Clinical Nutrition ESPEN 61 (2024) 369–376

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Educational Paper

LLL 44-1 Micronutrients in clinical nutrition: Trace elements

Alan Shenkin [a], Dinesh Talwar [b], Nawfel Ben-Hamouda [c], Karin Amrein [d], Michael P. Casaer [e], Angélique de Man [f], Oguzhan S. Dizdar [g], Kursat Gundogan [h], Hanna-Liis Lepp [i], Serge Rezzi [j], Arthur RH. van Zanten [k], Mette M. Berger [l, *], for the ESPEN Micronutrient Special Interest Group (SIG-MN)

[a] *Institute of Aging and Chronic Disease, University of Liverpool, Liverpool, UK*
[b] *Scottish Trace Element and Micronutrient Diagnostic and Research Laboratory, Department of Clinical Biochemistry, Glasgow Royal Infirmary, Glasgow, UK*
[c] *Dpt of Adult Intensive Care, Lausanne University Hospital, Lausanne Switzerland*
[d] *Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology, Austria*
[e] *KU Leuven, Department of Cellular and Molecular Medicine, Laboratory of Intensive Care Medicine, Leuven, Belgium*
[f] *Department of Intensive Care Medicine, Research VUmc Intensive Care (REVIVE), Amsterdam Cardiovascular Science (ACS), Amsterdam Infection and Immunity Institute (AI&II), Amsterdam Medical Data Science (AMDS), Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands*
[g] *Department of Internal Medicine and Clinical Nutrition Unit, University of Health Sciences Kayseri City Training and Research Hospital, Kayseri, Turkey*
[h] *Division of Intensive Care Medicine, Department of Internal Medicine, Erciyes University School of Medicine, Kayseri, Turkey*
[i] *North Estonia Regional Hospital, Tallinn, Estonia*
[j] *Swiss Nutrition and Health Foundation, Epalinges, Switzerland*
[k] *Gelderse Vallei Hospital, Ede and Division of Human Nutrition and Health, Wageningen University & Research, Wageningen, the Netherlands*
[l] *Faculty of Biology & Medicine, Lausanne University, Lausanne, Switzerland*

ARTICLE INFO

Article history:
Received 5 March 2024
Accepted 10 April 2024

Keywords:
Copper
Iron
Selenium
Zinc
Deficiency
Monitoring
Inflammation

SUMMARY

Background: Trace elements are an essential component of metabolism and medical nutrition therapy, with key roles in metabolic pathways, antioxidation, and immunity, which the present course aims at summarizing.

Results: Medical nutrition therapy includes the provision of all essential trace elements. The clinical essential issues are summarized for Copper, Iron, Selenium, Zinc, Iodine, Chromium, Molybdenum, and Manganese: the optimal analytical techniques are presented. The delivery of all these elements occurs nearly automatically when the patient is fed with enteral nutrition, but always requires separate prescription in case of parenteral nutrition. Isolated deficiencies may occur, and some patients have increased requirements, therefore a regular monitoring is required. The clinicians should always consider the impact of inflammation on blood levels, mostly lowering them even in absence of deficiency.

Conclusion: This text summarises the most relevant clinical manifestations of trace element depletion and deficiency, the difficulties in assessing status, and makes practical recommendations for provision for enteral and parenteral nutrition.

* Corresponding author.
E-mail addresses: shenkin@liverpool.ac.uk (A. Shenkin), dinesh.talwar@ggc.scot.nhs.uk (D. Talwar), Nawfel.Ben-Hamouda@chuv.ch (N. Ben-Hamouda), karin.amrein@medunigraz.at (K. Amrein), michael.casaer@uzleuven.be (M.P. Casaer), ame.deman@amsterdamumc.nl (A. de Man), oguzhansitki.dizdar@sbu.edu.tr (O.S. Dizdar), kursatgundogan@gmail.com (K. Gundogan), liis.lepp@gmail.com (H.-L. Lepp), serge.rezzi@nutritionhealthfoundation.ch (S. Rezzi), arhvanzanten@gmail.com (A.RH. van Zanten), Mette.Berger@unil.ch (M.M. Berger).

https://doi.org/10.1016/j.clnesp.2024.04.007

Abbreviations

APR	acute phase response
EN	Enteral nutrition
FSMP	Foods for Special Medical Purposes
PN	Parenteral nutrition
ROS	reactive oxidant species
sTfR	Soluble serum transferrin receptor

Learning objectives

- To be aware of the essential trace elements which need to be supplied to patients receiving artificial nutrition.
- To know the effects of deficiency of trace elements
- To understand the reasons why some patients receiving artificial nutrition may have increased requirements.
- To understand the impact of inflammation on trace element status
- To understand the value and limitations of methods of assessing trace element status in patients receiving nutritional support

Key messages

- Trace elements are an essential part of any form of nutrition, both in normal individuals and in those requiring medical nutrition therapy
- Patients requiring intravenous nutrition (PN) should receive trace elements together with vitamins from the beginning of the PN.
- Requirements in disease are often greater than in health to cope with increased metabolic requirements and increased losses.
- The inflammatory response complicates the assessment of trace element status and requires the simultaneous assessment of the level of inflammation using C-reactive protein (CRP) as a biomarker.
- Monitoring trace element status may require the determination of additional functional biomarkers.

1. Trace elements-the fundamentals

This is a large topic and readers are referred to the 2022 ESPEN guidelines [1] and to their practical version [2] for a more detailed discussion, as well as for the global strategy. The text hereafter provides a summary of functions, absorption/excretion pathways, deficiency symptoms, and biomarkers.

1.1. Copper

Copper, with its specific ability to adopt two different redox states (oxidized and reduced), has primarily a catalytic role for certain metalloenzymes which act as oxidases [1]. For example, cytochrome C oxidase is especially important in energy metabolism, lysyl oxidase produces cross-linkages in collagen and elastin, and ferroxidase oxidises iron to bind to transferrin for circulation in the plasma and delivery to the tissues. Copper enzymes regulate iron metabolism, energy production, connective tissue maturation, neurotransmission, and different hormones.

Copper homeostasis is controlled by modulating copper absorption from the small intestine (primarily duodenum) and its excretion in the bile. Urinary losses are very low. Copper is transported in plasma bound to caeruloplasmin, which participates in tissue iron release.

Copper depletion and deficiency are observed in some acute conditions of losses of biological fluids, such as major burns, or in patients requiring continuous renal replacement therapy [3]. It has also been observed in prolonged PN and EN (probably due to low intakes), and after gastric and bariatric surgery, or prolonged jejunal nutrition: in the latter cases, it is due to bypassing the duodenal absorption site [4]. It causes normocytic hypochromic anaemia, neutropenia, and neurological symptoms, mimicking B12 deficiency.

The best markers of copper status are plasma copper or caeruloplasmin in the absence of acute phase response (APR), which increases copper due to increased caeruloplasmin synthesis. Concentrations also increase in pregnancy and with the oral contraceptive pill. Erythrocyte superoxide dismutase may be helpful, although it can be elevated in situations of oxidative stress.

1.2. Iron

Iron is the most abundant trace element in the human body [1]. The main function of iron is for oxygen transport within haemoglobin, although a substantial amount is also required for myoglobin function in skeletal muscle. Proteins containing non-heme iron play an important role in fundamental cellular processes such as DNA synthesis, cell proliferation and differentiation (ribonucleotide reductase), gene regulation, drug metabolism, and steroid synthesis [5].

Iron status is largely maintained by regulation of absorption in the upper small bowel. Haem iron is absorbed separately and more efficiently than non-haem iron, which is improved by reducing agents such as vitamin C, which also form chelates with iron. Mucosal cells regulate the amount of iron absorbed, which is then carried by transferrin to the tissues, where uptake is controlled by expression of a membrane-bound receptor for transferrin. Iron is stored in the liver, spleen, and bone marrow in the form of ferritin and hemosiderin.

Worldwide, iron deficiency is the most common nutritional deficiency, affecting hundreds of millions of people. The signs of iron deficiency become progressively severe. Iron deficiency leads to impaired physical and cognitive functions, and to a high risk of morbidity for mother and child in pregnancy. Iron deficiency is often overlooked, especially when the complete blood count is abnormal. However, iron deficiency anaemia is less common than iron deficiency without anaemia.

There are many traditional and newer laboratory tests for iron status [1]: the difficulties come from their sensitivity to inflammation. Serum ferritin is usually the best marker of iron status, but it is increased in the presence of APR. Soluble serum transferrin receptor (sTfR) increases in iron deficiency, and it may be the best marker in inflammatory diseases. Serum hepcidin is also little affected by inflammation. Both biomarkers are not yet in widespread use.

Iron status is not directly affected by severe illness: it should be provided daily with any form of nutrition therapy. Iron deficiency should be treated when it is associated with anemia and/or low ferritin levels. Iron supplementation in the presence of normal or even high ferritin values is, however, not recommended and is potentially harmful There is however concern regarding high doses iron provision may exacerbate certain bacterial infections, possibly by providing iron as a substrate for the microorganisms. Hence iron

should not be provided during acute infection and inflammation, until it is resolved [6].

1.3. Selenium

Selenium is required for synthesis of the amino acid selenocysteine, an essential component of at least 25 selenoproteins in human tissues [7]. The biochemical functions of these selenoproteins include antioxidant and redox activity, control of thyroid hormone metabolism, together with several proteins of uncertain function [1]. The glutathione peroxidases (GPX) enzyme family is the first line of enzymes involved in antioxidant activity both in the extra- and intracellular milieu.

Absorption of selenium from the diet is very efficient – much is in the form of selenomethionine, a plant amino acid, or selenocysteine. Commercial selenium supplements in the form of selenite or selenate are well absorbed. Excess selenium is excreted in the urine.

Insufficient selenium intake is the most common cause of selenium deficiency, and is largely geography dependent, some areas of the world being characterized by low soil content, giving rise to a wide spectrum of diseases. Keshan disease is a cardiomyopathy of children in China and Kashin-Beck disease of cartilage in adolescents were the main syndromes from which the deficiency was first identified. Selenium deficiency is associated with increased incidence and virulence of viral infections [8]. In clinical nutrition, skeletal and cardiomyopathy have both been observed. Among the acute conditions at risk of deficiency due to losses are major burns and patients on continuous renal replacement.

Whole blood or plasma/serum selenium concentration is the main indicator of actual selenium status. Plasma selenium is affected by APR, but not as markedly as zinc or iron. Additional biomarkers are the plasma and erythrocyte GPX, and selenoprotein P [9] and red blood cell (RBC) selenium which is unaffected by APR (15).

1.4. Zinc

Zinc has three main types of functions, catalytic, structural, and regulatory. Approximately 200 enzymes require zinc for their catalytic activity, especially the enzymes of protein and nucleic acid synthesis. This accounts for the importance of zinc in growth and tissue repair. Zinc also permits the folding of other proteins by binding to cysteine and histidine residues, forming zinc fingers. These have extensive roles in controlling gene transcription, and in facilitating enzyme action, although not actually catalysing the enzyme e.g. zinc – copper superoxide dismutase. Zinc may also directly affect gene expression e.g. metallothionein synthesis in the liver.

Zinc is primarily absorbed in the jejunum and is efficiently excreted into bile. Absorption can be markedly affected by ingestion of large amounts of other elements such as iron or copper, or by the amount of phytate or fibre, which reduce the bioavailability. Over 85% of body zinc is found in skeletal muscle and bone, with only a very small amount (0.1% of total) in the plasma [1]. Homeostasis of body zinc is largely controlled by the amount of zinc absorbed or secreted into the gut. Zinc is mainly transported in plasma bound to albumin. Urine zinc is usually less than 10% of faecal zinc unless there is increased muscle protein catabolism.

Deficiency of zinc is well characterised. Reduced growth in children is an early sign. Severe zinc deficiency gives rise to alopecia, diarrhoea, delayed sexual maturation, and eczematous skin rash especially on the face and in body flexures, and impaired appetite. There are also important effects on immune function.

The most widely used marker of zinc status is plasma zinc concentration which correlates reasonably well with intake, provided there is no inflammatory response. However, any inflammatory condition causes an acute fall in plasma zinc. Changes in plasma zinc concentration must therefore be interpreted together with changes in its main binding protein, albumin (albumin-corrected i: Zn corrected = Zn measured - (0.352*(Albumin - 45)) correction) [10], and also changes in APR (simultaneous measure of C-reactive protein) [1]. Other methods of assessing zinc such as the zinc concentration in erythrocytes has not proved useful, whereas zinc in hair is too susceptible to methodological variation. Organ failure does not lead to significant changes in zinc requirement, except for major burns where exudative losses of zinc can be substantial.

1.5. Chromium

Chromium exists in several valence states: in its biologically active trivalent form (Cr^{3+}), chromium is stable, and enhance the action of insulin, possibly through amplifying insulin receptor tyrosine kinase activity [1]. This may lead to an improvement in glucose tolerance in some individuals.

Chromium absorption is tightly regulated not exceeding 2.5% [11], largely in the form of chromium^{3+}. Homeostasis is mainly by altering the excretion in the urine.

Some patients with acute illness due to metabolic stress (burns, trauma, infection), or decreased absorption/intake (short bowel syndrome and PN patients without chromium supplementation) may develop deficiency. The deficiency during PN manifests with weight loss, glucose intolerance, and peripheral neuropathy: they respond to chromium provision. Sub-clinical deficiency may lead to impaired glucose tolerance in type II diabetes.

Assessment of chromium status is extremely difficult due to the very low plasma concentrations and the difficulty in obtaining non-contaminated specimens. However, plasma concentration may help in specialised laboratories. The best assessment may be the response of glucose and insulin to chromium supplements.

1.6. Iodine

Iodine, in the form of iodide, plays a central role in thyroid physiology, being both a major constituent of thyroid hormones and a regulator of thyroid gland function which regulate metabolic rate and substrate metabolism [1].

A nearly complete absorption occurs in the stomach and duodenum. Importantly, healthy thyroid function depends also on an adequate provision of selenium and iron at any ag. Iron deficiency impairs thyroid metabolism. Deiodination of T4 to T3 by the liver is dependent upon Type 1 5′-deiodinase, a selenoenzyme [12].

Deficiency is a global public health problem, also persistent in Europe [13]. Diagnosis is based on the 24hr urinary excretion which reflects intake. Patients on long term PN or EN are at risk of deficiency.

1.7. Molybdenum

Molybdenum is a co-factor for several oxidiser enzymes, especially sulphite oxidase and xanthine oxidase. These are of special importance in disposal of sulphite which otherwise causes neurological damage, and in catabolism of purines.

Molybdenum absorption is a highly efficient passive process [1]. Deficiency of molybdenum is generally a genetic disorder. Deficiency may occur in long-term PN without provision of molybdenum. Nutritional deficiency has only been reported in one patient

who developed tachycardia, headache, and night blindness, which were corrected by molybdenum supplements.

Plasma concentration is very low and difficult to measure. The best markers are metabolic, molybdenum deficiency being linked to low serum urate, low urine sulphate and elevated urine xanthine and hypoxanthine. Since the primary route of excretion is the urine, renal failure will be associated with molybdenum retention and the risk of toxicity: there are no reports of toxicity with nutritional doses.

1.8. Manganese

Manganese is one of the most common metals in the human body. The metalloenzymes are involved in amino acid, cholesterol, and carbohydrate metabolism. The biological effects of manganese are due to the incorporation of the metal into metalloproteins including oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases [1] Glycosyl and xylosyl transferases are important in proteoglycan synthesis, required for bone formation.

Dietary manganese is poorly absorbed (less than 5%). It is transported in the blood bound to transferrin and albumin. Excretion is via the bile to the faeces, with little excretion in urine.

Manganese deficiency is exceptional, and only under experimental conditions have signs of a scaly rash and low plasma cholesterol been observed.

The best estimates of manganese status are from whole blood manganese since this is less affected by haemolysis or contamination during collection. Cholestatic liver damage leads to manganese accumulation, and this may reach toxic levels with subsequent accumulation in central nervous tissue and extrapyramidal syndrome. Many preparations of trace elements for PN have contained excessive amounts of manganese, leading to toxicity: the brain is the main target leading to potentially irreversible damage [14]. Therefore, monitoring is important, especially in long-term provision.

2. Clinical considerations

2.1. Definition of depletion and deficiency

The provision of an adequate amount of trace elements is an integral part of all nutrition support regimens by both parenteral and enteral routes. Depletion occurs when intake does not meet losses, resulting in low plasma concentrations, but no physical or metabolic signs of inadequacy are observable at this stage. Deficiency may occur after depletion, when intakes do not meet losses, plasma concentrations are low, AND physical and/or metabolic signs of inadequacy are present [1].

Classical nutritional deficiency usually results in a complex syndrome of typical signs and symptoms, and these have now been fully characterized for each of the vitamins and trace elements. These syndromes were the basis on which the essential micronutrients were initially identified, and there is now a reasonable understanding of the nutritional consequences of severe deficiency, and the intake necessary to prevent clinically obvious deficiency from developing.

As an individual develops progressively more severe depletion of one or more micronutrients, he/she will pass through a series of stages with biochemical or physiological consequences. The metabolic or physiological penalty of such a sub-optimal nutritional status is usually not clear, but the assumption remains that this impaired metabolism is likely to result in detrimental effects. Similarly, specific and localized tissue deficiencies can occur which can lead to pathological changes. Such situations can be defined as sub-clinical deficiency. The time course for development of a sub-clinical deficiency state varies for each individual micronutrient and depends upon the nature and amount of tissue or body stores.

The consequences of an inadequate intake are delineated in Fig. 1: with worsening and persistence of deficit biochemical functions will first be altered, before the clinical signs become visible.

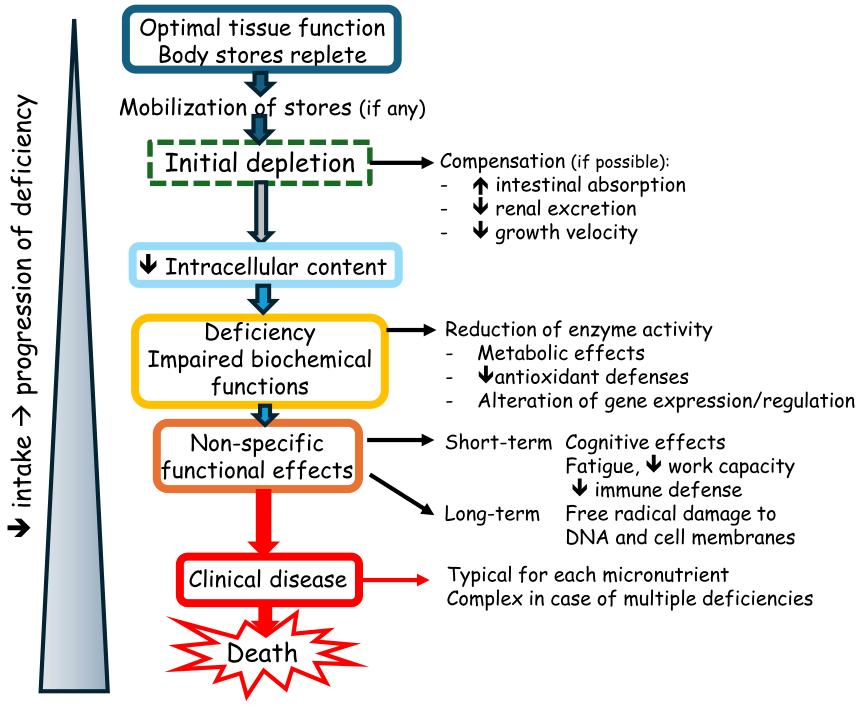

Fig. 1. With the progression of intake insufficiency, the consequence of intakes below DRI will first result in impaired biochemical functions that translate into clinically visible changes, and eventually death either persistence and aggravation of the deficit.

A sub-clinical deficiency state can be either absolute or relative. Thus, an intake less than the requirement in normal health will lead to sub-clinical deficiency, or to a typical clinical deficiency state. However, certain patients have significantly increased requirements as a result of their disease process, and hence an intake normally regarded as adequate may be relatively insufficient and lead to a sub-clinical deficiency state. Most of the recommendations for vitamin and trace element supplements in PN, and the content in enteral feeds, include an allowance for an increased requirement in disease.

2.2. Populations and individuals at risk of deficiency

By the time a patient commences nutritional support, he/she may already have developed a whole-body depletion of one or more essential nutrients. The extent of the status alteration will depend on several factors:

- The nutritional state of the patient on admission to hospital. The pre-existing illness may have caused a period of anorexia, or inadequate digestion or absorption of nutrients.
- The duration and severity of inadequate nutritional intake whilst in hospital, as a result of surgery or other treatment.
- Any increased losses through small bowel fistula/aspirate (rich in zinc), biliary fluid (rich in copper) burn exudate fluid (rich in zinc/copper/selenium), or dialysate (rich in water soluble nutrients).
- Compromised micronutrient absorption resulting from intestinal failure, intestinal resection of bypass procedures (obesity).
- Moreover, some individuals will have an increased daily requirement, partly to keep up with increased losses, and partly to meet metabolic requirements – these are particularly important when patients become anabolic after a period of catabolism or when normal growth resumes in a child.

Identification of potential micronutrient deficiencies should be part of the nutritional assessment of every patient, since conditions such as alcoholism, coeliac disease, inflammatory bowel disease, etc., predispose to such deficiencies.

2.3. Impact of inflammation

The presence of inflammation in the context of surgery, trauma, infection or many acute or chronic diseases, complicates the assessment of the status based on blood levels. Using the surrogate C-reactive protein (CRP) as a marker of its intensity, it has been clearly shown that inflammation induces a redistribution of most MNs from the circulating compartment to other organs, resulting in low MN levels [15]. Low blood levels therefore do not necessarily indicate deficiency or even depletion (Fig. 2). Within 24 h of elective surgery in otherwise healthy individuals, plasma concentrations of many trace elements and vitamins have fallen markedly, without any change in whole body MN status [16]. The effects of inflammation on blood levels in response to acute trauma or infection is usually rapid (it manifests within hours) but may also be prolonged in chronic illness.

Therefore, the ESPEN guidelines have specified as recommendation N°3, that CRP should be determined at the same time as any micronutrient analysis [1].

2.4. Optimisation of provision of trace elements

Defining the optimal intake of micronutrients is far from ideal. It is possible to make a reasonable assessment of the requirements of an individual, based upon the requirements in health, the likely underlying nutritional state of the patient at the time of presentation, and the ongoing effects of the disease process. Such a level of provision using the enteral feeds and intravenous multi-micronutrient products, which are currently commercially available, has been proved to be adequate in most cases to prevent the development of a deficiency state.

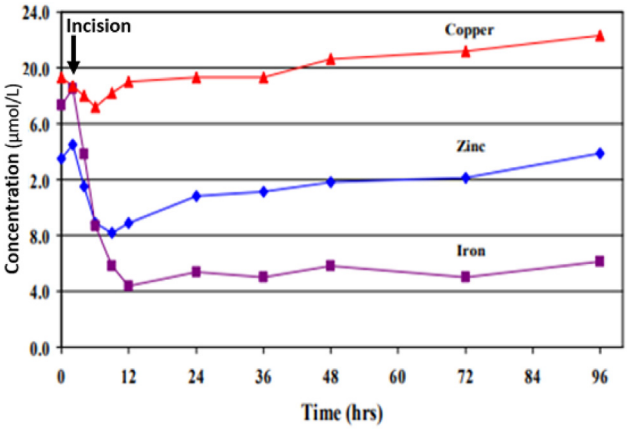

Fig. 2. Evolution of blood levels of Cu, Zn and Fe after a surgical incision (cholecystectomy): copper increases, while zinc and Fe decrease without any blood loss, reflecting redistribution our or circulating compartment. The levels normalise without intervention after a few days.

However, provision of MNs to ensure the best possible tissue function remains poorly defined. Possible methods of trying to optimise provision in relation to function can be considered with respect to the antioxidant system, and to the immune system.

It is to be expected that controlled clinical trials will help to clarify the situations where increased provision of these micronutrients is or is not helpful, both in reducing the biochemical effects of reactive oxidant species (ROS), and in altering complication rates and outcome in serious illness. Many of the disease states thought to be associated with ROS are chronic degenerative conditions, such as atherosclerosis and neoplastic disease. The increasing number of patients dependent on lifelong PN makes the long-term provision of adequate amounts of micronutrients an important part of nutritional therapy.

The trace elements are rarely available as single elements being usually provided in one permanent composition of multi-trace elements. The number of trace elements provided depends on the continent, being largest in Europe, and limited on the North American continent to 4 (Cr, Cu, Mn, Zn) or 6 (Cr, Cu, I, Mn, Se, Zn). The latter invariable results in iron deficiency during long-term PN [17].

2.5. European Union legislation and enteral nutrition

The European Union has issued a directive on Dietary Foods for Special Medical Purposes (FSMPS) [18]. This includes guidelines on vitamin and trace element content. In many cases, the minimum intake suggested for an individual with an energy intake of 2000 kcals is in excess of the reference intake in a normal population (but 2000 kcal are rarely achieved enterally). This allows for the increased requirement of most individuals receiving enteral nutrition. In the MN guidelines, these values were used to calculate minimum and maximum amount possible with 1500 kcal which is the most frequently delivered amount of feeding (Table 2) [1,18].

The directive defines FSMPs as

I. ***nutritionally complete standard formula*** – which can be used as a sole source of nutrition – these must comply with the guidelines for micronutrient composition, as shown in Table 3.

II. ***nutritionally complete, nutrient adapted disease specific formula*** – which also must be suitable as a sole source of nutrition.
III. ***nutritionally incomplete formulas*** – which are not suitable as a sole source of nutrition.

Selection of the most appropriate tube feed often requires assistance from an experienced dietician. Clinicians should be aware that although the micronutrient composition must lie within the ranges quoted. Different commercial products can have quite different amounts of micronutrients. The range of amounts present in different feeds, which are currently available in Europe, is therefore also shown as a guide in Table 2.

Practical examples from international surveys indicate this 1500 ml amount of energy as being a commonly prescribed target, while the feed delivery is generally below. The commercial feeding products contain a fixed amount of MNs: the amount of each MN supplied hence depends on the volume of feeds that is provided [19]. Using as example a standard enteral product (1 kcal/ml) Table 3 shows the amounts of MN provided for a given volume: when small amounts are delivered the DRI may not be covered, in this example for iron and iodine.

2.6. Trace elements in parenteral and enteral nutrition

Studies in patients who were depending totally upon their intravenous intake during total parenteral nutrition, especially for prolonged periods, have enabled through the demonstration of deficiencies an identification of the trace elements essential for human nutrition.

The key features of an essential trace element are that its removal or inadequate supply in the diet is associated with reproducible structural or biochemical changes, and that these are reversible on provision of the element. This has been convincingly demonstrated in PN for copper, selenium, iron, zinc, molybdenum, and chromium. In addition, there is strong evidence of biochemical essentiality of iodine and of manganese, and the nutritional benefits of fluoride on bones and teeth. Cobalt is also recognized as being essential, although all requirements seem to be met by supply of vitamin B_{12} alone.

A summary of suggested intravenous and enteral intakes of trace elements in nutritional support is provided in Table 2. It is important to note the significant difference between intakes by the intravenous and enteral routes, which are largely explained by the limited absorption efficiency from the gut.

Care must be taken to minimize interactions between nutrients, or between individual micronutrients and the infusion bags or giving sets. Instability caused by trace elements is unusual, although there are limitations to the amount of inorganic iron which is stable in infusion mixtures. Chemical interaction with trace elements, especially the oxidative effect of copper on vitamin C is minimized by addition immediately before infusion. In some hospitals, micronutrients are infused separately to prevent both the lipid emulsion stability issues and the inactivation of vitamins such as ascorbic acid.

2.6.1. Bioavailability of trace elements in enteral nutrition

The bioavailability of micronutrients is the efficiency with which each micronutrient is used in the body. It depends on absorption from the gut and utilization by the tissues. Intestinal factors are of primary importance and depend on:

– Dietary composition e.g. the chemical form of a nutrient (iron in heme, selenium in selenomethionine); the presence of antagonistic ligands (e.g. phytate, fibre); and competitive interactions (e.g. iron, zinc and copper can compete for absorption).

Table 1
Trace elements - Functions, biochemical model of action, effects of deficiency and methods of assessment.

	Function(s)	Biochemical modes of action	Effects of deficiency	Assessment of status	Comments
Zinc	Protein synthesis Control of differentiation	Enzyme cofactor "Zinc fingers" in DNA.	Growth ↓ Hair loss, skin rash Impaired night vision Immune function.↓	Plasma zinc - with albumin and CRP	Plasma Zn falls in APR.
Iron	O_2 transport Electron transport	Haemoglobin/myoglobin Cytochromes.	Hypochromic anaemia Altered resistance to infection	Serum iron/IBC Serum ferritin Hepcidin, sTfR Blood Hb	Serum Fe falls and ferritin ↑ in APR - care needed not to exceed IBC
Copper	Collagen/elastin synthesis Antioxidant	Lysyl oxidase Zn/Cu superoxide dismutase Caeruloplasmin	Subperiosteal bleeding Cardiac arrhythmia Anaemia Neutropenia	Plasma copper or caeruloplasmin with CRP	Plasma Cu increases in APR
Selenium	Antioxidant. Thyroid function Immune function	Glutathione peroxidase Tyrosine deiodinase T lymphocyte receptor expression	Cardiomyopathy Skeletal myopathy Nail abnormalities Macrocytosis Neoplastic risk ↑	Plasma Se RBC GPX Urine Se Whole blood/RBC Se Platelet GPX	Se depletion may be asymptomatic
Manganese	Not clear Some antioxidant	Enzyme cofactor Mitochondrial superoxide Dismutase (MnSOD)	Cholesterol↓ Red blood cells↓ Possibly mucopolysaccharide abnormalities	Whole blood Mn	Deficiency state not confirmed in man.
Chromium	Carbohydrate metabolism	Insulin activity Lipoprotein metabolism Gene expression	Glucose intolerance Weight loss Peripheral neuropathy	Plasma Cr	Contamination free blood sampling required Cr often a contaminant
Molybdenum	Amino acid & Purine metabolism	Sulphite oxidase Xanthine oxidase	Intolerance to S amino acids: - tachycardia - visual upset	Urinary hypoxanthine sulphite	Rarely measured
Iodine	Energy metabolism	Thyroid hormones	Hypothyroidism	Serum T_4 T_3, TSH.	
Fluoride	Bone/tooth mineralization	Calcium fluorapatite	Dental caries	Urine excretion	Provision in nutritional therapy is controversial

Table 2
Trace Elements in parenteral (PN) and enteral nutrition (EN) with available IV commercial products (adapted from ESPEN 2022 guidelines).

Trace element	PN Home & long-term A.	PN high requirements[a]	I.V. products available in Europe			EN in 1500 kcal[c] B.	EN high requirements in 1500 kcal[b]	DRI per day Age 31->70 yrs	EC directive[d]: Min & max per 1500 kcal [18]
			Addaven® Fresenius Kabi	Tracutil® BBraun	Nutryelt® Baxter				
Chromium	10–15 μg	15 μg	10 μg	10 μg	10 μg	35–150 μg	200 μg	20–35 μg	18.75–225 μg
Copper	0.3–0.5 mg	0.5–1.0 mg	0.38 mg	0.76 mg	0.3 mg	1–3 mg	Same as B	0.9 mg	0.9–7.5 mg
Fluoride	0–1.0 mg	Same as A	1 mg	–	0.95 mg	0–3 mg	3–4 mg	3–5 mg (AI)	0–3 mg
Iodine	130 μg	Same as A	130 μg	130 μg	130 μg	150–300 μg	Same as B	150 μg	97.5–525 μg
Iron	1.1 mg	Same as A	1.1 mg	1.95 mg	1.0 mg	18–30 mg	30 mg	8 mg (18 mg F 19–50yrs)	7.5–30 mg
Manganese	55 μg	Same as A	55 μg	55 μg	55 μg	2–3 mg	Same as C	1.8–2.3 mg	0.75–7.5 mg
Molybdenum	19–25 μg	Same as A	19 μg	10 μg	20 μg	50–250 μg	250 μg	45 μg	52.5–270 μg
Selenium	60–100 μg	150–200 μg	79 μg	20 μg	70 μg	50–150 μg	200 μg	55 μg	37.5–150 μg
Zinc	3–5 mg	6–12 mg	5 mg	337 mg	10 mg	10–20 mg	20 mg	8–11 mg	7.5–22.5 mg

[a] **PN** Increased requirements may occur in patients with on-going increased losses such as gastrointestinal losses, continuous renal replacement therapy, those who are hypermetabolic or who are depleted before commencing PN, and in pregnancy.
[b] EN high increased requirements during critical illness and in patients with acute admission with malnutrition (NRS ≥5): intended for max 14 days as repletion to avoid requiring intravenous supply.
[c] The 1500 kcal value has been chosen based on numerous studies confirming that this value seems to be a very common objective. In case of higher nutrient delivery (e.g. 2000 kcal per day or more), exceeding this recommendation is not exposing the patient to any risk considering upper tolerable level. The dose is not required in addition to EN but contained in most feeding solutions.
[d] The EC directive regulates the contents of FSMP (Food for Special Medical Purpose). Amounts are indicated per 100 kcal in the EC document. This column indicates the minimal and maximal trace element contents of such FSMP for 1500 kcal/day.

Table 3
Amounts of trace elements and some vitamins (see 44.2 for more) received by the patients depending on the quantity of energy prescribed using a commercial product "XYZ®", provided as 500 ml bags with 1 kcal/ml: the MN content in 500 ml (500 kcal) of the product is shown in the 2nd column "XYZ"). Compared with DRI, the table shows that the needs for iodine and iron are not covered which may be a problem on long term EN.

Micronutrient	„XYZ" content 500 ml 1 kcal/ml	Prescribed amount of energy:			DRI Age 31->70	EC directive [18]
		900 kcal	1500 kcal	1800 kcal		
Vit B1 mg	0,65	1,17	1,95	2,34	1.1–1.2	0.9–7.5
Vit A μg RE	70	630	1050	1260	700–900	525–2700
Vit C mg	33,5	60,3	100,5	120,6	75–90	34–330
Vit D μg	5	9,0	15,0	18,0	15–20	7,5–37,5
Vit E mg	6,5	11,7	19,5	23,4	15	7,5 - 45
Vit K μg	33,5	60	101	121	90–120	52.5–300
Copper mg	0,665	1,2	2,0	2,4	0,9	0.9–7.5
Chromium μg	33,5	60	101	121	20–35	18.75–225
Iodine μg	6,65	12	20	24	150	97.5–525
Iron mg	6,5	11,7	19,5	23,4	30	7.5–30
Manganese μg	1,35	2,4	4,1	4,9	1.8–2.3	0.75–7.5
Molybdenum μg	50	90	150	180	45	52.5–270
Selenium μg	33,5	60,3	100,5	120,6	55	37.5–150
Zinc mg	6	10,8	18,0	21,6	8–11	7.5–22.5

- Luminal/mucosal factors
- Redox state, dietary hydrolysis, and binding to amino acids or carrier proteins may all modify absorption.

2.6.2. Overprovision of trace elements

Excess trace elements may be provided inadvertently as contaminants of other nutrients in PN particularly Al in Ca/P supplements or albumin infusions. The manganese content of available products has been reduced and is of special importance during long term PN.

2.7. Provision and monitoring of trace element status

An accurate assessment of trace element status during nutritional support is difficult, especially in critically ill patients with evidence of APR. Some key points should be considered:

- Tests of plasma concentration are a poor reflection of tissue status.
- Plasma concentration of Zn, Fe, and Se fall during the APR, whereas Cu increases (see Fig. 2.).
- Plasma concentration may be of value in stable patients without an active APR.
- For some elements, measurement of enzyme activity (functional tests) may be helpful e.g. red blood cell or plasma glutathione peroxidase as a marker of selenium status.
- Plasma concentration may be helpful in identifying over-provision.

Indeed, in patients with lower body weight, monitoring is essential as the doses proposed for the emblematic 70 kg person may result in over-provision: at the other side of the weight scale, insufficient intakes may result.

Some tests commonly used to assess trace elements are included in Table 1. The acute phase reaction associated with trauma and infection markedly affects plasma concentration of many trace elements (Fig. 2) [15].

Because of the limitations in interpretation of these data, it is common practice, especially in patients receiving PN, only to assess on a regular basis the status of zinc, copper, selenium (mainly in long-term nutritional problems) and iron. A monitoring schema has been proposed including a baseline determination upon initiation of home-PN/EN with a 6 monthly interval [20]. The other

laboratory tests which are available to assess micronutrient are usually only used when there is a particular clinical problem where confirmation of micronutrient deficiency or excess is necessary. If such tests are not available, and a deficiency is suspected, a therapeutic trial of increased intake can usually be safely given if renal function and liver function are satisfactory. In patients receiving EN or PN where some intestinal absorptive capacity may still be present, an oral or enteral multi-mineral supplement may also be provided.

A two-week course of a well-balanced micronutrient supplement is unlikely to cause any harm and may occasionally be beneficial. In the critically ill patients such an administration during the first 5–7 days of progressive enteral feeding has been advocated to cover the basal needs and eventually to support immune and antioxidant function [21]. Alternatively, an increase in intravenous supply can be given for a limited period, with careful clinical monitoring. In such cases a blood/plasma sample at the beginning of supplementation should be stored for possible analysis at a later date.

Funding

There was no funding support.

Authors contribution

Under the coordination of AS and MMB, all authors contributed to the preparation of this LLL course manuscript and approved the final version.

Declaration of competing interest

None of the above authors declares any conflict.

References

[1] Berger MM, Shenkin A, Schweinlin A, Amrein K, Augsburger M, Biesalski HK, et al. ESPEN micronutrient guideline. Clin Nutr 2022;41:1357–424.
[2] Berger MM, Shenkin A, Dizdar OS, Amrein K, Augsburger M, Biesalski HK, et al. ESPEN practical short micronutrient guideline. Clin Nutr 2024;43:825–57.
[3] Ben-Hamouda N, Charrière M, Voirol P, Berger MM. Massive copper and selenium losses cause life-threatening deficiencies during prolonged continuous renal replacement. Nutrition 2017;34:71–5.
[4] Layec S, Garin L, Trivin F, Ménard D, Picot D. Neurological and hematological complications of copper deficiency during exclusive jejunal tube feeding. e-SPEN 2011;6:e187–9.
[5] Nairz M, Weiss G. Iron in infection and immunity. Mol Aspect Med 2020;75:100864.
[6] Lasocki S, Asfar P, Jaber S, Ferrandiere M, Kerforne T, Asehnoune K, et al. Impact of treating iron deficiency, diagnosed according to hepcidin quantification, on outcomes after a prolonged ICU stay compared to standard care: a multicenter, randomized, single-blinded trial. Crit Care 2021;25:62.
[7] Shenkin A. Selenium in intravenous nutrition. Gastroenterology 2009;137:S61–9.
[8] Bermano G, Meplan C, Mercer DK, Hesketh JE. Selenium and viral infection: are there lessons for COVID-19? Br J Nutr 2021;125:618–27.
[9] Xia Y, Hill KE, Li P, Xu J, Zhou D, Motley AK, et al. Optimization of selenoprotein P and other plasma selenium biomarkers for the assessment of the selenium nutritional requirement: a placebo-controlled, double-blind study of selenomethionine supplementation in selenium-deficient Chinese subjects. Am J Clin Nutr 2010;92:525–31.
[10] Hedegaard CV, Soerensen MD, Jorgensen LH, Schaffalitzky de Muckadell OB. Investigating hypozincemia and validity of plasma zinc measurements in infected patients. Scand J Clin Lab Invest 2022;82:371–7.
[11] Moukarzel A. Chromium in parenteral nutrition: too little or too much? Gastroenterology 2009;137:S18–28.
[12] Köhrle J. Selenium and the thyroid. Curr Opin Endocrinol Diabetes Obes 2013;20:441–8.
[13] Network Iodine Global, (IGN). Global scorecard of iodine nutrition in 2021 in the general population based on school-age children. 2021. https://ignorg/app/uploads/2023/04/IGN_Global_Scorecard_2021_7_May_2021pdf.
[14] Santos D, Batoreu C, Mateus L, Marreilha Dos Santos AP, Aschner M. Manganese in human parenteral nutrition: considerations for toxicity and biomonitoring. Neurotoxicology 2014;43:36–45.
[15] Duncan A, Talwar D, McMillan DC, Stefanowicz F, O'Reilly DS. Quantitative data on the magnitude of the systemic inflammatory response and its effect on micronutrient status based on plasma measurements. Am J Clin Nutr 2012;95:64–71.
[16] Salota R, Omar S, Sherwood RA, Raja K, Vincent RP. Clinical relevance of trace element measurement in patients on initiation of parenteral nutrition. Ann Clin Biochem 2016;53:680–5.
[17] Hwa YL, Rashtak S, Kelly DG, Murray JA. Iron deficiency in long-term parenteral nutrition therapy. JPEN - J Parenter Enter Nutr 2016;40:869–76.
[18] Parliament European, Council. Commission delegated regulation (EU) 2016/128 supplementing Regulation (EU) No 609/2013 for food for special medical purposes. Official Journal of the EU 201625/30-42.
[19] Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med 2009;35:1728–37.
[20] Berger MM, Talwar D, Shenkin A. Pitfalls in the Interpretation of blood tests used to assess and monitor micronutrient nutritional status. Nutr Clin Pract 2023;38:36–69.
[21] Preiser JC, Arabi Y, Berger MM, Casaer MC, McClave S, Montejo-Gonzalez JC, et al. A guide to enteral nutrition in intensive care units: 10 expert tips for the daily practice. Crit Care 2021;25:424.