: short bowel, intestinal fistulas, extensive small bowel mucosal disease, intestinal dysmotility, and mechanical obstruction. In the former three conditions, the primary cause of intestinal failure is malabsorption and/or high intestinal losses of nutrients, whereas in the two latter conditions it is intolerance to oral/enteral nutrition with inadequate/totally absent oral or enteral nutritional intake [1▪].

Treatment of chronic intestinal failure

When CIF is irreversible, the treatment options are lifelong home parenteral nutrition (HPN) or intestinal transplantation (ITx). Based on data on safety and efficacy data, HPN is considered the primary treatment for CIF, whereas ITx is reserved for those patients at risk of death because of life-threatening

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KEY POINTS

- An increased risk of iodine deficiency has been reported in adult patients with chronic intestinal failure on long-term parenteral nutrition.
- Iodine nutrition can be assessed by measuring iodine in spot or in 24-h urine samples, thyroid function tests and thyroid size assessment.
- Iodine intake could be increased by adding iodized salt to food of patients with some enteral feeding conserved, or by intravenous supplementation in those totally fed by parenteral nutrition.

complications related to HPN or to the underlying disease [2].

In long-term HPN it becomes essential to maintain the nutritional status of micronutrients (vitamins and trace elements). Micronutrients imbalance (deficiency or excess) can lead to clinical compromise as they play a central role in metabolism and in tissue functions; therefore, the micronutrients' nutritional status must be routinely assessed, in order to ensure an adequate parenteral provision [3,4].

IODINE

In mammals, iodine is an essential trace element for thyroid hormone synthesis. Iodine deficiency has many adverse effects because of inadequate synthesis of thyroid hormones (hypothyroidism, iodine-induced hyperthyroidism, and so on) [5]. In developed countries, salt iodization is the most cost-effective strategy to address the problem of inadequate oral intake. The recommended daily iodine intake for adults is 150 μg (1.3 μmol) [6].

Absorption and metabolism

In healthy adults about 90% of dietary iodine is absorbed in the stomach and duodenum. Iodine is cleared from circulation by the thyroid and by the kidneys. Thyroid clearance varies according to the iodine intake. In chronic iodine deficiency, the thyroid could clear more than 80% of circulating iodine, with a consequent reduction of the amount excreted by kidney [7].

Notwithstanding that the number of 'iodine-sufficient' countries has markedly increased over the past decade, many regions with inadequate iodine intake are still present (i.e. Great Britain, Italy, Australia, and many African countries) [8,9].

Assessment of iodine nutrition

Several methods are recommended to asses iodine nutrition:

(1) urinary iodine: marker of recent iodine intake (days);
(2) thyroid function tests, including thyroid stimulating hormone (TSH) and thyroglobulin (Tg): markers of intermediate iodine intake (weeks to months); and
(3) thyroid size: reflects long-term iodine nutrition (months to years).

Urinary iodine is a good marker of recent iodine intake, as more than 90% of absorbed iodine is excreted by the kidneys. Urinary iodine could be expressed as a concentration (μg/l), or as the 24 h excretion (μg/day). As it is impractical to collect 24-h urine, in clinical research, urinary iodine can be measured in spot urine specimens in a representative sample of the target group, and it can be expressed as a median (μg/l). A low median urinary iodine concentration is indicative of insufficient iodine intake and suggests a high risk of developing thyroid dysfunction in the population (Table 1).

On an individual level, assessment of iodine nutrition, because of a wide day-to-day variation of iodine intake, should be performed by means of at least three 24-h urine collections over a week in which the routine diet is consumed [7,10,11].

Thyroid function tests

Thyroid stimulating hormone

TSH is a good marker of iodine intake in newborns. In older children and adults, TSH is relatively insensitive because both high iodine store and low turnover allow the thyroid to compensate low iodine intake for several months. In the early stage of iodine deficiency, TSH usually rises whereas thyroxine falls, but generally within the normal ranges, whereas triiodothyronine may increase. Thus, normal values of TSH cannot rule out the presence of iodine deficiency. Conversely, a TSH above the normal levels is suggestive of iodine imbalance (deficiency or excess) [7,10,11].

Thyroglobulin

In iodine-sufficient subjects, the serum Tg, a glycoprotein precursor of thyroid hormones, is very low. In iodine deficiency serum Tg rises because of an increase of TSH stimulation and thyroid cell mass. In order to avoid potential Tg underestimation, simultaneous measurement of anti-Tg antibodies should be performed [7,10,11].

Table 1. Epidemiological criteria for assessing iodine nutrition at a population level, based on a median of UI concentrations (school-aged children: ≥6 years)[a]

Median UI (μg/l)	Iodine intake	Iodine nutrition
<20	Insufficient	Severe iodine deficiency
20–49	Insufficient	Moderate iodine deficiency
50–99	Insufficient	Mild iodine deficiency
100–199	Adequate	Optimal
199–299	More than adequate	Risk of iodine-induced hyperthyroidism in susceptible group
>300	Excessive	Risk of iodine-induced hyperthyroidism and autoimmune thyroid disease

UI, urinary iodine.
[a]Adapted with permission from [7,11].

Thyroxine and triiodothyronine

Serum concentration of thyroid hormones is not considered a good marker of iodine nutrition in adults. Normal circulating level of thyroid hormones does not exclude the presence of iodine deficiency. Another major limitation is because of 'euthyroid sick syndrome', which often occurs in unstable patients with major trauma, sepsis, or organ failure. Its main feature is the low level of thyroid hormones associated with a low or normal value of TSH, suggesting central hypothyroidism [7,10,11].

Thyroid size

Thyroid enlargement (goiter) is the classical sign of iodine deficiency as a result of physiological adaptation to chronic iodine deficiency. Ultrasound estimation is the accepted method for the assessment of the thyroid gland volume.

IODINE IN INTESTINAL INSUFFICIENCY/ DEFICIENCY

In patients with intestinal insufficiency, the occurrence of iodine deficiency is unlikely because the impairment of gut function may be compensated by adaptive hyperphagia, by oral nutritional supplements (ONS), and finally by tube feeding (EN) [1▪]. In iodine deficiency, the recommended daily iodine intake does not differ from that of a healthy population.

In intestinal insufficiency requiring only compensation by adaptive hyperphagia, the probability to develop inadequate iodine intake would not be increased, because of high food intake and to the very efficient absorption of dietary iodine in the stomach and in the duodenum.

In Europe, the majority of ONS contain iodine, at concentration ranging from 15 to 35 μg/100 ml, with a supply of 30–75 μg per serving (usually 200 ml). Two servings a day would ensure 50–100% of the daily iodine intake recommended by WHO [6]. Currently, the mean labeled iodine content of products for EN in Europe is 10–15 μg/100 ml. The actual amount supplied daily depends on the feed volume.

In patients with normal intestinal absorption, unable to eat any food (swallowing disorders), who are exclusively fed by EN iodine intake may be inadequate, depending on the iodine content in the volume of enteral formula used.

Takeuchi *et al.* found low urinary iodine excretion in a group of 35 Japanese patients on long-term total-EN, for severe motor and intellectual disability, and observed hypothyroidism in a third of them. Because of the low iodine content of EN formulas available in Japan, the mean daily iodine intake was far below that recommended for adults [12,13].

IODINE IN INTESTINAL FAILURE

In the past, it has been considered unlikely that adults on parenteral nutrition develop iodine deficiency, even if iodine is not added to parenteral nutrition admixtures [10,11]. Several adventitious iodine sources are available in patients receiving parenteral nutrition. They can absorb iodine through the skin from topical iodine-antiseptic used in routine central line care. Iodinate contrast for radiographic study may provide an additional iodine source. The increasingly widespread use of chlorhexidine in place of iodine-antiseptics is deemed to be responsible for the marked reduction of adventitious iodine supply in patients with parenteral nutrition [10,11,14▪▪].

Several parenteral nutrition products, especially lipid emulsions and amino acid solutions, could contain iodine as contaminant. Belford *et al.* [15] found 15.1 and 2.5 μg/l of iodine in a soy-based lipid emulsion and in an amino acids solution,

respectively. The reduction of lipid amount to treat/prevent intestinal failure associated liver disease, may be an underestimated cause of decreased iodine exposure in patients with parenteral nutrition [14▪▪].

Intestinal failure patients having a normal duodenum, who are able to eat, may absorb dietary iodine. This quantity may be elevated in patients with short bowel syndrome (SBS) with adaptive hyperphagia and, obviously, it becomes absent in patients totally fed by parenteral nutrition.

It has been suggested that in adults with normal iodine nutritional status at the beginning of a total parenteral nutrition treatment, thyroidal stores are sufficient to meet the iodine needs for about 3 months [10,11].

For these reasons, Clinical Nutrition Societies have no uniform opinion about the need to supplement iodine routinely in adult parenteral nutrition (Table 2). The recent position paper of American Society for Parenteral and Enteral Nutrition (ASPEN) does not recommend iodine supply and monitoring of iodine nutrition in parenteral nutrition [17], whereas ESPEN [16] and the Australian Society for Parenteral and Enteral Nutrition [18] (AuSPEN) endorse routine supplementation of iodine (Table 2).

Very few studies have been performed to investigate iodine requirements on parenteral nutrition, probably because of the absence of clinical evidence of thyroid function impairment in adults on parenteral nutrition. However, recent studies suggest that patients with CIF on long-term parenteral nutrition may be at risk of iodine deficiency.

Thus, in 2005 normal iodine status and thyroid function were found in Brazilian SBS patients on long term parenteral nutrition without iodine [10].

In 2011, Ishizuko *et al.* [19] evaluated the serum levels of thyroid hormones in critically ill patients with acute intestinal failure, on total-parenteral nutrition supplemented by 127 μg/day (1 μmol/day) of iodine, the higher level of the range recommended by ESPEN. They were not able to measure urinary iodine. Because of the significant increase of T3 values during a 4 weeks parenteral nutrition treatment, the authors concluded that 127 μg/day (1 μmol/day) of iodine might be excessive in critically ill patients with acute IF. However, because T3 also rises in iodine deficiency it may be misleading to use thyroid hormone levels to make conclusions without knowing the actual iodine nutritional status [10,11]. In the last year, two papers were published about iodine nutrition in young adults and adults on long-term parenteral nutrition [14▪▪,20▪].

A case of severe iodine deficiency in a young adult (16-year-old male), who had been parenteral nutrition dependent since his early childhood for chronic intestinal dysmotility, and on total parenteral nutrition from the age of 12 years because of almost total enterectomy, has been described [14▪▪]. The presence of thyromegaly was incidentally found, because monitoring of iodine nutrition was not done routinely. At first analysis, normal TSH and free-T3 and low free-T4, but undetectable level of iodine in 24-h urine were found, indicating the presence of iodine deficiency. Authors decided to initially treat with enteral iodized salt (one-quarter of teaspoon by mouth or by G-tube) in addition to levothyroxine; they hesitated to use multitrace element products for parenteral use because of fixed concentrations of individual trace elements, which limits flexibility in dosing. Iodine could also be added to parenteral nutrition admixtures as sodium/potassium iodide, without stability problems [10].

The second paper analyzed iodine nutrition in a cohort of 31 patients with CIF on long-term parenteral nutrition (parenteral nutrition duration: 117 ± 94 months) and compared it with the amount of iodine supplied with parenteral nutrition, categorized as below or within the range recommended by ESPEN guidelines [20▪]. All patients used chlorhexidine for central line care. The amount of iodine supplied in the parenteral nutrition was in agreement with the ESPEN guideline in 26% of patients, it was less in 19% whereas 55% of the patients did not receive any parenteral nutrition iodine. In the whole group of patients, the median of urinary iodine concentration (UIC), measured in spot samples, was lower than 100 μg/l (63 μg/l; 95% confidence interval 26–99), as it was in the group including both the patients with no iodine-parenteral nutrition and those with iodine-parenteral nutrition lower than ESPEN recommendation (56 μg/l; 95% confidence interval 24–99) and also in the group of patients with iodine-parenteral nutrition meeting the ESPEN guideline (77 μg/l). The iodine requirements seem to be underestimated, as even those patients who received a parenteral nutrition iodine

Table 2. Recommendation for daily iodine intake for parenteral nutrition in adult patients

	Iodine amount
ESPEN[a] 2009	1.27–127 μg (0.1–1.0 μmol)
ASPEN[b] 2012	not well defined
AuSPEN[c] 2014	127 μg (1.0 μmol)

[a]The European Society for Clinical Nutrition and Metabolism [17].
[b]American Society for Parenteral and Enteral Nutrition [18].
[c]Australasian Society for Parenteral and Enteral Nutrition [19].

supply according to ESPEN guidelines had a low UIC.

Despite the low values of UIC, TSH was low only in 22% of patients (median UIC <50 μg/l), in whom serum thyroid hormones concentration was normal. The UIC was significantly associated with the underlying cause of intestinal failure. Patients with SBS had lower UIC than non-SBS (38 vs. 76 μg/l). This was related to the lower prescribed parenteral nutrition iodine supply for patients with SBS.

Iodine toxicity

A high dietary intake of iodine is well tolerated by most healthy adults, when it remains below 1 mg/day. As iodine overload may inhibit its uptake by thyroid and impair thyroid function, attention must be paid to not supplement too much iodine to depleted patients [5,10].

When iodine and selenium deficiencies occur simultaneously, supplementation of iodine alone may lead to thyroid damage, because the key enzymes involved in activation/inactivation of thyroid hormones and in thyroid protection from reactive oxygen species are selenoproteins [21,22]. Acute adverse reaction to parenteral injection of iodine (angioedema, fever, arthralgia, and so on) may occur, whereas chronic iodine poisoning may cause headache, gastrointestinal mucosal disease, and so on [10].

CONCLUSION

Patients with intestinal insufficiency with adaptive hyperphagia are not at increased risk of iodine deficiency, because of high food intake and efficient absorption of dietary iodine. In intestinal insufficiency requiring long-term total-EN, an increased risk has been described, depending on the iodine content of the enteral formula used.

In patients with chronic intestinal failure on long-term parenteral nutrition, an increased risk of iodine deficiency has been reported. The use of chlorhexidine instead of iodine-antiseptics, the length of parenteral nutrition treatment, and the low oral intake, seem to be the predisposing factors. This would suggest routine monitoring of iodine status to prevent deficiency.

The assessment of iodine nutrition is based on several complementary diagnostic indices: urinary iodine (index of recent iodine intake), thyroid function tests (index of intermediate iodine intake) and thyroid size (related to long-term iodine intake).

In adult patients with chronic intestinal failure on long-term parenteral nutrition:

(1) an increased risk of iodine deficiency has been reported;
(2) the low oral intake, the length of parenteral nutrition treatment, the use of chlorhexidine instead of iodine-antiseptics seem to be the predisposing factors;
(3) when some enteral feeding is conserved, iodine intake could be increased by adding iodized salt to food or by mixing it in a small volume of water given by tube feeding;
(4) iodine nutrition could be assessed by measuring urinary iodine in three 24-h urine samples collected over a week during habitual enteral feeding in those who have some enteral intake; and
(5) iodine nutrition could be reasonably assed by measuring iodine in spot urine collection, in those on total parenteral nutrition with no enteral feeding.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
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