# REVIEW

## THE IMPORTANCE OF MICROELEMENTS IN HUMAN BODY

**Victoria-Madalina MIHAESCU[1], Raluca-Ioana DASCALU[1], Andra Ioana NUTA[2], Luminita-Bianca GROSU[2]**

[1] *Department of Gastroenterology, Clinical Emergency Hospital of Bucharest, Romania*
[2] *Department of Cardiology, Elias University Emergency Hospital, Bucharest, Romania*

**Correspondence to:** Victoria-Mădălina Mihăescu, Department of Gastroenterology, Clinical Emergency Hospital of Bucharest, Romania, e-mail: madalina.mihaescu10@yahoo.com

**Abstract:** *Microelements play a central role in metabolism and the maintenance of tissue function. In good health and with an adequate diet individuals will have optimal tissue levels. Trace elements are those minerals essential for normal function of the body found in quantities less than 5g. The following minerals are considered to be essential: chromium, cobalt, copper, fluoride, iodine, iron, selenium and zinc. An adequate intake of microelements is necessary to sustain metabolism and tissue function, but the excess supplements to individuals who do not need them may be harmful. Severe deficiency of trace elements may lead to a characteristic disease state which can be corrected only by supply of the deficiency micronutrient.*

**Keywords:** microelements, vitamins, chromium, cobalt, copper, fluoride.

DOI https://doi.org/10.56082/annalsarscimed.2022.2.28

**ABREVIATIONS**

CRP - C-reactive protein; DRI - dietary reference intake; EAR - estimated average requirement; ESPEN- European Society for Clinical Nutrition and Metabolism; GPX-3 - Glutathione peroxidase 3; MNs - micronutrients; RDA-Recommended Daily Allowances; TSH - thyroid stimulating hormone.

### Introduction

Trace elements are essential for human body metabolism and components of nutrition in health and disease. Recent research has shown the importance of this micronutrients (MNs) in common pathologies with significant deficiencies impacting the outcome. Trace elements are less known than vitamins, so iodine, iron and vitamin A deficiencies are the world's most frequently deficiency [1].

Recent international and ESPEN recommendations that include MN information are therefore available for parenteral nutrition, chronic intestinal failure, inflammatory bowel diseases, liver diseases, surgery, cancer and intensive care unit population. Most patients with nutritional support present depleted MNs status and it is very important to provide adequate amounts of all micronutrients from the start of the nutrition. In many clinical situations MNs can be provided orally or enteral to correct the depletion or the deficiency and it may be in pill, tablet and liquid form. For the rapid correction of the deficiency and where absorption is poor, the parenteral route, intravenous or intramuscular, can be used [2], [3], [4].

The diagnosis is rarely addressed and needs searching laboratory sources. The rational interpretation of an abnormal laboratory result requires the integration of

the blood value below the reference range with clinical symptomatology and concomitant inflammatory response [5]. Referring to micronutrients, it is very important to make the difference between the words adequate, depletion, deficiency, overdose and toxicity.

In 1940, the National Academy of Sciences received the mandate to study nutrition problems in the United States. This resulted in the first Recommended Daily Allowances (RDA). The goal was to recommend "allowances sufficiently liberal to be suitable for maintenance of good nutritional status" in the general population. In the subsequent decades, a different nutritional health challenge began to emerge for an increasing proportion of the population, that of overweight and obesity and risk of diet-related chronic disease [8]. Chronic diseases are multifactorial in nature and not directly nutrient specific (Table 1).

**Table 1.** Chronic diseases and microelements depletion and deficiency

| Chronic disease | Depletion or deficiency in trace elements and vitamins |
|---|---|
| Chronic intestinal failure | copper, iron, zinc |
| Liver disease | selenium, zinc |
| Obesity post bariatric surgery | copper, iron, zinc |
| Renal failure | copper, selenium |

There are medical treatments associated with micronutrients depletion or deficiency (Table 2).

**Table 2.** Medical treatments and micronutrients depletion or deficiency

| **Medical treatment** | **Microelements depletion or deficiency** |
|---|---|
| Renal replacement therapy | copper and iron |
| Diuretic therapy | selenium |
| Proton pump inhibitors | iron |

## 1. CHROMIUM

Chromium (Cr) is an element which exists in different valence states. Chromium IV, V, VI are carcinogenic, while Chromium III is stable and is the biological active form. Chromium III is an essential element and is a component of metalloenzymes. It intervenes in the metabolism of carbohydrates, protein, fat and in the oxidative state.

The main sources are foods (mainly high-bran cereals) and dietary supplements. The absorption of chromium is taking place in the small bowel and most of the absorbed chromium is excreted in the urine. This important element is stored in organs like liver, spleen, bone and soft tissue [7], [9].

The oral chromium adequate intake is 35 μg/day for young men and 25 μg/day for women. Enteral nutrition should provide at least 35 μg/day while parenteral nutrition should provide at least 10 μg/day of chromium. Serum chromium concentrations range from 1 to 5 μg/L [7].

Insufficient intakes of chromium are frequent in industrial countries and are associated with alterations of glucose metabolism because chromium enhances insulin action in peripheral tissues. Low levels of chromium may be present at patients with acute illness due to metabolic stress (burns, trauma) or patients with decreased absorption/intake and also at patients with chronic diseases. Low plasma chromium level is associated with hyperglycemia, insulin resistance, high inflammatory status and increased cardiovascular risk in humans. Some studies have showed that chromium insufficiency is a contributing factor to the development of type 2 diabetes and a negative relationship between serum chromium and HbA1c [10], [11].

Chromium deficiency may be treated by oral or intravenous supplementation. Oral chromium is poorly absorbed. Intravenous chromium, 200-250 μg/day for 2 weeks or longer has been used at parenteral nutrition patients with chromium deficiency. Intravenous chromium may be used at ICU patients with major insulin resistance (doses ranging from 3-20 μg/h and up to 4 days) [11].

The toxicity of chromium is variable and it depends on chromium valences. Chromium VI is carcinogenic, nephrotoxic and causes dermatitis. Chromium VI and Chromium III are capable of producing reactive oxygen species. Oral intoxication is rare because of poor absorption. Instead, parenteral chromium has a higher potential toxicity. High levels of chromium in serum and urine have been found in adults and children treated with parenteral nutrition. In autopsy tissues of this class of patients, chromium levels were 10-100-fold higher than normal concentration in heart, skeletal muscle, liver and kidney. Chromium accumulates in the bones of patients with end stage renal disease. For the treatment of chromium toxicity, it can be used plasmapheresis, chelators and antioxidants [11] [12].

## 2. COBALT

Cobalt (Co) is an essential element for the formation of vitamin B12 (hydroxicobalamin).

The main source of cobalt is diet or industrial exposure. The average nutritional intake is 5 to 45 μg/day.

General population may be exposed to cobalt through occupational contact (glass, inks), hard-metal industry and the manufacture of ceramics. Cobalt is toxic for the heart muscle and it may produce the syndrome of "beer drinker cardiomyopathy" observed in Quebec. It is characterized by pericardial effusion, high hemoglobin concentration and congestive heart failure which can be fatal [13].

Determination of the cobalt may be required in case of suspicion of toxicity in the context of cardiomyopathy and serum and urine levels of cobalt may be used for the assessment of the status.

## 3. COPPER

This micronutrient has two different redox states: the oxidized cupric ($Cu^{2+}$) and reduced cuprous ($Cu^{+}$). Copper absorption occurs in the stomach and small intestine, primarily in the duodenum and most of the copper is lost via biliary excretion [14].

Main sources of copper: cereals, fresh fruits and vegetables, fish and seafood. The DRI for copper is 1.1-2 mg/day in adults, but the absorption is ranging between 20 and 50%. Copper may be delivered by the oral, enteral or intravenous routes. Enteral nutrition should provide 1-3 mg/day, while parenteral nutrition should provide 0.3-0.5 mg/day [15].

Blood samples may be used for the diagnosis of deficiency or toxicity of copper. Urine measurements are of limited value for status assessment considering the small proportion of copper that is excreted by the kidney, but this method may be used for diagnosis and monitoring Wilson's disease.

98% of circulating Copper is bound to ceruloplasmin, an alpha-2-globuline which is synthesized by the liver and 2% of copper exists in plasma as "free" form. Ceruloplasmin is a positive acute phase reactant which means that copper levels increase in the context of inflammation. Copper status shall be determined by measurement of plasma copper simultaneously with CRP determination. A normal serum copper in the presence of an elevated CRP suggests copper depletion or deficiency. In case of uncertainty, ceruplasmin concentration will assist diagnosis, low levels of ceruloplasmin confirm the deficiency.

Copper depletion or deficiency may appear in acute condition such as major burs, gastric and bariatric surgery and the symptoms include cardiac arrhythmias, myeloneuropathy and delayed wound healing. The chronic symptoms include microcytic anemia, neutropenia and hair depigmentation (copper is essential for melanin synthesis). High levels of copper may be found in inflammatory conditions, Alzheimer's disease, infections, hemochromatosis, liver cirrhosis and physiologically in pregnancy [16], [17].

The symptoms in copper intoxication include hematemesis, hypotension, melena, coma, headaches, fever, abdominal cramps, brown ring-shaped markings in eyes (Kayser-

Fleicher rings). Wilson's disease and Menke's syndrome are two genetic disorders characterized by high levels of copper [18]. In acute toxicity, oral D-penicillamine represents the treatment.

## 4. FLUORIDE

Fluoride is the world's 13th most abundant element because it is widely distributed in the environment occurring in soils, rock sand water [19]. The absorption occurs in the small intestine and it gets attached to bones and teeth transforming apatite into fluroapatite. Half of the absorbed fluoride is excreted by the kidney.

Main sources: foods, fluoridated water and fluoridated toothpaste [20]. Tea is an important source of fluoride as shown in a well-documented intoxication report [21]. It is an important element for dental health of humans. Nutritional intakes of fluoride are safe up to 4 mg/day in men and 3 mg/day in women. Enteral nutrition should provide 3 mg/day and for parenteral nutrition there is no equivalent recommendation.

Serum and 24 hours urine collection may be used for fluoride determination. The reference values are <50 ug/l in serum and <0,5 mg/24h urine.

Fluoride is principally a public health issue. Inadequate intake of fluoride can cause dental carries and excessive intake can cause dental fluorosis [22]. Dental fluorosis is diagnosed by bilateral symmetrical developmental enamel opacities (brown discoloration). Chronic toxicity may occur in industrial exposure and along with excessive water supplies and patients present symptoms like gastric complains, anemia, osteomalacia, teeth problems. Skeletal fluorosis is a toxic osteopathy characterized by massive bone fluoride fixation and it appears with doses 10-25 mg/day for years and there is no establish treatment for it, except controlling the source of the excess fluoride exposure [23], [24]. Toxicity treatment includes administering a solution containing calcium, monitoring and managing plasma calcium and potassium concentration, acid-base status and supporting vital functions [21].

## 5. IODINE

Iodine plays a central role in thyroid physiology. It is a major constituent of thyroid hormones and a regulator of thyroid gland function. Iodine is well absorbed and may even results in acute toxicity symptoms. Nutritional intakes are dependent on the content of iodine in the soil and the fortification strategies in different foods. According to Iodine Global Network, there are 23 countries in the world classified with insufficient intake, while it is classified as excessive in 14 countries [25], [26], [27].

The main sources of iodine are fish, seaweed, shrimps, dairy products and iodized salt. The DRI for iodine is 150 μg/day in adults, 220 μg/day in pregnant women and 290 μg/day in breast-feeding women [28]. Enteral nutrition should provide 150 μg/day with an upper level of μg/day and parenteral nutrition should provide the standard dose of 130 μg/day. Iodine may be administrated oral, enteral, intravenous or intramuscular. Serum TSH is not a sensitive indicator of iodine status. The best way to determinate iodine status is 24 hours urine collections. The reference values of serum iodine are 40-100 μg/L and for urine iodine 100-300 ug/24 hours.

Iodine deficiency is a worldwide public health problem and it causes goiter and hypothyroidism, increases the risk of developing autonomous thyroid nodules that are unresponsive to TSH control [29], [30]. During pregnancy and breastfeeding, iodine deficiency affects the development of the child that includes mental retardation, cretinism and varying degrees of growth and development abnormalities, so pregnant and lactating women living in iodine deficient countries should take daily 150 μg of iodine [31]. Universal salt iodization is the preferred strategy of iodine deficiency disorder prevention and is recommended by WHO and the Iodine Global Network as the most cost-effective method [32], [33].

Excess consumption of iodine is uncommon, but it may be found in the context of iodinated agents used for radiologic studies, topical iodine disinfectants or chronic

intake of amiodarone. Chronic excess of iodine intake can produce autoimmune thyroiditis. Clinical symptoms of toxicity are abdominal pain, loss of appetite, metallic taste, delirium, diarrhea, gum and tooth soreness. There is no antidote for iodine poisoning. It can be used only symptomatic treatment [34].

## 6. IRON

Iron is the most abundant trace element in the human body and it is required in small amounts to maintain normal physiological process. The two states of iron are the divalent ferrous ($Fe^{2+}$) and the trivalent ferric ($Fe^{3+}$). Iron has several important functions such as functional component of heme, oxygen binding and transport, oxygen metabolism, cellular respiration and electron transport [35], [36]. Iron is stored in the form of ferritin and hemosiderin in the liver, spleen, bone marrow and the circulating iron is bound by transferrin. Humans lose small amounts of iron through urine, feces, gastrointestinal tract, uterus and skin. The absorption and distribution of iron are regulated by hepcidin [37].

The DRI for iron varies according to stages of life and gender. Adult men and postmenopausal female need 8 mg/day, while pre-menopausal females need 18 mg/day. Enteral nutrition should provide 18-30 mg iron/day and parenteral nutrition should provide at least 1 mg iron/day [15].

Sources: lean meat, liver, black pudding and seafood.

There are a lot of methods used to determinate iron status. The methods available in most laboratories require the simultaneous determination of hemoglobin, ferritin, transferrin saturation and total iron binding capacity. The most recent methods include the determination of hepcidin, zinc protoporphyrin and soluble transferrin receptor [38]. The reference values can be found in table 3.

**Table 3.** Reference values of the most frequent biomarkers of iron status.

| **Biomarkers** | **Reference values** |
|---|---|
| Plasma Iron | 50-175 μg/dL |
| Hemoglobin | **M**: 13.5-17.5 g/dL<br>**F**: 12.0-15.5 g/dL |
| Transferrin | 200-400 mg/dL |
| Transferrin saturation | 20-50% |
| Total iron binding capacity | 250-370 μg/dL |
| Hepcidin | 6.7-10.4 ng/mL |
| Ferritin | **M**: 24-336 mg/L<br>**F**: 11-307 mg/L |

Iron deficiency and depletion has 3 stages: 1. Storage iron depletion; 2. Marginal deficiency, mild functional deficiency, iron-deficient erythropoiesis; 3. Iron deficiency anemia. Iron deficiency anemia is less common than iron deficiency without anemia [39] [40]. Three important causes of this element deficiency are bleeding in gastrointestinal, urological and gynecological disorders. Also, it may appear in inadequate iron intake or reduced absorption.

Iron deficiency should be treated when it is associated with anemia and/or low ferritin levels. Oral and parenteral administration can be used. Doses of oral iron supplements are 100-200 mg/day, but gastrointestinal effects are frequently (constipation, diarrhea, nausea). When iron losses need to be rapidly replaced, intravenous administration is preferential. Iron sucrose and ferric gluconate are widely used but may require multiple administration. To evaluate the success of treatment, blood tests should be repeated after 8-10 weeks [41] [42].

Hereditary hemochromatosis is a rare genetic disorder characterized by iron excess which may leads to end-organ failure, involving particularly the pancreas and the liver. Symptoms of iron excess are chronic fatigue, joint pain and diabetes. The treatment includes iron removal by blood donation/phlebotomy in the absence of anemia [43].

## 7. SELENIUM

Selenium is an essential micronutrient for the synthesis of the amino acid selenocysteine. Seleno-proteins are involved in antioxidant and redox activity, control of thyroid hormone metabolism, control of cell proliferation and apoptosis and protection of vascular endothelium. The glutathione peroxidases (GPX) enzyme family is involved in antioxidant activity in the extra and intracellular milieu [44], [45].

Selenium is well absorbed from the digestive tract. The DRI is 20 μg/day to 90 μg/day Most recommendations for daily oral intake of selenium range between 50-70 μg/day. Enteral nutrition should provide 50-150 μg/day and parenteral nutrition should provide 60-100 μg/day of selenium [45]. Blood selenium is required to determinate the status, but ideally the plasma GPX-3 shall be determined to reflect functional status. Simultaneous determination of CRP and albumin is required for interpretation.

Insufficient dietary intake is the most common cause of selenium deficiency. Keshan cardiomyopathy and Kashin-Beck osteochondropathy in China are two specific chronic pathologies determined by selenium deficiency [46]. It is associated with increased incidence and virulence of viral infections, metabolism and tissue malfunction, cancer and type 2 diabetes [45]. Others symptoms of selenium deficiency are cardiac and muscle myopathy, skin and nail effects.

There are several groups of patients who may need higher requirements such as patients who are depleted because of a recent reduced intake, burns patients, patients with major trauma, cardiac surgery and patients receiving renal replacement therapy. Deficiency may also occur during prolonged enteral nutrition due to low selenium concentrations in feeding products [48], [49], [50].

Selenium overexposure is positively associated with type 2 diabetes and high-grade prostate cancer. Selenium toxicity in resulting in clinical symptoms of selenosis. A natural experiment has suggested that overexposure to inorganic hexavalent selenium is associated amyotrophic lateral sclerosis and Parkinson's disease [51].

**Author Contributions:**

*V.M.M. conceived the original draft preparation. V.M.M., R.I.D., A.I.N. and L.B.G. were responsible for conception and design of the review. V.M.M., L.B.G., A.I.N. and R.I.D. were responsible for the data acquisition. V.M.M. was responsible for the collection and assembly of the article/published data, and their inclusion and interpretation in this review. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.*

**Compliance with the Ethics Requirements:**

*"The authors declare no conflict of interest regarding this article".*

**Acknowledgemets:**

*None*

**References**

[1] Yaktine AL, Ross AC. Milestones in DRI Development: What Does the Future Hold? Advances in Nutrition 2019;10(3):537-545.

[2] Parrott J, Frank L, Rabena R, Craggs-Dino L, Isom KA, Greiman L. American Society for Metabolic and Bariatric Surgery Integrated Health Nutritional Guidelines for the Surgical Weight Loss Patient 2016 Update: Micronutrients. Surgery for Obesity and related Diseases 2017;13(5):727-741.

[3] Blaauw R, Osland E, Sriram K, AdvAPD AA, Allard JP, Ball P, et al. Parenteral Provision of Micronutrients to Adult Patients: An Expert Consensus Paper. Journal of Parenteral and Enteral Nutrtion 2019;43(S1):S5-S23

[4] Pironi L, Arends J, Baxter J, Bozzetti F, Pelaez RB Cuerda C, et al. ESPEN endorsed recommendations. Definition

and classification of intestinal failure in adults. Clinical Nutrition 2015;34(2):171-180.

[5] Duncan A, Talwar D, McMillan DC, Stefanowicz F, O'reilly DSJ. Quantitative data on the magnitude of the systemic inflammatory response and its effect on micronutrient status based on plasma measurement. The American Journal of Clinical Nutrition 2012;95(1):64-71.

[6] Moukarze A. Chromium in Parenteral Nutrition: Too Little or Too Much? Gastroenterology 2009;137(5):S18-S28.

[7] Vanek VW, Borum P, Buchman A et al. Recommendations for Changes in Commercially Available Parenteral Multivitamin and Multi–Trace Element Products. Nutrition in clinical Practice 2012;27(4):440-491.

[8] Yaktine AL, Ross AC. Milestones in DRI Development: What Does the Future Hold? Advances in Nutrition 2019;10(3):537-545.

[9] Moukarzel A. Chromium in Parenteral Nutrition: Too Little or Too Much? Gastroenterology 2009;137(5):S18-S28.

[10] Oh WC, Mafrici B, Rigby M, Harvey D Sharman A, Allen JC, Mahajan R, Gardner DS, Devonald MAJ. Micronutrient and Amino Acid Losses During Renal Replacement Therapy for Acute Kidney Injury. Kidney International Reports 2019;4(8):1094-1108.

[11] Surani SR, Ratnani I, Guntupalli B, Bopparaju S. Severe insulin resistance treatment with intravenous chromium in septic shock patient. World J Diabetes 2012;3:170e3.

[12] Tian H, Guo X, Wang X, He Z, Sun R, Ge S, et al. Chromium picolinate supplementation for overweight or obese adults. Cochrane Database Syst Rev 2013:CD010063.

[13] Packer M. Cobalt cardiomyopathy: a critical reappraisal in light of a recent resurgence. Circ Heart Fail 2016:9.

[14] Kiela PR, Ghishan FK. Physiology of intestinal absorption and secretion. Best Pract Res Clin Gastroenterol 2016;30:145e59.

[15] Food and Nutrition Board Institute of Medicine (IOM). Dietary reference intakes for vitamin A, vitamin K, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, D.C.: National Academy Press; 2001.

[16] Altarelli M, Ben-Hamouda N, Schneider A. Berger MM. Copper deficiency: causes, manifestations, and treatment. Nutr Clin Pract 2019;34:504e13.

[17] Kumar N. Copper deficiency myelopathy (human swayback). Mayo Clin Proc 2006;81:1371e84.

[18] Collins JF, Klevay LM. Copper. Adv Nutr 2011;2:520e2.

[19] Bergmann KE, Bergmann RL. Salt fluoridation and general health. Adv Dent Res 1995;9:138e43.

[20] Kanduti D, Sterbenk P, Artnik B. Fluoride: a review of use and effects on health. Mater Sociomed 2016;28:133e7.

[21] Whyte MP, Essmyer K, Gannon FH, Reinus WR. Skeletal fluorosis and instant tea. Am J Med 2005;118:78e82.

[22] Peckham S, Awofeso N. Water fluoridation: a critical review of the physiological effects of ingested fluoride as a public health intervention. Sci World J 2014;2014:293019.

[23] Sellami M, Riahi H, Maatallah K, Ferjani H, Bouaziz MC, Ladeb MF. Skeletal fluorosis: don't miss the diagnosis! Skeletal Radiol 2020;49:345e57.

[24] Martınez-Mier E. Fluoride: its metabolism, toxicity, and role in dental Health. J Evid Based Comple Alter Med 2012;17(1):28e32.

[25] Cavalieri RR. Iodine metabolism and thyroid physiology: current concepts. Thyroid 1997;7:177e81.

[26] Leung A, Pearce EN, Braverman LE. Role of iodine in thyroid physiology. Expet Rev Endocrinol Metabol 2010;5:593e602.

[27] Network IG. 2019 Annual report (preliminary). 2019.

[28] Food and Nutrition Board Institute of Medicine (IOM). Dietary reference intakes for vitamin A, vitamin K, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, D.C.: National Academy Press; 2001.

[29] Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol 2015;3:286e95.

[30] Laurberg P, Pedersen KM, Vestergaard H, Sigurdsson G. High incidence of multinodular toxic goitre in the elderly population in a low iodine intake area vs. high incidence of Graves' disease in the young in a high iodine intake area: comparative surveys of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland. J Intern Med 1991;229:415e20.

[31] Laurberg P, Cerqueira C, Ovesen L, Rasmussen LB, Perrild H, Andersen S, et al. Iodine intake as a determinant of thyroid disorders in populations. Best Pract Res Clin Endocrinol Metabol 2010;24:13e27.

[32] Consortium E. The Krakow declaration on iodine. 2018.

[33] Zimmermann MB, Andersson M. Update on iodine status worldwide. Curr Opin Endocrinol Diabetes Obes 2012;19:382e7.

[34] Southern AP, Jwayyed S. Iodine toxicity. Treasure Island (FL): StatPearls; 2022.

[35] Pantopoulos K, Porwal SK, Tartakoff A, Devireddy L. Mechanisms of mammalian iron homeostasis. Biochemistry 2012;51:5705e24.

[36] Frauenfelder H, McMahon BH, Austin RH, Chu K, Groves JT. The role of structure, energy landscape, dynamics, and allostery in the enzymatic function of myoglobin. Proc Natl Acad Sci U S A 2001;98:2370e4.

[37] Drakesmith H, Prentice AM. Hepcidin and the iron-infection axis. Science 2012;338:768e72.

[38] Gelaw Y, Woldu B, Melku M. The role of reticulocyte hemoglobin content for diagnosis of iron deficiency and iron deficiency anemia, and monitoring of iron therapy: a literature review. Clin Lab 2019:65.

[39] Levi M, Rosselli M, Simonetti M, Brignoli O, Cancian M, Masotti A, et al. Epidemiology of iron deficiency anaemia in four European countries: a population-based study in primary care. Eur J Haematol 2016;97:583e93.

[40] Zimmermann MB, Hurrell RF. Nutritional iron deficiency. Lancet 2007;370: 511e20.

[41] Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019;38:48e79.

[42] Iacone R, Scanzano C, Santarpia L, D'Isanto A, Contaldo F, Pasanisi F. Micronutrient content in enteral nutrition formulas: comparison with the dietary reference values for healthy populations. Nutr J 2016;15:30.

[43] Osland EJ, Ali A, Isenring E, Ball P, Davis M, Gillanders L. Australasian Society for Parenteral and Enteral Nutrition guidelines for supplementation of trace elements during parenteral nutrition. Asia Pac J Clin Nutr 2014;23:545e54.

[44] Shenkin A. Selenium in intravenous nutrition. Gastroenterology 2009;137: S61e9.

[45] Rayman MP. Selenium and human health. Lancet 2012;379:1256e68.

[46] Food and Nutrition Board of the Institute of Medicine (IOM). DRI – dietary reference intakes for Vitamin C, Vitamin E, Selenium and Carotenoids. Washington DC: National Academy Press; 2000.

[47] Li S, Xiao T, Zheng B. Medical geology of arsenic, selenium and thallium in China. Sci Total Environ 2012;421e422:31e40.

[48] Berger MM, Baines M, Raffoul W, Benathan M, Chiolero R, Reeves C, et al. Trace element supplements after major burns modulate antioxidant status and clinical course by way of increased tissue trace element concentration. Am J Clin Nutr 2007;85:1293e300.

[49] Berger MM, Soguel L, Shenkin A, Revelly JP, Pinget C, Baines M, et al. Influence of early antioxidant supplements on clinical evolution and organ function in critically ill cardiac surgery, major trauma, and subarachnoid hemorrhage patients. Crit Care 2008;12:R101.

[50] Ben-Hamouda N, Charriere M, Voirol P, Berger MM. Massive copper and selenium losses cause life-threatening deficiencies during prolonged continuous renal replacement. Nutrition 2017;34:71e5.

[51] Thomson CD. Assessment of requirements for selenium and adequacy of selenium status: a review. Eur J Clin Nutr 2004;58:391e402.